THE UNIVERSITY OF HULL

REVEALING THE DIFFERENCES BETWEEN NORMAL AND PATHOLOGICAL AGEING USING FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI)

being a Thesis submitted for the Degree of Doctor of Philosophy
in the University of Hull

by

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September 2005

ABSTRACT

The aim of the present study was to use fMRI to examine the brain activation patterns found in normal and pathological ageing on specific cognitive tasks. The cognitive paradigms that were chosen, consisted of an n-back working memory task and a semantic memory and processing task. Manipulation of the n-back task enabled vigilance and working memory load to be investigated. Patients with Alzheimer's Disease (AD) and individuals with amnestic Mild Cognitive Impairment (MCI) were compared to normal elderly and young controls. The experiments showed that the patterns of brain activation found in normal and pathological ageing do not appear to fall along the same continuum. When comparing the elderly group to the young group, areas of under-activation could be seen, in addition to other regions of activation which were thought to be due to compensation. The comparison of the normal to the pathological groups revealed distinct differences in the levels and locations of the significant activations. On the vigilance and working memory tasks, the behavioural scores and reaction times of the pathological groups were not significantly different from the normal elderly, yet substantial differences could be identified in the brain activation patterns. The semantic memory task, contrary to expectation, revealed a significant difference in behavioural performance between the young group and the elderly group. Both the reaction times and the performance scores of the AD group were significantly different compared to the elderly, however. Significant differences also occurred in the brain activation patterns of both pathological groups (AD and MCI) compared to the elderly. The differences that were present between the normal and pathological groups on each of the tasks, suggest that sensitive cognitive fMRI paradigms might be very useful in resolving diagnostic ambiguity in people at increased risk of developing AD.

Thanks to my parents who supported me one hundred percent throughout this venture. I appreciate everything you have done for me and I promise I will put you both in the hat soon and pay back some money!

ACKNOWLEDGEMENTS

I would like to thank Professor Annalena Venneri for her assistance and guidance throughout the PhD. While working for her during the last year she has been very accommodating despite the fact that the PhD has taken four years to complete. Thanks for all the late nights that were spent discussing the results of this project. Thanks to Dr Mike Shanks for his kind help in recruiting the patients for this study and for his expertise knowledge of dementia.

I am grateful to Dr Katrina Forbes-McKay for her help with the patients and for taking the time to teach me how to use a number of the neuropsychological tests that are used in the diagnosis Alzheimer's disease. I am appreciative of the time spent by Mario Ries and Gordon Waiter as they patiently trained me in fMRI. Thanks also to the radiologists in the Aberdeen Royal Infirmary and to Dr Alison Murray. I am indebted to the patients and volunteers that participated in this study. Without them, none of this would have been possible. The Aberdeen Royal Infirmary Endowment Funds, Royal College of Radiologists and Novartis Pharma AG funded this study. I would like to thank these organisations as well as the William Henderson Trust, the Grindley Grant, the Organisation for Human Brain Mapping, the British Psychology Society, John Reid's Trust Scheme, the Sir Philip Reckitt Educational Trust, Brain and the Departments of Psychology in the Universities of Aberdeen and Hull for providing travel grants for the conferences I attended.

Thanks to all my relatives, I bet you thought I would never finish! Cheers also to all my friends that kept me going throughout this project. There would be no room for the thesis if listed all of you. Thanks especially to Peter, Dave, Chiara and Maria. I promise not to complain anymore! Finally and possibly most importantly thanks have to go to Sarah, you put up with me throughout the entire journey of the PhD, through the ups and downs. I want you to know I appreciate everything you did for me. Thanks.

CONTENTS

CHAPTER 1: INTRODUCTION

1.1 Alzheimer's Disease

Alzheimer's disease is a form of dementia characterised by progressive cortical neurodegeneration. It mainly affects those over sixty-five years of age. Cases do exist of onset before the age of fifty (Miklossy et al., 2003), but these are rare. One of the characteristics of Alzheimer's disease (AD) is its insidious onset, during which only minor and often occult cognitive changes may occur. Alzheimer's disease initially tends to affect memory, although other changes may occur, for example, subtle changes in personality and emotion. As the disease progresses, a wide range of cognitive and behavioural impairments become obvious. Finally, in the terminal stages of the disease the individuals become totally disorientated, inattentive and are unable to care for themselves. The entire course of the disease may last many years, often over a decade (Almkvist, 2000).

A large number of individuals become demented late in their adult life with estimates reaching one in five of those over eighty. Alzheimer's disease is the most common dementia that occurs in the elderly population. It is not only the number of patients with AD at the present time that should be a cause for concern but also the high rate of people that are diagnosed with the disease every day.

Both the incidence and prevalence of AD in the population increase with age. The results from a Swedish community based sample analysed in the Karolinska Institute in Stockholm, Sweden, suggested that the prevalence of AD continues to increase even in the most advanced ages (Strauss, Viitanen, De Ronchi, Winblad, & Fratiglioni, 1999). Strauss et al. found that the odds ratio of AD for participants 90 to 94 years old and 95 years old plus, compared to 77-84 year olds were 4.8 and 8.0 respectively.

Epidemiological studies on populations such as that of Rochester, Minnesota, by the Department of Neurology in the Mayo Clinic (Kokmen, Beard, O'Brien, & Kurland, 1996) and the study in Stockholm, Sweden (Fratiglioni, 1993), have attempted to identify risk factors for Alzheimer's disease. Occupation, marital status, type of dwelling (Kokmen et al., 1996), gender (Fratiglioni, 1993), and education (Fratiglioni, 1993; Kokmen et al., 1996) do not appear to be risk factors according to the cited studies. Whereas, it has been suggested that excessive alcohol consumption and manual work might present high relative risks for late-onset AD (Fratiglioni, 1993). Depression has also been proposed as a possible risk factor (Kokmen et al., 1996). In addition to the possible socio-demographic risk factors, Fratiglioni (1993) suggested that a risk factor for both early and late-onset AD appears to be a family history of dementia. It is important to attempt to discover the risk factors that contribute to the onset of AD and to attempt to find out why older individuals appear to be at higher risk from the disease as opposed to the younger individuals.

The high prevalence of AD in the population is a huge problem for the people it affects, their families and loved ones, as well as being a large economic drain on the country's resources. It is, therefore, paramount that a cure for the disease, or a prophylaxis be found. Many years ago, the diagnosis or early prediction of AD did not appear to be as important as it does today, because anyone presumed to have AD could only accept the consequences, as there were no methods of prevention or cure. Nowadays however, symptomatic treatment is available e.g. Rivastigmine, Donepezil, Galantamine and Memantine. The effects of these drug treatments are presently under investigation. If the onset of AD could be predicted, it might be possible to apply drug therapies very early in the course of the disease. Early intervention might be useful in minimising the damage to the brain before any major deterioration in cognition can occur.

1.1.1 Diagnostic Issues in Alzheimer's Disease

The only definitive diagnosis for Alzheimer's disease is thought to be at post-mortem. Post-mortem evaluation for Alzheimer's disease generally involves the examination of the number and distribution of neuritic plaques and neurofibrillary

tangles (abnormal neuropathological formations in the brains of patients with AD). There is the possibility of biopsy, an invasive procedure in which cells are removed in vivo from the individuals brain, but this is generally not feasible and is considered an unethical method of definitive diagnosis in life. It is because of the uncertainty of the presence of Alzheimer's disease until post-mortem, that the disease has sometimes been termed Alzheimer's Type Dementia (DAT). DAT refers to dementia that appears to resemble Alzheimer's disease more than any other dementia, but the actual origin of the disease cannot be confirmed until post-mortem examination.

At present, with the use of clinical interviews and neuropsychological testing, diagnostic accuracy is reasonable, but still not perfect. It is predicted that with sensitive neuropsychological testing, a neurological examination and an experienced clinician, AD can be diagnosed correctly up to 86% of the time (Tierney et al., 1988). In one small series clinical diagnosis was claimed to be 100% accurate (E. M. Martin et al., 1987). In this small sample (n=11) however, the patients with AD were restricted to those who had very typical symptoms. In a larger study (n=150) using clinical diagnosis (confirmed by autopsy) diagnostic accuracy reached 87% (J. C. Morris & Rubin, 1991).

Ideally, definitive diagnosis of Alzheimer's disease should be made in vivo, but at present non-invasive neuro-imaging techniques do not provide sufficiently detailed resolution. Very recent technology offers some hopes for the future, although there may be safety issues. For example, 7 Tesla MRI scanners are now capable of imaging the plaques found in the brains of patients with AD, however, diagnosis via this method has not as yet been investigated, as there are concerns about the health of human participants at such a high magnetic fields.

It should be noted that examination by biopsy or autopsy alone, might not be accurate enough to diagnose individuals with Alzheimer's disease definitively. Diagnosis should be made by an experienced clinician, the reason being that none of the pathological features that can be observed at the present time, are specific to AD alone. Pathologists or radiologists are also not aware of the cognitive status of the individual when they are alive and therefore, would not be able to make a diagnosis with all the information that should be available. For example, the results of a study investigating

the brains of fifty-nine elderly volunteers showed that many of the participants had an abundance of senile plaques and neurofibrillary tangles, but did not show any cognitive impairment (Davis, Schmitt, Wekstein, & Markesbery, 1999). Using the Braak and Braak (1991) method of classification for pathological features, four of the elderly participants were found to be in stage V and one of the participants was in stage VI, even though no cognitive deficit was apparent. Fifteen of the elderly participants were also found to meet the requirements of the Consortium to Establish a Registry of Alzheimer's Disease (CERAD) (Mirra et al., 1991), even though no cognitive impairment was observed. This study shows that pathological features associated with dementia may be present even when dementia is not.

A study on sixty patients with probable Alzheimer's disease revealed that 30% of the individuals over seventy-four years of age did not show any neocortical neurofibrillary tangles (Terry et al., 1987). The findings from this study illustrate that even people classified with probable AD might not exhibit the pathological features associated with AD.

A more recent investigation by the Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) (2001) also revealed extensive overlap of Alzheimer-type pathology between demented and non-demented elderly groups. The MRC CFAS (2001) found that 33% of non-demented individuals had moderate or severe neuritic plaque scores. Additionally, the MRC CFAS (2001) showed that most of the patients in their sample had mixed Alzheimer-type and vascular pathology and that there were no pathological features alone that could predict dementia status. The MRC CFAS (2001) used multivariate analysis to create a model for diagnosis. When the interaction of various pathological features within the sample was included in the model, correct classification of dementia occurred in approximately three out of four cases. However, as the authors stated, the model also attributed dementia to approximately one out of four controls when none was present.

Pathological studies such as these illustrate the problems of using pathological markers alone. The findings also highlight the need for a multidisciplinary approach towards the diagnosis of AD, with evidence from as many diagnostic techniques that are available in order to establish the presence of Alzheimer's disease as accurately as possible.

Studies on genetics have also provided evidence that certain variations in genes may be an important risk factor for AD. If this is the case then the use of genotyping may be useful in the early diagnosis of AD. The presence of apolipoprotein E (ApoE) ε4 has been suggested to be a risk factor for AD (R. C. Petersen, Waring, Smith, Tangalos, & Thibodeau, 1996). Higher conversion rates have been observed in people with Mild Cognitive Impairment that possess the ApoE ε4 allele compared to those that do not e.g. R. C. Petersen et al. (1996). It should be noted that the presence of the ApoE ε4 allele does not guarantee AD, and cases of AD exist in people that do not possess this allele. Further investigation is therefore required into the predictive power of the ApoE ε4 allele and its interaction with other factors such as age, gender and environmental conditions. The ApoE ε4 allele is associated with late onset Alzheimer's disease. Genetic mutations which are related to the early onset of AD have also been investigated. Mutations related to AD have been observed on the amyloid precursor protein (APP) and presenilin (PS1, PS2) genes (Marechal, Campion, & Hannequin, 2003). These genetic mutations are more rare than the presence of the ApoE ε4 allele, but are much better predictors of AD. As knowledge of the processes and interactions involved with the genes related to AD grows, earlier prediction and better treatment strategies may be possible than are presently available.

1.1.2 Neuropathology of Alzheimer's Disease

Alzheimer's disease is associated with progressive damage to the brain. The disease mainly targets the temporo-parietal lobes but becomes more widespread later in the disease process. As it is impossible to perform longitudinal studies of Alzheimer's disease pathology, the progression of the disease instead has been studied by conducting autopsies on a cross section of brains of various ages that have been affected by AD at death. Structures in the medial-temporal lobe tend to be the first areas in the brain that are affected by AD. The medial-temporal structures include for example, the entorhinal cortex, the hippocampal structures, the parahippocampus and the amygdala. These areas are constituents of the limbic system, which is associated with memory and is modulated via cholinergic neurotransmission.

Extensive damage of the cholinergic system has been found in the brains of patients with AD. Impairment of cholinergic production is suggested to occur because of damage to the nucleus basalis of Meynert (Mesulam, 2000). Neurofibrillary tangle (NFT) formation can be observed extensively in the nucleus basalis of patients with AD, as well as the depletion of cholinergic axons in the cerebral cortex (Geula & Mesulam, 1994). The cholinergic deficit found in the brains of patients with AD does not appear to be generalised throughout the cortex but seems to be selective, targeting the cholinergic axons of the pathway that connects the nucleus basalis to the cerebral cortex (Mesulam, 2000). Cholinergic depletion can be observed to affect the limbic system and the temporal lobe, but does not seem to impinge significantly on sensory-motor areas (Mesulam, 2000).

It has been suggested that AD may be related to a vicious cycle in which dysfunctional cholinergic neurotransmission causes increases in the toxicity and the production of amyloid and that these increments in turn impair cholinergic neurotransmission (Mesulam, 1998).

Beta-amyloid is the principal constituent for the majority of plaques found in AD (Mesulam, 2000). The peptide is a relatively insoluble fragment of the larger beta-amyloid precursor protein. Diffuse beta-amyloid plaques appear to cause no local tissue damage (and can be found in normal ageing), whereas the beta-pleated form of amyloid found in compact or neuritic (containing degenerated axons or dendrites) plaques seems to promote substantial neurotoxic effects (Mesulam, 2000). The neuritic components of plaques tend to contain Tau Paired Helical Filaments (PHFs). The creation of neurofibrillary tangles occur when tau-PHF's condense, and plaques containing these insoluble filaments are only found in regions of the brains that contain neurofibrillary tangles (Mesulam, 2000).

Braak & Braak (1991) define six stages in the progression of AD pathology that can be characterised by the pattern of distribution of the neurofibrillary plaques and tangles (see Fig 1.1). The initial two stages (transentorhinal stages I-II) are defined as a mild or severe alteration of the transentorhinal layer Pre-alpha. Next comes the involvement of the limbic system (stages III-IV). The changes in this system affect the layer Pre-alpha in the transentorhinal region and the proper entorhinal cortex (as well the mild involvement of the first sector of Ammon's horn). The isocortical stages (stages V-VI) are characterised by damage to virtually all isocortical association areas.

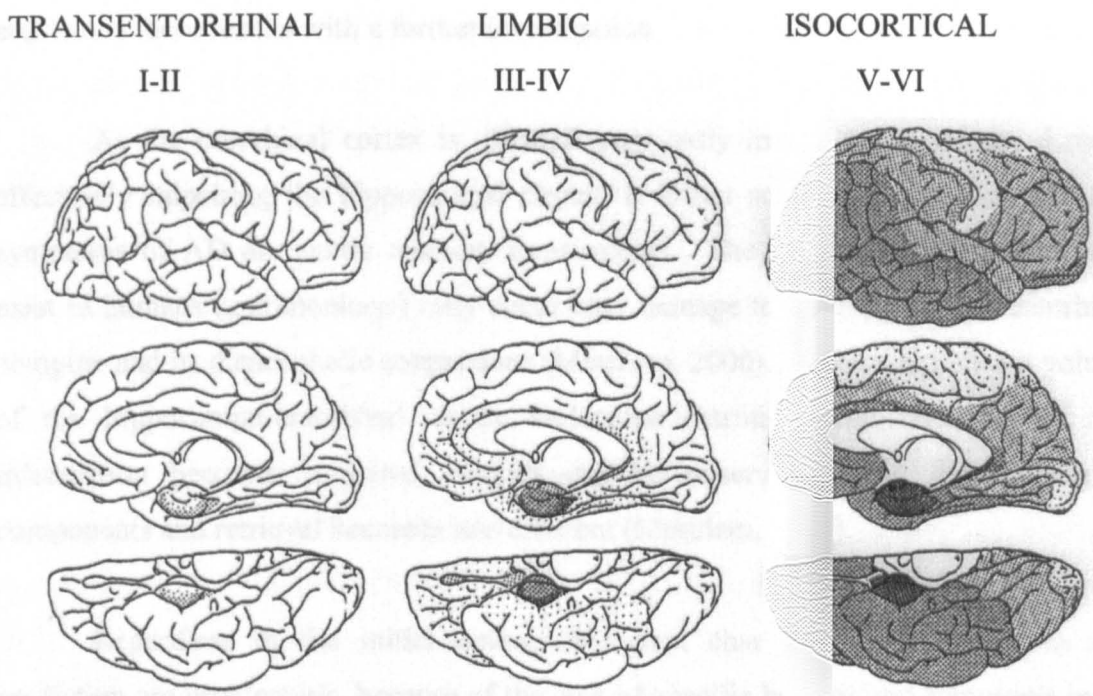

Fig 1.1: Reproduction from the Braak and Braak (1991) study on the progression of neurofibrillary changes. Increased density of shading relates to the increasing severity of neurofibrillary changes. With kind permission of Springer Science and Business Media.

The entorhinal cortex (EC) is affected very early in the disease process. The EC plays an important role in connecting the hippocampal formation to the neocortex. A study carried out by Gomez-Isla et al. (1996) involved counting the numbers of neurons in the entorhinal cortex of the brains of elderly participants after death. Individuals with a clinical dementia rating (CDR) score at death of 0 (cognitively normal), 0.5 (very mild), 1 (mild), and 3 (severe) were examined. The number of neurons in the individuals with a CDR score of 0, were approximately 650000 neurons in layer II, 1 million in layer IV, and 7 million in the entire EC. This was in great contrast, even to the individuals with very mild dementia that had a CDR score of 0.5, which had 60% less neurons in layer II, 40% less in layer IV, and 32% less EC neurons than the CDR 0 group. The CDR 0.5 individuals also had a sufficient number of neurofibrillary tangles and senile plaques to be diagnosed with AD. The findings concerning the CDR 3 group were even more marked, layer II neurons decreased by approximately 90% and layer IV

neurons decreased by approximately 70%. These findings illustrate the extent of the damage to certain cortical areas, even in very mild AD. Juottonen et al. (1998) later confirmed these results with a further investigation.

As the entorhinal cortex is affected very early in the course of the disease, effectively impairing the hippocampal circuit, it is not surprising that often the first symptoms of AD are subtle memory impairments. The most striking amnesias that exist in humans (and monkeys) only occur after damage to the hippocampo-entorhinal complex and its diencephalic connections (Mesulam, 2000). When a significant volume of the hippocampo-entorhinal cortex undergoes detriment, the encoding of new information becomes impaired, deficits can be observed during the binding of components and retrieval becomes less efficient (Mesulam, 2000).

Regardless of the initial neuropathological changes in AD, diagnosis and prediction are problematic, because of the lack of specific behavioural symptoms in the very early stages of the disease. Cognitive changes associated with the neuropathological alterations are difficult to detect and distinguish from normal age-related decline at the beginning of the disease process and it is only when the damage becomes widespread that the symptoms become evident.

1.1.3 Progression and Neuropsychological Profile of Alzheimer's Disease

AD is characterised by an insidious onset and a progressive decline in cognitive ability. In the very early stages, Alzheimer's disease causes impairments in episodic memory, recent memory and learning (Collie & Maruff, 2000). These deficits however, are not always the earliest or the only initial signs of the disease that may be observed. There may be subtle personality changes, problems with simple arithmetic, lessened spontaneity (e.g. problems initiating conversations), difficulties with word retrieval (for example, nouns and names), or disorientation in time and space (Terry, 2000).

Later in the course of the disease, the damage to cognitive function becomes more widespread. Additional impairments may be observed, for example, aphasia, apraxia, agnosia and executive dysfunction. In combination with memory decline, these impairments tend to cause a breakdown in the everyday functioning of the impaired

individual. Most sensory and motor functions, however, appear to remain relatively spared even in the later stages of the disease process.

As AD progresses to a terminal stage, patients are totally disorientated in time and space, unable to comprehend, have severe memory impairments, are incapable of caring for themselves, and ultimately the outcome is death often from secondary causes such as pneumonia.

As described above, one of the types of memory that is generally affected very early in the disease process is episodic memory. Deficits in episodic memory can be observed reliably five years before the onset of AD (Nestor, Scheltens, & Hodges, 2004). Problems in semantic memory (such as the naming of famous people, category fluency and naming) also consistently occur very early in AD (Nestor et al., 2004). A further aspect of cognition that is impaired early in the stages of AD is attentional processing (Mesulam, 2000) and mental speed (Nestor et al., 2004). Deficits can be seen, for example, in the symbol/digit substitution task, in the self ordering task and in the time taken to complete the Trails B test (Nestor et al., 2004).

Backman, Jones, Berger, Laukka and Small (2005) carried out a meta-analysis of the cognitive impairment in preclinical AD. The study consisted of 47 studies, which included 9097 controls and 1207 preclinical AD cases. Deficits in global cognitive ability, episodic memory, executive functioning and perceptual speed were present in preclinical AD. Smaller impairments were also observed in attention, verbal ability and visuo-spatial skill.

Sensitive neuropsychological testing may reveal a wide range of cognitive impairment very early in the course of AD. Differential diagnosis may still be problematic however. For example, episodic memory impairments have been reported in the normal elderly population (Ritchie, Touchon, Ledesert, Leibovici, & Gorce, 1997), as well as in AD (Nestor et al., 2004). Deficits that are shared in AD and normal ageing (although possibly varying in severity) do not make diagnosis an easy task. The deficits that can be observed in patients with AD and normal elderly may be due to different underlying functional impairments. By examining the differences in the brain activation patterns of AD patients and normal elderly controls while they perform certain cognitive tests may help to resolve difficult decisions in diagnosis.

1.1.4 Evidence from Brain Imaging in AD

Many brain-imaging techniques have been used to examine the effects of Alzheimer's disease on the brain. These techniques tend to be one of two types: Functional imaging or Structural imaging.

Functional imaging techniques enable neuronal activity to be inferred from physiological or neurochemical changes in the brain. Examples of these are Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), Functional Magnetic Resonance Imaging (fMRI), and electrophysiological methods such as the Electroencephalogram (EEG). The functional methods allow brain activity to be measured in response to certain tasks (although they differ considerably in spatial and temporal resolution between methods). Functional MRI makes use of neural correlates i.e. the Blood Oxygenation Level Dependent (BOLD) response. By measuring the changes in the BOLD response to certain tasks the activation of neural areas can be inferred. Perfusion abnormalities can be detected by examining Cerebral Blood Flow (CBF) and glucose metabolism, using techniques such as SPECT and PET.

Structural imaging examines the anatomical characteristics of the brain and includes for example, Computerized Axial Tomography (CAT), or Magnetic Resonance Imaging (MRI). The structural methods enable brain anatomy to be scrutinised, allowing the examination of the levels of atrophy and co-morbid vascular changes (if they occur). Using these techniques or a combination of the techniques much can be learnt about the effects of AD on the brain.

In a review of studies that used fMRI, PET, SPECT, and EEG in conjunction with cognitive paradigms, a number of differences were found between patients with AD and normal elderly (Almkvist, 2000). Examples of these differences were a failure to activate certain brain regions, reduced levels of activation possibly due to neuronal degeneration and the spread of activation to new regions possibly due to compensation.

These changes reveal that the course of AD alters the neural networks that are usually involved in normal elderly. The pattern of activation is generally dependant on the stage of the dementia, the pattern of atrophy in the brain, the task difficulty and the specific neuronal circuits that are required for task completion (Almkvist, 2000).

The differences observed in the brains of patients with AD may be of clinical importance in diagnosis. The altered neural patterns observed in the AD brains in response to certain cognitive tasks provide a visual analogue of the brain at work and in addition to cognitive behavioural data and a clinical interview, may increase the likelihood of an accurate diagnosis.

Studies have also investigated the activation patterns found in groups of people at risk of developing AD. An experiment by C. D. Smith et al. (1999) examined differences in the patterns of activation between two groups of women (which differed only on their APOE allele status i.e. age, education and cognitive profiles were matched) when performing visual naming and letter fluency tasks. The researchers found that although no differences existed between the groups of women on their performance on the tasks, the group at risk of developing AD had significantly reduced activation in the middle and posterior inferotemporal regions bilaterally.

Bookheimer et al. (2000) carried out a study which compared two groups, one of which was at risk of developing AD (APOE-ε4 carrier), the other of which was not (APOE-ε3). The participants were matched for age and education. The task required participants to memorise and recall pairs of words. The results showed that the group at risk of developing AD exhibited greater levels of activation in the left hippocampus, the left parietal and the left prefrontal regions.

A further study by C. D. Smith et al. (2002) investigated the activation patterns of two groups of women (which differed in risk of AD, as identified by familial history and APOE allele status, but were otherwise matched for age, education and cognitive profile) on a letter fluency task. The group at high risk of developing AD revealed significantly increased activation in the left parietal region compared to the group with a low risk of developing the disease.

The above studies appear to show that people at risk of developing AD can have different brain activation patterns to normal controls. If appropriate cognitive paradigms are applied during brain imaging, it might be possible to identify patterns of

activation that are unique to preclinical AD. If this is the case, the combination of brain imaging during cognitive testing may be a useful diagnostic tool.

1.1.5 Neuropsychological Testing for AD

Due to the nature of Alzheimer's disease i.e. the insidious onset and the progressive deficits in differing cognitive domains, various neuropsychological tests can be sensitive at different stages of the disease. If inappropriate tests are applied during certain stages of the disease real change may be masked and go unnoticed.

Tests such as the MMSE are poor indicators of the onset of AD. The MMSE is not sensitive enough to detect the initial changes in the disease. For example, there is only one question that examines learning, even though learning has been identified as one of the earliest behavioural changes in patients with AD. The low sensitivity of the MMSE means it must be amplified by other neuropsychological tests e.g. tests of verbal episodic memory that are sensitive to the early signs of the disease.

The Weschler Adult Intelligence Scale-Revised (WAIS-R) and Weschler Memory Scales-Revised (WMS-R) have also been criticised in respect of sensitivity for pathological cognitive change, in these cases concerning the normative data for elderly individuals. The normative group data for the tests may be contaminated with individuals suffering from early dementia. The exclusion criteria for the elderly in the normal sample took into account psychiatric illness, hypertension and stroke history, but it did not include any criteria for the removal of elderly individuals from the sample who were at a high risk for AD, or that were later diagnosed with the condition (Collie & Maruff, 2000). These examples illustrate the importance of choosing appropriate neuropsychological tests that are sensitive to the subtle changes that occur early in the AD process.

One of the earliest impairments that can be seen in AD is a deficit in episodic memory (Collie & Maruff, 2000). There are problems with using tests of episodic memory as tools for diagnosis however, as episodic memory impairments are not specific to AD and tend to occur in the normal aging process in addition to other types of dementia e.g. Vascular dementia and Lewy Body dementia.

When attempting to establish the onset of AD, the neuropsychological tests that have been used previously tended to focus on the cognitive impairments that can be observed in the initial stages of AD i.e. various memory functions (Collie & Maruff, 2000). Impairments in the activities of everyday life have also been suggested as possible indicators of the onset of AD. Examples of these are disorientation, subtle personality changes and language difficulties (i.e. discrete impairments in reading or subtle semantic deficits in writing). Such changes tend to be noticed by those who are close to the individual with the impairment, and are often the reason that the individuals are referred for assessment. Some people may believe that they have memory difficulties and decide to seek specialist advice. Patients with subjective memory complaints can be tested neuropsychologically to rule out hypochondriasis or "worried well" individuals and to obtain objective memory ratings (an informant is helpful to confirm subjective memory complaints). Neuropsychological batteries and clinical interviews can therefore be employed at this stage to determine those elderly people at risk of AD and to establish which cognitive domains are affected.

Neuropsychological testing on patients with AD can often reveal problems with attention, episodic memory (as mentioned above), working memory and semantic memory functioning, amongst other cognitive impairments. The attentional deficits that might be observed in AD can consist of problems that involve the dividing and shifting of attention (Parasuraman & Haxby, 1993). Impairments in vigilance have also been observed in patients with AD (Baddeley, Cocchini, Della Sala, Logie, & Spinnler, 1999).

Problems in working memory have been detected in patients with AD, for example in digit span tests (Belleville, Peretz, & Malenfant, 1996). Deficits in working memory have also been reported in normal ageing (Gregoire & Van der Linden, 1997). The deficits reported for working memory in normal ageing appear to be more readily observed during the completion of more complicated tasks than for example, the forward digit span task. Although impairments of working memory have been suggested to occur both in normal ageing and AD, the impairments appear to be greater in patients with AD. By using working memory tasks with fMRI, significant differences in brain activity might be evident between normal elderly and AD patients.

The performance of patients with AD on semantic cognitive tests has been shown to be different from that of normally aged individuals and different from that seen in other neurological disorders such as Frontal dementia, Vascular dementia, Lewy

body dementia or Parkinsons disease (Venneri, Turnbull, & Della Sala, 1996). When applied in conjunction with fMRI, cognitive tests examining semantic memory function may reveal differential brain activity in AD patient brains when compared with normal elderly.

1.2 The Effects of Normal Ageing

The effect that the natural ageing process has on the brain and on cognition complicates the prediction of AD. There are controversial points of view in the literature about the cognitive and neurobiological effects of normal ageing. Some authorities hold that "normal" aging should refer to healthy aging without any detectable cognitive impairment. In this view, detectable cognitive deficits are always disease related.

Another view is that cognitive decline may occur which is due to the biological effects of normal aging and does not necessarily involve neurodegenerative disease. There is a degree of consensus that the only specific age related decline in cognition is in episodic memory performance e.g. Ritchie et al. (1997); Small, Stern, Tang and Mayeux (1999). Episodic memory impairment has been alleged to be one of the first signs of the development of AD, however, and this complicates matters concerning early diagnosis.

Ageing appears to affect the hippocampal structures and the dorsolateral prefrontal cortex. This view is supported by functional brain-imaging studies (e.g. Esposito, Kikby, Van Horn, Ellmore and Berman (1999) and Small, Perera, DeLaPaz, Mayeux, Stern, (1999)), and by morphometric studies (e.g. Coffey et al. (1992) and Salat et al. (2004)). The effect of ageing therefore, appears to be selective in the neuro-anatomical areas that are affected. The variations in regional atrophy seem to be due to age-related changes (biological and environmental) that take place during the lifespan.

The evidence from animal studies suggests that all non-human mammals undergo an age-related deterioration of hippocampus related functions (Barnes, 1994; Rapp & Amaral, 1992). None of these animal studies reported the development of pathological features that resemble those of AD. It is very unlikely that the age-related

memory decline observed in all the other mammalian animal groups would spare humans (Small, 2001). With that in mind, it is also highly unlikely that very early Alzheimer's disease accounts for all the age-related memory problems observed in the elderly population. Ageing and Alzheimer's disease do not appear to fall along the same continuum.

Age-related decline is not observed as frequently in cognitive domains outside of memory. The study by Small et al. (1999) for example, reported an age-related decline in memory performance, but intact cognitive functions in elderly participants when tested on visuospatial ability, language and abstract reasoning.

Memory problems affect around 40% of the population over the age of sixty (Hanninen et al., 1996). The causes of these deficits are varied. Early Alzheimer's disease is known to be one of the main contributing factors. Alzheimer's disease is not the only cause however, and although a higher percentage of elderly people with memory impairments progress to fulfil criteria for Alzheimer's disease, some never do. There are many other possible causes of age-related memory impairment. These include nutritional factors, cerebro-vascular disease and general medical disorders

Genetics have been suggested to play a role in the effect of ageing on i.e. the hippocampus. It is possible that the ApoE gene may contribute to making the hippocampal memory system more vulnerable to degeneration. A study by Cohen, Small, Lalonde, Friz and Sunderland (2001) showed that healthy women in their sixth decade of life underwent greater hippocampal decline (over a two year period) if they were ApoE ε4 positive compared to negative. The results suggested that elderly individuals might all be exposed to similar environmental effects, but those that have the ApoE ε4 allele may be at increased risk of developing hippocampal impairments as they grow older.

1.2.1 Neuropathology of Ageing

Neurofibrillary tangles and senile plaques are common neuropathological findings in normal brain aging (Arriagada, Marzloff, & Hyman, 1992; Hof, Glannakopoulos, & Bouras, 1996). In a study of 1144 non-demented cases by Hof et al. (1996) it was found that layer II of the entorhinal cortex was involved with

neurofibrillary tangle formation in all cases (the CA1 field of the hippocampus and the subiculum were generally less affected when compared to MCI and AD patients). Neocortical area 20 was also found to be prone to neurofibrillary tangles in intellectually preserved elderly cases (whereas, other neocortical areas were comparatively spared). Substantial senile plaque formation was also found in the neocortex of the non-demented cases. Figure 1.2 provides a diagram that shows the various composites of the hippocampal region.

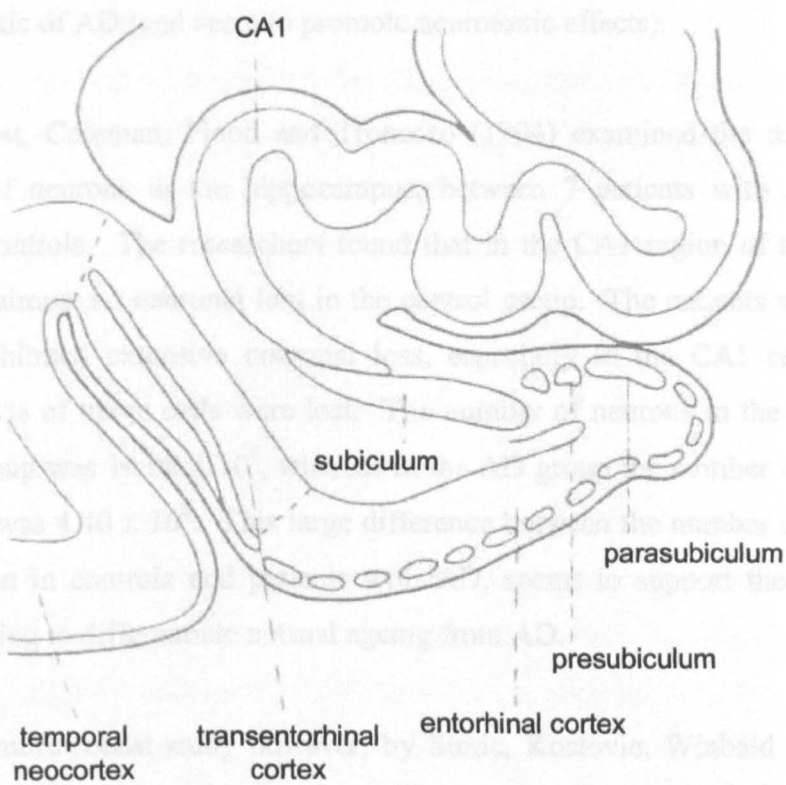

Fig 1.2: The different areas that compose the hippocampal region.

A study at the Alzheimer Disease Core Center in Portland investigated the hippocampal regions of a control group which was termed "super normal." The control group did not have risk factors for dementia such as diabetes and hypertension, and had excellent preservation of their cognitive abilities until very close to death. The hippocampal structures of seven participants were examined. The hippocampal pyramidal layer had focally severe, but microscopic neurofibrillary and granuovacuolar degeneration. The affected neurons were usually found in Rose's H1 field and in the glomerular substance of Arnold, in the entorhinal cortex (Ball & Murdoch, 1997).

Definitive diagnosis of AD at post-mortem is supported by the presence of sufficient numbers of plaques and tangles in specific locations (CERAD criteria). It appears however that there is an age-related build up of plaques and tangles, but perhaps not as rapidly as in the case of AD. Mesulam (2000) has suggested that the constituents of plaques differ between normal ageing and AD. It was reported that diffuse beta-amyloid plaques (which appear to cause no local tissue damage) can be found in normal ageing, whereas compact or neuritic plaques containing beta-pleated amyloid are characteristic of AD (and seem to promote neurotoxic effects).

West, Coleman, Flood and Troncoso (1994) examined the differences in the numbers of neurons in the hippocampus, between 7 patients with AD and 14 age matched controls. The researchers found that in the CA1 region of the hippocampus there was almost no neuronal loss in the control group. The patients with Alzheimer's disease exhibited extensive neuronal loss, especially in the CA1 region, where on average 68% of nerve cells were lost. The number of neurons in the CA1 area in the control group was 14.08×10^6, whereas in the AD group the number of neurons in the CA1 area was 4.40×10^6. This large difference between the number of neurons in the CA1 region in controls and patients with AD, seems to support the possible use of neuroimaging to differentiate normal ageing from AD.

A more recent study however, by Simic, Kostovic, Winbald and Bogdanovic (1997) found that neuronal loss occurred with age in the subiculum ($r = -0.49$, $p < 0.05$) and the CA1 region ($r = -0.84$, $p < 0.0001$), but not significantly in other regions. In another study, the other sub-regions of the hippocampus were less involved, and the entorhinal cortex appeared to be spared (Gomez-Isla et al., 1996). There appears to be a discrepancy between the West et al. (1994) study and the Simic et al. (1997) study. West et al. claimed that there was almost no neuronal loss to the CA1 region in the aged group that they examined, whereas, Simic et al. reported that significant loss to the CA1 region was found with advanced age. Despite the discrepancy in CA1, the lack of neuronal loss to the entorhinal cortex with advanced age looks to be a promising feature for diagnosis, as this region appears to be affected greatly early in the course of AD.

In addition to the neuronal changes in normal ageing, decreases in the resting brain glucose utilisation of elderly individuals compared to young people have been observed. By measuring glucose metabolic rate this decrease has been estimated to be approximately 6% for every 10 years (Petit-Taboue, Landeau, Desson, Desgranges, & Baron, 1998).

In summary, as in AD, plaques and neurofibrillary tangles can be observed in normal ageing. The plaques that occur in normal ageing may be qualitatively different, however, to the plaques found in AD. Numbers of plaques and neurofibrillary tangles also tend to increase substantially after AD has become established. A loss of neurons has been observed in various areas of ageing brains, for example, in the subiculum and in the CA1 area. The entorhinal cortex appeared to be relatively spared from neuronal loss, however, and may be useful in predicting the onset of AD, as a large number of neurons are lost in this area during the disease.

1.2.2 Neuro-imaging Evidence and the Theories of Ageing

Various theories have been proposed to attempt to explain the effects of ageing on cognition. The Right Hemi-Aging Model (Dolcos, Rice, & Cabeza, 2002) states that the right hemisphere undergoes more cognitive decline than the left hemisphere during ageing. The evidence for this theory is derived mostly from neuropsychological testing. and has been suggested by a number of researchers, for example, Albert & Moss (1988), Brown & Jaffe (1975) and Lapidot (1987). The left hemisphere is known to play the dominant role in verbal processing, whereas the right hemisphere has been observed to be dominant in spatial processing. Goldstein & Shelley (1981) found that older participants appeared to be more impaired on the spatial component of the Weschler Adult Intelligence Scale (WAIS), than on the verbal component. Similar evidence was also presented by Klisz (1978) when using a neuropsychological battery that was directed at diagnosing lateralised brain injury.

The Right Hemi-Aging Model does not receive uniform support however, and a number of researchers have made controversial findings e.g. Elias & Kinsbourne (1974), Park et al. (2002), Schear & Nebes (1980). In the study by Schear and Nebes

(1980) verbal versus spatial memory was investigated, and there were no age-related differences in performance.

Elias & Kinsbourne (1974) examined the reasons that the greater impairment to the right hemisphere during ageing has been observed. When the complexity between the tasks was equated, the elderly did not appear to differ significantly in verbal or spatial task performance (Elias & Kinsbourne, 1974).

Park et al. (2002) investigated the differences between visuospatial and verbal memory across the lifespan, reporting a continuous decline from the age of twenty on processing-intensive tasks (e.g. speed of processing, working memory and long-term memory). The authors did not conclude that any greater impairment existed however, on tasks concerning one hemisphere over the other.

Various explanations have been offered for these discrepant findings. Differences in the methodology of the tasks may have affected the results of the experiments. If it can be assumed that complex tasks tend to involve greater co-operation between hemispheres and simple tasks involve more lateralised involvement (Weissman & Banich, 2000), it might follow that complex tasks may reveal a change in hemispheric asymmetry more readily than simple tasks (Dolcos et al., 2002).

Another possible explanation proposed by Dolcos et al. (2002) is that different areas of the right hemisphere may be targeted in response to the various tasks. This would mean that some tasks would show a significant impairment on the right, whereas, other tasks which target different areas in the right hemisphere would not show a deficit. If this were the case, it could account for the mixed findings in that some tasks reveal right hemisphere impairments, whereas others do not. Indeed it has been reported that tasks which are related to posterior regions of the right hemisphere are more susceptible to age related decline (Gerhardstein, Peterson, & Rapcsak, 1998).

A different theory of age-related decline is the model of Hemispheric Asymmetry Reduction in Older Adults (HAROLD) (Cabeza, 2002). The HAROLD model states that frontal cortex activity tends to be less lateralised in the elderly than in the young. Evidence for this model has been reported in many domains including episodic, semantic and working memory.

Usually during episodic memory encoding, the young activate the left Pre-Frontal Cortex (PFC) and during retrieval activate the right PFC. This asymmetry has been termed the Hemispheric Encoding/Retrieval Asymmetry (HERA) model (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994).

The asymmetry between encoding and retrieval has been demonstrated on many occasions, for example, in the studies of Habib, Nyberg and Tulving (2003); Nyberg et al. (1996); Tulving et al. (1994). In episodic memory retrieval tasks the young tend to activate the right PFC (Nyberg et al., 1996; Tulving et al., 1994). On the same tasks however, older people have been shown to activate the PFC bilaterally (Cabeza et al., 1997). Furthermore, during a test of episodic memory encoding, younger adults activated the left PFC (Logan, Sanders, Snyder, Morris, & Buckner, 2002). In older adults however, activations of a similar level were observed bilaterally.

This bilateral effect of ageing has also been demonstrated in other tasks, for example, in word recognition (Madden et al., 1999). In working memory tasks verbal working memory is associated with the left hemisphere and spatial working memory with the right hemisphere (E. E. Smith & Jonides, 1999). Evidence from a delayed response working memory task revealed bilateral activation in the elderly and lateralised activation in the young (Reuter-Lorenz et al., 2000) supporting the increase in bilateral activity with age seen in the episodic memory tasks.

Dolcos et al. (2002), stating evidence from a study by Logan et al. (2002), claimed that the use of different cognitive strategies cannot explain the occurrence of HAROLD. In the study by Logan et al. (2002), when participants were provided with explicit encoding strategies, the activations in the older adults reached the same levels as the younger adults, but the patterns of activation remained bilateral. This experiment showed that with environmental support levels of activation in the elderly could be raised, but the bilateral effect remained.

In summary, two theories of ageing have been commented on, the right hemi-ageing model (Dolcos et al., 2002) and the HAROLD (Cabeza, 2002). The right hemi-ageing model states that the right hemisphere undergoes greater cognitive decline during ageing than the left. The HAROLD hypothesises that a reduction in hemispheric asymmetry occurs in older adults compared to the young.

1.2.3 Comparing Neural Networks in Normal Young and Elderly

Various explanations have been offered that attempt to account for the differences in activation observed in the elderly. HAROLD has been thought to occur due to an attempt at compensation by the elderly. Support for this explanation has been derived from observations that increased bilateral activity has been associated with increased performance e.g. Reuter-Lorenz (2000).

Dedifferentiation, the concept that older individuals lose the ability to engage specialised functional mechanisms that are available to the young, has also been suggested to account for HAROLD. Dolcos et al. (2002) reported that observations of bilateral activity in the elderly are better accounted for by the compensation explanation than dedifferentiation.

Cabeza, Anderson, Locantore and McIntosh (2002) carried out a PET study in which a young group and two groups of older adults were tested on source memory. The older adult groups were divided into high and low performers according to their performance on a battery of memory tests (the high performers scoring in the same range as the young, and the low performers scoring significantly lower than the young). The results showed that the young people activated the right prefrontal cortex, as was predicted from a previous study by Cabeza, Anderson, Kester, Lennartsson and McIntosh (2001). The activations of the older adults in the low performance group appeared to be similar to that of the young. The older adults in the high performance group however, revealed bilateral activation. The dedifferentiation explanation for asymmetry reduction would predict that the low performers would show bilateral activation. This would be because the elderly would not be able to recruit the specialised right lateralised mechanisms that the young do and would have bilateral activation. On the other hand, the older adults that perform behaviourally in the same range as the young would not have bilateral activation as they are performing the task using the same specialised lateralised mechanisms that the young use. This was not what was seen however, as it was the high performers that revealed bilateral activation. As bilateral activation was observed in the older adults that performed well, the reduction in asymmetry in older adults appears to be better explained in terms of compensation.

Evidence from patients with unilateral brain damage suggests that during the recovery period the activations of these patients tend to occur in the contralateral hemisphere to the one that has been damaged (Cao, Vikingstad, George, Johnson, & Welch, 1999). This evidence supports the belief that asymmetry reduction in older adults reflects a compensatory reaction (Dolcos et al., 2002).

Older individuals have been observed to have activation in different areas of the brain than younger individuals, even when carrying out the same cognitive task and scoring the same behaviourally (Grady, 2000). These observations could be due to alternative functional brain networks being accessed in the elderly brain in order to compensate and perform more efficiently (Grady, 2000). Sometimes the recruitment of other brain areas due to age do not appear to relate to intact behavioural performance, however, and instead, reduced performance compared to the young can be observed (Grady, 2000).

A number of differences have been observed between the neural networks of the young and the elderly. These have been documented as under-activation in certain brain structures, activations in different regions, decreased laterality, compensatory activations, dedifferentiation and non-selective over-activation (Reuter-Lorenz, 2002).

Older adults may perform less well than young adults because they tend to under-activate the same regions of the brain that are utilized by young adults for efficient performance (Reuter-Lorenz, 2002). In concordance with the lesion model (in which neuropsychological patient populations are used in order to attempt to explain deficits that are attributed to be due to "normal" ageing), neuro-imaging has revealed that the prefrontal cortex appears to be a common site which is under-activated in aged participants (Reuter-Lorenz, 2002).

An fMRI study on memory encoding illustrated that elderly brains under-recruited or activated non-selective regions of the concerned structures, unlike young brains (Logan et al., 2002). The under-recruitment of the brain structures could be reversed with semantic elaboration (environmental support) leading to the activation of these brain structures (Logan et al., 2002). This finding suggested that the same structures may be used by the young and by the elderly, but that the elderly might need

help in activating these regions. The non-selective recruitment of areas of the frontal lobes has been associated with the cognitive decline in aging (Logan et al., 2002).

Even when performance was equated between the elderly and the young, older brains often showed activations differing from the young while completing the same tasks. The increase in bilateral activation in the elderly has already been emphasized. It has been suggested that younger adults often have highly lateralized networks in different cognitive domains, for example, verbal working memory appears to be mostly lateralised to the left hemisphere and spatial working memory to the right hemisphere (Reuter-Lorenz et al., 2000; E. E. Smith, Jonides, & Koeppe, 1996). Using PET, verbal working memory can be observed to activate areas on the left hemisphere in the young, whereas, in the elderly, regions in both hemispheres are activated including the dorso-lateral prefrontal cortex (DLPFC), which was activated at a lower level in the young (Reuter-Lorenz et al., 2000). Older participants, therefore, can be seen to exhibit a decrease in laterality for certain tasks.

It has also been demonstrated that in order to increase performance accordingly, as task difficulty is increased, the elderly tend to compensate with increased activation in bilateral cortical areas (Anderson et al., 2002). Bilateral activation can also be induced in younger brains by applying difficult tasks, for example increased working memory load (Klingberg, O'Sullivan, & Roland, 1997). It is reasonable therefore, to presume that the elderly recruit additional brain structures (often bilaterally) to attempt to improve performance, as possible deficits resulting from slower processing abilities, depleted attentional resources or ineffective strategies may be present. The extra regions recruited by the elderly brains may be compensating for deficits that limit the optimal functioning of the brain. It should be noted, however, that if behavioural scores in a cognitive task are at ceiling, low activations may not be signs of impairment but rather of efficient strategies, or that the task is too easy to invoke higher activations.

The elderly brain appears to recruit similar structures to the young brain, sometimes at a lower level of activation, sometimes in a more widespread manner (possibly resulting in bilateral activation), however, activated neural networks of AD patient brains tend to differ from both young and elderly brains.

1.3 Mild Cognitive Impairment

1.3.1 Definition and Features

Mild Cognitive Impairment (MCI) generally refers to a mild memory or cognitive deficit in a non-demented individual, which has not been accounted for by any recognisable organic disorder.

A number of studies have investigated the prevalence of mild cognitive impairment in the population. Callahan, Hendrie and Tierney (1995) found the rate of MCI in a population of elderly primary care patients to be 10.5% in over 60 year olds (In addition, 5.2% patients had moderate to severe cognitive impairment). Hanninen, Hallikainen, Tuomainen, Vanhanen and Soininen (2002) studied a population in Finland of 806 people (age 60-76) and found 43 participants (5.3%) met their criteria for MCI. In a different study by Larrieu et al. (2002) the prevalence of MCI was reported to be 2.8% of the sample.

The differences in the prevalence of MCI may be due to differences in the populations (for example, the ages of the individuals in the studies), as well as the definition of MCI used to categorise the participants. Mild cognitive impairment has been described in the past under a number of different terms, for example, Age-associated Memory Impairment (AAMI) (Crook, Bahar, & Sudilovsky, 1987), Late-Life forgetfulness (LLF) (Blackford & La Rue, 1989), Age-Related Cognitive Decline (ARCD) (Celsis et al., 1997), Age-Associated Cognitive Decline (AACD) (Levy, 1994), Isolated Memory Impairment (IMI) (Berent et al., 1999) and Age-Consistent Memory Impairment (ACMI) (Blackford & La Rue, 1989). These different terms and associated definitions contribute to the controversy over the prevalence of the condition in the population.

Schroder et al. (1998) investigated an elderly group between the ages of 60 to 64 years old. The researchers classified the elderly individuals using the criteria for AAMI, ACMI, LLF and AACD. The following prevalence rates were reported: 23.5% for AACD, 13.5% for AAMI, 6.5% for ACMI, and 1.5% for LLF. The results of the

Schroder et al. (1998) study reveal that the diagnostic criteria employed, are very important when determining the prevalence of mild cognitive impairment in the population.

It is not only the differing definitions of a mild cognitive deficit which cause difficulties, but also the variable criteria used within each definition, i.e. the term "Mild Cognitive Impairment" has been defined differently in various studies. Some authors would classify MCI patients as individuals that receive a Clinical Dementia Rating (CDR) score of 0.5. However, a CDR of 0.5 extends not only to Mild Cognitive Impairment but also into the category of probable Alzheimer's disease. Furthermore, other authors do not use the CDR scale at all in their studies. The consequence of some researchers adopting, for example, the CDR scale in their studies, and other researchers choosing not to use the CDR, is that the criteria used to define MCI will differ between experiments. This can be problematic when attempting to interpret the results over a number of investigations. The comparison of studies, therefore, must take account of the different inclusion criteria and variability in definitions.

R. C. Petersen et al. (1997) defined MCI using the diagnostic criteria: 1) A memory complaint; 2) Normal activities of daily living; 3) Normal general cognitive function; 4) Abnormal memory for age; 5) Non-demented. This definition of MCI appears to be quite widely accepted and has been used in a number of different studies, for example, Ritchie, Artero and Touchon (2001); R. C. Petersen et al. (1999). The R. C. Petersen et al. (1997) definition of MCI is not employed universally however, and various researchers and clinicians are known to have their own diagnostic criteria.

The definition by R. C. Petersen et al. (1997) has since been relabelled, amnestic MCI because the criteria emphasise memory loss, with retention of other cognitive functions within the normal range (R. C. Petersen et al., 2001). Some studies have employed cut-off scores in order to use a standard method of defining impairment e.g. the study of Age-Associated Cognitive Decline by Levy et al. (1994), which specified that an impairment existed if a drop in performance occurred of more than one standard deviation from age matched controls. R. C. Petersen (2004) stated that the individuals defined as MCI in the cohort study at the Mayo Clinic, had a decrement of at least 1.5 standard deviations below age-matched controls.

Batteries of neuropsychological tests can be used to cover a wide range of cognitive functions. These should contain tasks that are sensitive enough to detect subtle changes in cognitive performance and distinguish those with MCI from age-matched controls.

The definition of MCI by R. C. Petersen et al. (2001) appears to be useful, as subsequent studies will hopefully use the same criteria for selection. This will enable more accurate comparisons to be made between studies.

1.3.2 Conversion to Alzheimer's Disease

The rate that healthy control participants convert to Alzheimer's disease has been found to be approximately 1-2% per year according to a longitudinal study of more than 500 control participants for 10 years (R. C. Petersen et al., 1999). This is very different from the conversion rate to AD found in individuals with amnestic MCI. The conversion rate per year for the MCI group was 12% in a 4 year follow-up study (R. C. Petersen et al., 1999). The much higher conversion rate in Mild Cognitive Impairment individuals suggests that MCI may be a stage between probable Alzheimer's disease and the normal aging process. As MCI patients have a much higher conversion rate than control participants, the MCI stage may be seen as a possible intervention period for drug therapies, in order to halt or delay progression to Alzheimer's disease. This concept is problematic as not all MCI patients convert to AD.

One cause of variable conversion rates may be that the MCI group is contaminated with "healthy" individuals, i.e. those that have had a long-standing memory impairment that may not be progressive. The memory impairments these patients demonstrate may have arisen from a range of other factors, for example, arteriosclerosis, toxic effects of medications, trauma, etc.

In addition to the problems of having widely agreed diagnostic criteria for MCI, there is the added difficulty of defining the conversion criteria for probable AD. These problems may also influence the differing conversion rates of MCI to probable AD.

Individuals with MCI compared to very mild AD patients appear to have similar memory impairments, but the AD patients are also impaired in other cognitive domains (R. C. Petersen et al., 1999). The more cognitive domains that are impaired in

individuals with MCI, the higher the rate of progression to AD (Meyer, Xu, Thornby, Chowdhury, & Quach, 2002).

The cognitive state of individuals with MCI declines at an increased rate when compared to controls but less rapidly than patients with mild AD (R. C. Petersen et al., 1999). If the MCI individuals can be accurately classified into converters to AD and non-converters, then drug therapies and other interventions can be better targeted and their effects monitored.

There is evidence that drug therapy intervention is most beneficial if the deterioration of the brain is minimal, i.e. in the very early stages of the disease as suggested by Farlow (2002). Furthermore, drug treatments such as Donepezil, have been reported to slow the rate of progression to AD in individuals with MCI during the first twelve months of treatment (R. C. Petersen et al., 2005). These drug therapies are not cures for AD, but they do appear to have benefits if applied early in the disease process.

1.3.3 Neuropathology of MCI

Impairment of memory is a prerequisite for a person to be labelled with amnestic MCI. It is no surprise therefore, that atrophy of the hippocampus can be observed in individuals with MCI.

Wolf et al. (2001) investigated hippocampal volume in people with MCI that had a Clinical Dementia Rating (CDR) of 0.5. The participants were not demented, but had a significantly reduced hippocampal volume of 14.3% in the left and 11.3% in the right, compared to normal participants. The researchers also measured the hippocampi of patients with mild AD (CDR 1), finding reductions of 28.1% in the left and 25.9% in the right, compared to the controls. The results show that hippocampal volume tends to be reduced both in individuals with MCI and in patients with AD, compared to the normal population.

A longitudinal study by Jack et al. (1999) examined hippocampal size in individuals with MCI. Participants with MCI underwent clinical/cognitive assessment approximately every year. The authors found that the rate of conversion to AD was faster for those individuals with MCI that had smaller hippocampal volumes at the initial time of testing.

The studies on hippocampal volume show that measurements of the hippocampi may be of use in discriminating individuals with MCI from normal controls. Furthermore, hippocampal atrophy seems to be a risk factor for the conversion to AD.

Pathological formations associated with AD may be observed in those individuals with MCI that subsequently convert to AD (see Fig 1.3). In MCI, neurofibrillary tangle formation may spread into paralimbic, fusiform and inferotemporal regions, as opposed to being restricted to the entorhinal/limbic areas as in normal ageing (Mesulam, 2000). The numbers of neurofibrillary tangles may also increase in the entorhinal/limbic areas (Mesulam, 2000).

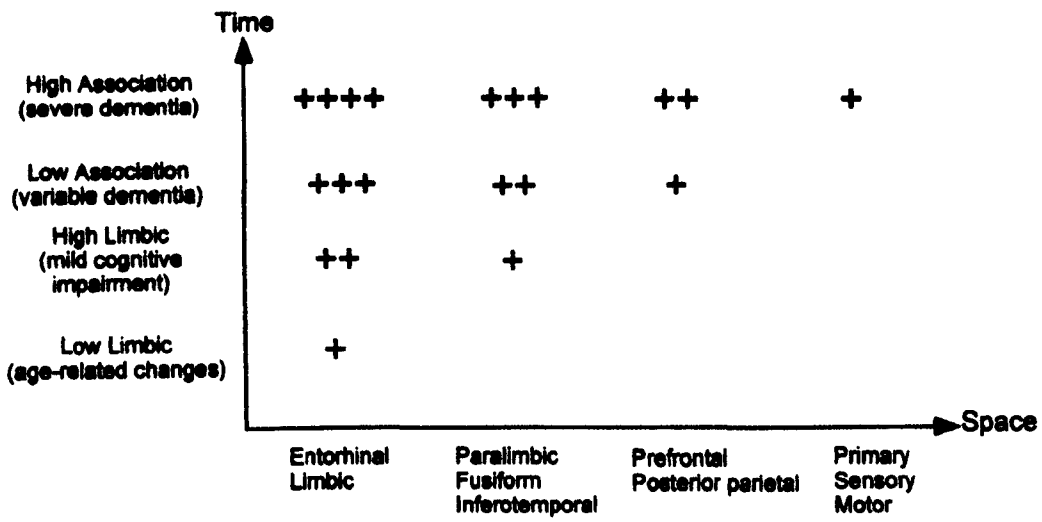

Fig 1.3: The spread of neurofibrillary tangles in normal ageing, mild cognitive impairment, variable dementia and severe dementia. Reproduced from "Principles of Behavioural and Cognitive Neurology" by Marek-Marsel Mesulam (2000), with kind permission of Oxford University Press.

In individuals with MCI that subsequently convert to AD, neuropathological changes may be observed which reflect the modifying effects of AD. To summarise, the changes that have been described are increases in the numbers of neurofibrillary tangles in entorhinal/limbic areas, spreading of the distribution of the neurofibrillary tangles and atrophy of the hippocampal region.

1.3.4 Problems in Differentiating Normal Ageing, MCI and AD

The distinction between normal ageing, MCI and AD using measures of cognition and/or neuropathology, may be possible, but there is overlap between the different groups. This overlap can be observed in the evidence from batteries of neuropsychological tests and rating scales applied in dementia. A Clinical Dementia Rating (CDR) of 0.5 can include both MCI and a percentage of probable AD patients (questionable dementia according to the scale). On the Global deterioration scale (GDS), MCI could fall under a rating of either 2 or 3, whereas a GDR of 3 also incorporates a percentage of the probable AD group (mild dementia). The rating scales are a useful method of classifying the stage of the dementia (e.g. very mild, mild, severe), but can create confusion when attempting to assign an individual to MCI or AD groups. An overlap in disease symptoms, therefore, creates problems in classification (MCI or AD) and the prediction of conversion (MCI to AD).

Accurate methods are needed to differentiate normally aging people with a mild cognitive impairment that will not convert to Alzheimer's disease, from those with MCI that will convert. A step beyond this would be to distinguish aged individuals in the normal range of cognitive function that will convert to AD from those that will not.

Depression is also common in preclinical AD. According to Visser, Verhey, Ponds, Kester and Jolles (2000) depressed individuals with depression-related cognitive impairment can be accurately distinguished from preclinical AD patients. Visser et al. (2000) states that whether depressed people go on to develop Alzheimer's disease can be predicted accurately by their age and the severity of the associated memory impairment (specificity = 94%, sensitivity = 90%). The researchers suggested that individuals with depression should not be excluded from investigations into preclinical AD, as preclinical AD is often accompanied by depression.

Other complications arise in group differentiation because of the different patterns of progression in Alzheimer's disease. There appear to be subtypes of AD with distinctive early clinical, neuropsychological and neuroimaging features. For example, variants of AD can be observed with predominant left or right hemispheric degeneration (Almkvist, 2000). Studies do not tend to account for subtypes of AD and this may cause problems in predicting the onset of AD in MCI individuals or elderly controls,

unless an experienced clinician is employed to differentiate between the sub-types of the disease.

CHAPTER 2: AIMS OF THE STUDY

2.1 Aims and Objectives

The principle aim of this dissertation is to attempt to discriminate pathological from normal ageing using fMRI. This is to be endeavoured by investigating the effects of normal ageing, the effects of pathological ageing (in the form of AD), and the effects of Mild Cognitive Impairment, on the brain, while participants are engaged in various cognitive tasks. It is hoped that it will be possible to differentiate between the different classes of participants (i.e. young individuals, elderly individuals, patients with AD and individuals with MCI) using patterns of brain activation alone.

Initially the effect of normal ageing will be investigated, by examining the brain activations of an elderly group of individuals compared to a group of young individuals. A number of age-related effects have been described in the introduction and these will be discussed in detail in the following chapters. Different cognitive paradigms will be used to see which aspect of memory gives the best profile to distinguish normal from pathological age-related decline.

The importance of this project is to attempt to identify patterns of cognitive activation that might reveal the onset of pathological ageing as early as possible. Recent studies have shown that the earlier in the course of AD that pharmacological treatment can be applied, the greater the potential benefits (Farlow, 2002). For this reason, in the current experiments only patients with minimal to mild AD will be investigated. Patients that are further in the course of the disease will be excluded. Substantial differences in functional brain activations are expected to exist between normal elderly individuals and patients further on in the course of Alzheimer's disease. There may also however, be subtle, but important differences between normal and pathological ageing at much earlier stages. It follows that if significant differences exist

in the brain activations between patients with early AD (that have very good behavioural scores) and normal elderly, then fMRI might provide an additional diagnostic tool to be used in distinguishing pathological from normal ageing. This method might be beneficial in helping to solve diagnostic problems in cases in which conventional clinical and neuropsychological testing is not sufficient.

Participants with Mild Cognitive Impairment will also be investigated, as a higher proportion of the people with this condition convert to AD, than in the normal population. Individuals with MCI are, therefore, an informative population to examine when attempting to identify markers of pathological ageing. Those with MCI that go on to convert to AD can be regarded as a set of people intermediate between normal ageing process and AD.

To address the problem of which individuals with MCI will convert and which will not convert to AD, the best design would be a longitudinal study. Those who convert to AD (the preclinical population) could be examined and scanned using fMRI, as could those that do not convert. These groups of individuals with MCI (converters and non-converters) could then be compared in order to see whether a pattern of activation exists, which predicts which individuals will convert to AD (and which will not). Due to the relatively short time scale of the PhD, the present study was not designed to be a longitudinal study, but rather a cross-sectional study of individuals with MCI. Four out of the six participants with MCI subsequently converted to AD, however, which enables retrospective insight with regard to the analysis. Note that the individuals with MCI that converted to AD were not re-scanned and only the data scans at the time they met the criteria of MCI are available.

The MCI group in the present study, therefore, included 4/6 converters (two out of six did not convert to AD by the time of this writing, but of course may still convert, or may since have converted). This MCI group is likely to be an interesting population to compare to normal elderly participants and patients with AD. It will be informative, for example, to observe (for the different cognitive tasks used with fMRI) whether the patterns of brain activation found in the MCI group appear more similar to the patterns of activation seen in normal or pathological ageing.

One possible outcome of the present study may be to provide a method to predict from brain activation patterns in response to cognitive tasks, which individuals are more or less likely to convert to AD. If markers of preclinical AD could be identified before any behavioural signs are detectable, this would be an opportunity for very early intervention with the drug therapies, at the time when both the patients and their families might benefit most.

In Experiment 1 an n-back working memory task will be used to investigate the effects of normal ageing (young group and elderly group comparisons) on vigilance and working memory. Experiment 1a will examine vigilance, Experiment 1b, a light working memory load, Experiment 1c, a more demanding working memory load and Experiment 1d will use a parametric design to examine the effects of a progressively increased working memory load. Experiment 2 will also make use of an n-back working memory task, but this time the effects of pathological ageing (elderly group, AD group and MCI group comparisons) will be investigated. Experiment 2a will examine vigilance, whereas Experiment 2b will involve a light working memory load. Experiment 2 is not designed to incorporate the more demanding working memory load or the parametric design. Experiment 3 will investigate the effects of normal ageing (young group and elderly group comparisons) on a semantic memory and processing task. Experiment 4 will use the same semantic memory and processing task but will look at the effects of pathological ageing (elderly group, AD group and MCI group comparisons), rather than normal ageing.

The n-back working memory task was chosen for the present study because working memory load could be incremented through the conditions. This feature was useful when converting the task to an fMRI paradigm. Working memory functioning is thought to undergo decrements during the process of normal ageing. The impairments that are found in patients with Alzheimer's disease tend to be much more severe, however, which suggests that differential patterns of activation may be observed between normal and pathological groups. The literature on verbal working memory also describes the results of a number of n-back tasks, which is beneficial as it means the pattern of activation that is considered normal on the task is well documented.

The Pyramids and Palm Trees test (D. Howard & Patterson, 1992), used with fMRI, was chosen to investigate semantic memory and processing. These functions will be examined as recent evidence has shown that they may be impaired early in the course of AD (Forbes, Venneri, & Shanks, 2002; Hodges & Patterson, 1995). Semantic memory has also been reported to remain relatively stable throughout the course of the lifespan (Nilsson, 2003), which means that it may be useful in discriminating the effects of normal from pathological ageing.

CHAPTER 3: AGE AND DISEASE EFFECTS OF WORKING MEMORY

3.1 Introducing Working Memory

Working memory (WM) is the memory system that makes use of the input from the sensory systems, either to maintain the information (temporarily) and/or to make use of the information in the present by integrating it with prior knowledge. Working memory has been likened to Short Term Memory (STM), as the information that is to be maintained is retained only as long as it is required and both of the proposed systems are limited in capacity. In this sense it is not like Long Term Memory (LTM), which appears to be a memory system that is extensive both in the capacity of the information that can be stored and in the duration of the storage of information that can be retrieved. The concept of working memory differs from STM, however, as working memory can also include the manipulation of information during the limited period of time it is to be maintained. The concept of STM on the other hand refers to an information store in which information can be maintained, but not manipulated.

3.2 Theories and Models of Working Memory

One of the most popular models of working memory is that of Baddeley and Hitch (1974). The model introduced two hypothetical slave components, which are now known as the phonological loop and the visuo-spatial sketch pad. The model also included that these slave components are modulated by a central executive system.

The phonological loop is thought to be composed of a phonological store which retains auditory information over a period of a few seconds, unless the information is renewed by a process of phonological/articulatory rehearsal (Baddeley, 2000). The visuo-spatial sketch pad has been proposed to be the component of working memory in

which visual representations of objects and their spatial locations can be retained for a limited period of time (Baddeley, 1998). Baddeley (1998) suggests that the retention of information by the visuo-spatial component may involve actively maintaining attention to specific parts of the visuo-spatial processing system.

Unfortunately, the rehearsal processes behind the visuo-spatial sketch pad component are much less understood than its phonological counterpart. It may not be appropriate to consider the visuo-spatial sketch pad as a single component, but as a collective descriptor of the cognitive functions that are involved. Logie (1995) describes visuo-spatial working memory as a system which incorporates a visual temporary store and a spatial temporary store. These stores have been termed the visual cache and inner scribe, respectively. Logie (1995) suggests that visual stimuli calls upon LTM representations of the visual form of objects or the spatial dynamics of the information. After the LTM representations are activated the information is proposed to enter either the visual cache (the visual component) or inner scribe (the spatial component) depending on the type of stimuli. The visual cache is thought to store visual information, but is prone to decay and interference. The inner scribe on the other hand is suggested to be used to both to plan movement and to rehearse the contents of the visual cache.

The central executive was suggested as the system that is in control of the perceptual slave components (Baddeley & Hitch, 1974). It is this system that co-ordinates working memory activity and enables participants to perform two or more tasks simultaneously. The central executive has been proposed to be an attentional system that allocates the available resources and modulates the slave components.

The Baddeley & Hitch (1974) model, although able to account for the results from a number of experimental studies, could not account for some interesting findings. For example, the observation that some patients with severe phonological STM problems, that have an auditory memory of 1 digit, can often recall up to 4 digits when presented visually (Baddeley, 1987). Evidence suggests that the visuo-spatial sketch pad is good at storing, for example, a complex pattern, but is not suited to storing serially presented visual stimuli (Phillips & Christie, 1977). There is the problem, therefore, of how these visually presented digits are stored, if the phonological loop is impaired and the central executive is presumed to have no capacity for storage. A different problem arises with the observation that a greater amount of information can be retained in memory when the stimuli are chunked. Individuals can typically

remember about 5 words but if the words are placed in a meaningful sentence the number of words remembered can be increased greatly, for example, a span of sixteen or more is possible (Baddeley, 1987). This finding appears to demonstrate that information is integrated with information from LTM in order to increase capacity by creating a smaller number of chunks. The dilemma in this instance is where the information is integrated and where these chunks of information are stored. If the information was stored in the phonological loop, it does not explain the findings of Vallar and Baddeley (1984), that patient PV, although presenting phonological loop deficits and capable of storing only one word, managed to recall, for example up to five words when placed in a meaningful sentence. The phenomenon does not also appear to occur purely in LTM as patient PV had intact LTM, although the number of words that she remembered in sentence format was reduced compared to the approximate fifteen words recalled by normal participants (Baddeley, 1987).

Examples such as these that did not fit with the initial Baddeley & Hitch (1974) model led Baddeley to reconfigure the model with an additional storage site that was named the episodic buffer (Baddeley, 2000). The episodic buffer is assumed to be a temporary storage system with a limited capacity that has the capability of integrating information from a number of sources i.e. from LTM and/or from the slave systems. The central executive is thought to act upon the episodic buffer by modulating the content of the storage site by allocating attentional resources to the various sources of information available.

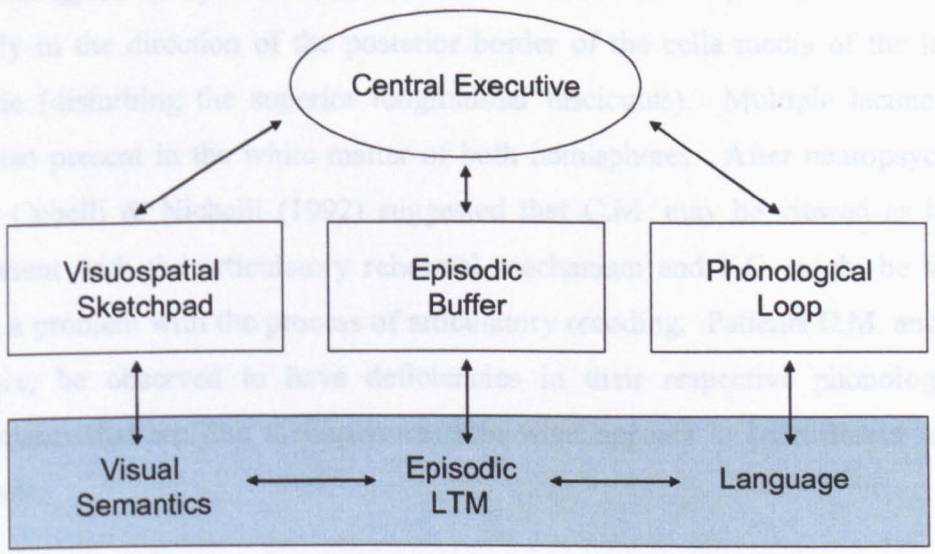

Fig 3.1: Baddeley's reviewed working memory model, which illustrates the hypothetical components of working memory (Baddeley, 2000). With kind permission of Elsevier.

3.3 Introducing the Neuropsychology of WM

The fractionation of working memory has been demonstrated in patients with neuropsychological deficits. Vallar and Baddeley (1984) presented patient PV, who had a defective phonolological store that was capable of retaining a decreased amount of material, compared to normal individuals. Patient PV suffered damage to her left hemisphere after a stroke. The phonological store was considered to still work to a certain extent, as information (albeit it a very reduced amount) could be retained with auditory presentation.

Patients whose phonological/articulatory loop is impaired can also be observed. Cubelli and Nichelli (1992) reported the case studies of two such patients C.M. and F.C. Patient C.M. had the clinical diagnosis of a "locked in" syndrome. An MRI scan revealed a bilateral pontine lesion (possibly ischemic) found in the median and paramedian portion of the ventral pons, which was anterior to the fourth ventricle. Patient F.C. was anarthric, for up to 4 months after onset the patient was unable to utter a single phoneme. After five months of rehabilitation patient F.C. could articulate some speech, but, the language was so dysarthric that it was mainly useless for communication. MRI scans revealed that a lesion had affected the lower half of the precentral gyrus (subjacent white matter was also affected). The lesion stretched medially in the direction of the posterior border of the cella media of the left lateral ventricle (disturbing the superior longitudinal fasciculus). Multiple lacunar infarcts were also present in the white matter of both hemispheres. After neuropsychological testing Cubelli & Nichelli (1992) suggested that C.M. may be viewed as having an impairment with the articulatory rehearsal mechanism and F.C. might be viewed as having a problem with the process of articulatory recoding. Patients C.M. and F.C. can therefore, be observed to have deficiencies in their respective phonological loop mechanisms that are due to impairments in what appears to be different underlying processes.

Experiments performed by Della Sala, Gray, Baddeley, Allamano and Wilson (1999) provide evidence of the distinction between visual and spatial working memory.

The pattern of impairment of three patients is particularly noteworthy. Two patients, one of which had suffered a stroke affecting the left middle cerebral artery (rendering the patient aphasic), and the other who had obtained a head injury that caused a left-side anterior lesion (leaving the patient aphasic), performed below the 5th percentile on the Corsi blocks task, but performed above the median for the visual patterns test. The performance of the third patient however, who had endured a stroke which caused anterior lesions bilaterally (the patient remained non-aphasic), followed the opposite pattern, in which performance on the visual patterns test was considerably below the cut-off, whereas performance on the Corsi block task was well above the median. The dissociation as measured by these tasks provides evidence of a distinction between the visual and spatial components of working memory.

The central executive system appears to be active in tasks that involve shifts of attention, inhibition, updating and dual-task co-ordination, amongst others. When the brain areas are damaged that underlie these central executive functions, various corresponding impairments can be observed.

Delayed-alteration tasks can be used to reveal impairment of the central executive system of working memory. An example of one of these tasks involves the participant having to choose the opposite location to one which was previously reinforced. Patients with lesions to the frontal lobes perform poorly on this task, especially if the lesions are bilateral (Gazzaniga, Ivry, & Mangun, 1998). For the successful completion of a delayed alteration task many central executive processes would most likely be occurring, for example, responses to the stimuli that were viewed initially must be inhibited, as these stimuli do not represent the correct responses. The individual must also use a form of task switching in order to switch attention during the delay period to the alternative (and correct) stimuli. A further feature of the delayed alteration tasks is whether the individual uses a phonological code and/or a visuo-spatial code in order to maintain the information throughout the delay, the central executive is most likely being used in order to control or co-ordinate this activity. As mentioned by Gazzaniga et al. (1998), patients that have lesions to the frontal lobes perform delayed alteration tasks poorly. The reason for the reduced performance on these tasks is thought to be because the central executive processes are not functioning correctly.

Perseverations are often common after frontal lobe damage and can be seen during tasks such as the delayed-alteration task. Perseverations are the tendency for the individual to repeat or persevere, to the point where it is no longer appropriate. There are different kinds of perseverations in which the individual repeatedly says the same word or phrase or performs the same action (Gathercole & Baddeley, 1993). The perseverations that can usually be observed in delayed-alteration tasks, are repetitions of older visual cues when the new visual cue is needed to fulfil the task requirements.

Shallice (1988) suggested that perseverations occur when an action is controlled at a low level by a single powerful schema that inhibits all others. As the central executive is impaired it cannot intervene sufficiently to dull the activation of this single schema and to enable the possibility of switches to other more appropriate schemas.

The findings from experimental research and case studies suggest that the working memory system consists of a number of components of working memory, for example, a phonological loop and store, a visual cache and inner scribe, and a controlling central executive. The patient studies have also revealed some of the resulting outcomes when damage occurs to the areas that underlie these working memory functions.

3.4 Animal Studies of Working Memory

Animal lesion studies have demonstrated that the lateral prefrontal cortex plays a role in maintaining information in working memory. The use of a delayed response task in monkeys has previously been used to show that lesions to the lateral prefrontal cortex results in very poor performance on such a task (Goldman-Rakic, 1992). In this task two wells are exposed to the monkey and food is placed in one of these. The wells are then covered up for a delay period. When the wells are exposed again the monkey must choose which one contains the food. On this delayed response task the monkeys with lesions to the lateral prefrontal cortex perform very badly.

The monkeys do not lose the ability to form associations however, and if a visual cue is presented along with the well that contains food, the food then covered and the delay period presented, the monkey is able to choose correctly, when the correct

visual cue is presented over the well that contains the food. In the delayed response task however, the monkey cannot rely on the stimulus itself, it must hold information in working memory in order to successfully complete the task.

3.5 From Neuropsychology to Neuroimaging of Working Memory

The lesion studies already discussed attempted to localise the components of the working memory system by examining the nature of the impairment and the area of the lesion. In this sense functional neuro-imaging studies can add to the knowledge on working memory as the studies can systematically examine different parts of the tasks e.g. by increasing working memory load in stages. This can reveal the areas involved in the working memory system more accurately than lesion studies might, since very small details in the tasks can be altered and the effects of these changes examined. In contrast, in lesion studies the presence of a lesion may disrupt the working memory network but the reason behind the disruption might not be evident. A further disadvantage of lesion studies is that the lesions often vary in size and location between participants, making the interpretation of the findings more controversial. Neuro-imaging studies can offer a more accurate spatial representation of the functional networks in the brain.

Neuro-imaging techniques such as fMRI and PET can also allow the whole brain to be examined during cognitive tasks, whereas lesion studies and single cell recordings are severely limited in revealing the functional interactions that are being used to complete the tasks.

A benefit of neuro-imaging is that even when different groups have equal levels of performance, for successful completion some groups may be employing more effort or performing the tasks in different ways. Neuro-imaging techniques provide a quantitative and qualitative measure of the underlying brain regions that are used in the completion of the tasks. It follows that while behavioural scores might discriminate poorly between patients with very early Alzheimer's disease, individuals with MCI, and controls, neuro-imaging techniques may provide valuable insight into the processes that the different groups are using to complete the tasks. Functional neuro-imaging can

reveal differences in strategies and/or differences in functional networks between groups.

A further useful advantage of neuro-imaging is that studies can be used to show what the "normal" pattern of activation looks like in control participants and to examine the pathological effects of e.g. Alzheimer's disease, on the functional networks in the brain. If the "normal" pattern of activation is known for a given task then a deviation from this pattern may discriminate those individuals that are ageing pathologically from those that are ageing normally. The importance of studying MCI is that such people demonstrate a higher conversion rate than normal elderly. Individuals with MCI that do later convert to AD, in retrospect, may be viewed as being in the very early stages of AD while demonstrating the behavioural signs of MCI. If different patterns of activation can be observed in MCI, between those that convert to AD and those that do not, then brain imaging may be used to discriminate between these converters and non-converters, possibly before the behavioural symptoms of AD develop. If converters to AD can be discriminated from non-converters using brain imaging techniques, an important opportunity for drug therapy interventions may become available for patients with AD in the preclinical stages of the disease.

There are drawbacks of brain imaging techniques, however. It is difficult to know how individuals or groups of people perform cognitive tasks when being scanned. They may be using different strategies (e.g. due to choice, or for example, due to possible attentional deficits) rather than demonstrating different brain activation patterns due to neuro-anatomical deficits. Neuro-imaging studies may show that in order to perform a certain task, discrete brain regions are activated. Lesion studies, however, may show that when areas activated in the neuro-imaging study are damaged, the task can still be performed. Findings such as these create problems, as there are then discrepancies between the areas that have previously been thought to be used for the completion of the task and those areas are seen to be utilised after lesions, for the successful completion of the task. Findings like these are also interesting, however, as a number of explanations could account for the results. The participants may be using different strategies, the lesions do not fully incorporate the area(s), or the area(s) being completely intact is not essential for the completion of the task. Certain brain regions

that are seen to be active may not be specific to the task in question and there may be other routes that the brain can take in order to complete the task.

Even with the possible discrepancies that can arise between neuro-imaging and lesion studies, the combination of the findings from both methods of investigation can provide us with a more concise understanding of the working memory networks that are present in the brain. Results such as those mentioned above should not be looked upon as disadvantages of neuro-imaging or lesion studies, but instead as a means which may further the available knowledge about the cognitive process being examined.

It is important to understand which brain structures are involved with working memory and how they interact, as it is only when these areas that form the "normal" working memory network are known, that the areas that form a pathological working memory network can be identified.

3.6 The Neuro-anatomical Substrate of Working Memory: Evidence from Neuroimaging

To have a better understanding of the relationship between the different working memory components and the brain, investigations which make use of functional neuroimaging might be beneficial. These studies may provide insight into the links between the various working memory components and their associated brain structures. A number of studies have attempted to further our knowledge of working memory using this method.

Paulesu, Frith and Frackowiak (1993) used PET in order to try to isolate the neuroanatomical regions that correspond to the hypothetical working memory components. The 1st experimental condition involved a phonological short term memory task in which a series of six English letters were presented, after which a final letter was presented. A judgement then had to be made of whether or not the final letter that was shown was present in the series of six letters. The 1st experimental condition enabled the participant to phonologically code the letters and rehearse them (silently) in this manner. The baseline condition for the 1st experimental condition involved the

same format of paradigm but Korean letters were used. It was predicted that the Korean letters in the baseline condition would undergo visual memory processes but not phonological coding. The 2nd experimental condition involved the presentation of six English letters and the participants had to judge which of the letters rhymed with the letter "B" (which was always present on the screen). One out of the six letters rhymed. The baseline condition for the 2nd experimental condition involved the participants making judgments whether or not the six serially presented Korean letters were visually similar to a target Korean letter (which was always present on the screen).

The first analysis that Paulesu et al. (1993) carried out was to examine phonological processing. The two experimental conditions were combined and then compared to the two baseline tasks. The results revealed activations to Brodmann's area (BA) 44 bilaterally, the superior temporal gyrus (BA 22/42) bilaterally, the supramarginal gyrus (BA 40) bilaterally and the insula bilaterally. Paulesu et al. (1993) proposed that these activated areas represent the anatomical correlates of the articulatory loop.

Additional cerebral areas were activated which are believed to be involved with the motor control of the planning and execution of speech. The areas activated were the SMA, cerebellum, the possible primary sensorimotor areas of the mouth and larynx (BA 1, 2, 3 and 4) and BA 6. The researchers also found activation in the lingual gyrus (BA 18), which is suggested to be due to the visual processing of the English letters.

The researchers then attempted to illustrate the underlying neuroanatomy of the phonological store. To attempt to demonstrate this, the 1st experimental condition was compared to the 2nd experimental condition. The researchers proposed that the 1st experimental condition (the phonological STM task) involved the use of the phonological store, whereas the 2nd experimental condition (the rhyming task) did not. The comparison revealed activation in left BA 40, which the authors state to be the primary correlate of the phonological store.

In summary, the authors reported that subvocal rehearsal involves left BA 44 and that the main location of the phonological store is in the left supramarginal gyrus (BA 40). The authors also suggested that phoneme processing involves (BA 22/42) and that left BA 18 (the lingual gyrus) is involved with the visual processing of the English letters. The authors stated that more general areas devoted to the planning and execution of language (without overt speech) are the supplementary motor area (SMA),

cerebellum, possible primary sensorimotor areas of the mouth and larynx (BA 1, 2, 3, 4) and BA 6.

An experiment by Awh et al. (1996) also involved the use of PET to investigate the working memory network. A verbal working memory paradigm was used to identify the brain regions that were needed to complete the task. The working memory paradigm consisted of four stages. The first, the presentation of a probe, the second, the presentation of four letters surrounding the probe, the third, only the probe for a delay period of 3 seconds, and the final stage, a target letter which replaces the probe. If the target letter was presented previously in the second stage as one of the letters surrounding the probe, the participant would click the mouse button once, if the letter presented in the final stage was not presented earlier in the second stage the participant would push the mouse button twice. The control condition was similar and closely matched the perceptual and motor responses found in the working memory condition. The difference between the conditions was that in the control condition the initial letters that surrounded the probe were present in the final stage, during which time the target letter was presented. This meant the control condition was a perceptual matching task with no working memory component. The results revealed areas of activation in Broca's area (BA 44), the left SMA, and the left premotor area (BA 6). There was also activation in the right cerebellum. The researchers suggested that as there was no spoken response during the test periods, the activation of these structures probably related to the process of subvocal rehearsal. The results also showed activation in the left parietal regions BA 7 and BA 40. The authors proposed that this activation might be due to phonological storage mechanisms. Activation of the anterior cingulate (BA 32) was also observed. The activation in this area was considered to be due to the additional attentional demands of the working memory condition. Activation occurred in the thalamus and the insular cortex. The authors offered no explanation for the role of these structures in this contrast.

Jonides, Schumacher, et al. (1998) carried out a PET experiment to investigate the role of the parietal cortex in verbal working memory. The experiment consisted of four conditions. These were 1) a storage condition, 2) an encoding condition, 3) a retrieval condition, and 4) a non-word control condition. All the conditions used non-word stimuli which were demonstrated in two behavioural experiments by Jonides,

Schumacher, et al. (1998) to be more dependent on phonological coding than real word stimuli.

The behavioural data collected during the PET scans revealed a phonological similarity effect in which for the encoding and retrieval conditions, reaction times were longer and errors more likely, for the stimuli that consisted of phonologically similar non-words than the stimuli that consisted of phonologically dissimilar non-words. This finding as with the previous behavioural studies by Jonides, Schumacher, et al. (1998) suggests that participants encode and store phonological representations of the non-words.

The storage versus fixation control condition activated the left inferior frontal gyrus (Broca's area), the SMA, the left premotor cortex, the dorsolateral prefrontal cortex (DLPFC) bilaterally and the right cerebellum. Additional activations included the right inferior frontal gyrus, and the left cerebellum (these activations were in approximately homologous areas to the activations in the opposite hemisphere). Significant activation was also observed in the right lateral posterior parietal cortex (BA 40) with an indication of activation (not significant) in the homologous region on the left.

Two Region of Interest (ROI) analyses that were based on previous working memory studies were carried out on the parietal cortex. One analysis was based on the sites of activation revealed in the experiment by Awh et al. (1996). The analysis showed two reliable sites of activation in the posterior parietal cortex, one in each hemisphere.

The other ROI analysis was based on the results of the experiments by Schumacher et al. (1996), E. E. Smith, Jonides and Koeppe (1996), and Jonides et al. (1997). This analysis also revealed reliable activations in two posterior parietal regions, one in each hemisphere. Using the ROI's from the second analysis, the magnitude of the activation was found to be largest in the right parietal region (however, the activations between the right and left hemisphere parietal regions did not differ significantly).

Jonides, Schumacher, et al. (1998) proposed that the activated posterior parietal regions were used in storage. From the storage versus control comparison it is unclear whether these areas are used as part of a network for controlling shifts of attention (in which the right parietal region is involved more than the left as suggested by e.g.

Corbetta, Miezin, Shulman and Petersen (1993); Heinze et al. (1994)), or whether the posterior parietal regions are concerned with the actual storage of information.

The Retrieval versus non-word control condition revealed activation in some areas very similar to the storage versus fixation control comparison i.e. right DLPFC and right posterior parietal. As these results come from two different sets of scans and reveal overlap between the storage and retrieval areas, they suggest that the processes have some circuitry in common. Jonides, Schumacher, et al. (1998) suggested that a common factor that could provide an interpretation for the observed posterior parietal activations, may be that of storage, as it is the defining feature of the storage vs fixation control comparison, and during the retrieval condition storage will also be required, while the participant matches the stored non-words to the probes.

The encoding versus non-word control revealed no significant activations (an area of the left extrastriate occipital cortex approached significance). Jonides, Schumacher, et al. (1998) suggested that the load to be encoded may not have been great enough to reveal the mechanisms that perform the encoding. The researchers commented however, that no parietal activation was observed and the lack of activation in this area suggested that the posterior parietal cortex is not a primary region that is employed during encoding.

In summary, the posterior parietal areas in both hemispheres appear to have roles in the storage and retrieval of verbal information. It is not clear if the posterior parietal areas are employed purely for storage or if one or both of the areas are also involved in controlling shifts of attention.

Rypma and D'Esposito (1999) demonstrated using event-related fMRI that activation due to a higher working memory load increased only in the dorsal prefrontal cortex. Right hemisphere activation was also found to be greater than the left during the high memory load, but not in the low memory load. The researchers found that the dorsal prefrontal cortex played a greater role in information retrieval for slower individuals.

A study by D'Esposito, Postle, Ballard and Lease (1999) lends further support to a ventral/dorsal processing differentiation. The researchers carried out an event-related fMRI study investigating the maintenance of sequences of letters over a delay period and the manipulation of letter sequences. In the manipulation condition the letters had to be alphabetically reordered during the delay period. The results revealed that the

DLPFC and the ventrolateral prefrontal cortex (VLPFC) were activated during both types of task, however, activation in the DLPFC was greater during the manipulation task.

A study by Honey et al. (2001) used a 2x2 factorial design to investigate the working memory system. The two factors were maintenance (high vs low letter load) and manipulation (retain original order vs reorder alphabetically). The DLPFC and VLPFC were activated in all the factorial combinations. Greater activation was observed in the manipulation than the maintenance condition. For the activation of the DLPFC and VLPFC, the type of task appeared to be more important than the effect of load.

Rypma, Berger and D'Esposito (2002) suggested that the ventrolateral prefrontal cortex mediates a capacity-limited storage buffer and that the dorsolateral PFC appears to mediate organisational memory processes which are associated with supracapacity memory storage. In the study, the researchers used Event-related fMRI to test working memory for the maintenance of between 1 - 8 letters. The researchers found that with increased working memory load during encoding, activation decreased in the VLPFC, and during maintenance and retrieval activation increased in the DLPFC.

In summary, it appears that a differentiation exists between the ventrolateral and dorsolateral PFC, in terms of processing. The VLPFC seems to be activated during the maintenance of relatively light loads of information. Whereas, the DLPFC appears to be activated, in addition to the VLPFC, when working memory load increases too much for the VLPFC to handle by itself. The DLPFC also appears to be employed when information has to be manipulated as well as maintained.

Using fMRI, D'Esposito, Ballard, Aguirre and Zarahn (1998) have demonstrated that the lateral prefrontal cortex can be activated during tasks which are not related to working memory. This is in concordance with the findings of Funahashi, Bruce and Goldman-Rakic (1989), who, using single unit neuron recordings in primates during delayed response tasks, found that 24% of the neurons they studied in the prefrontal cortex, responded only to the motor response. The findings of Funahashi et al. (1989) and D'Esposito et al. (1998) suggest that certain areas of the DLPFC when activated, may not be specific to working memory alone. DLPFC regions which are activated in certain working memory tasks might therefore, represent for example, the recruitment

of strategies designed to cope with higher task loads, processes concerning the manipulation of information, and furthermore, processes which are non-specific to working memory e.g. possibly the planning and preparation of motor responses to various stimuli.

Steffener, Bly, Janal and Lange (2001) examined the encoding, maintenance and storage of verbal working memory using fMRI. The researchers manipulated both working memory load and the delay period. The results showed that increased working memory load activated BA 46 bilaterally and the left BA 44 in the PFC, as well as the left superior parietal lobe (BA 7). The effect of delay corresponded with the activation of the anterior cingulate (BA 32) and the inferior parietal lobe (BA 40). Common activations were observed in BA 6 and 9 under both types of manipulation.

An event-related fMRI study by Durgerian, Bobholz and Rao (2001) used the Sternberg working memory task to investigate the neuroanatomical areas that were engaged in order to complete the task. The researchers had both encode (1, 2 or 4 digits) and maintain (2500, 5000, 7500ms) conditions. During encode, load dependent activations were observed bilaterally in the lateral premotor cortex (BA 6), the preSMA (BA 6) regions, the lateral extrastriate (BA 9), and the superior parietal (BA 7) region. Bilateral subcortical activations were also found in the thalamus, the putamen and the lateral cerebellum (R>L). For the maintain condition load dependent activations were seen in the right DLPFC (BA 9) and the striate cortex (BA 17).

A clear pattern appears to emerge throughout the studies in which a fronto-parietal working memory network is observed. This working memory network tends to have increased frontal activation when the load is increased. A DLPFC and VLPFC distinction also seems to be present, in which activation of the VLPFC is associated with relatively low working memory loads and activation of the DLPFC is associated with higher working memory loads and when the information must be manipulated in some way. Posterior regions of the parietal cortex (e.g. BA 40 and BA 7) appear to be involved with the storage of information in working memory.

3.7 Neuro-imaging Evidence of the N-back Working Memory Task

Awh et al. (1996) followed up the experiments on working memory using a verbal working memory task called the n-back task. In this additional experiment, PET was used to investigate the effects of continuous updating in working memory. The n-back task consisted of three conditions. All the conditions involved the participant looking at a computer screen on which letters were presented in serial order. Each letter appeared on the screen for 500ms with a 2500ms inter-stimulus interval. The first condition was a 2-back task that involved the participant remembering which letter was two letters back. The participant responded with one click of the mouse if the current letter was presented two letters back and two clicks if the letter was not shown two letters back in the serial order of presentation. In this task the participant had to be able to hold two letters constantly in working memory for the successful completion of the task, as the last two letters defined the next two responses.

The second condition was what the authors call the search control task. This type of task is also known as a 1-back task. This condition involved the participant remembering one letter back in the serial presentation of the letters. The mouse was clicked once if a letter was repeated directly afterwards in the serial presentation and two clicks if the letter directly afterwards was a different letter. This task involved a light working memory load, but had very similar perceptual input and motor responses to the 2-back task. Therefore, comparing the activation found in the 2-back task to that of the 1-back task was predicted to reveal the areas used for phonological storage and rehearsal in verbal working memory.

The third condition was a rehearsal control condition, this involved the participant clicking the mouse button once when a letter was presented and subvocally rehearsing that letter until the presentation of the next letter in the sequence, at which point the participant would re-click the mouse button and start rehearsing the newly presented letter. The perceptual input and motor responses were similar for this condition and the 2-back task. If the 2-back task were compared to the rehearsal control condition, the remaining areas of activation should be those involved with phonological storage, because the components of subvocal rehearsal should be removed due to the comparison. The authors posited that this comparison would also enable the components of subvocal rehearsal to be identified by inference.

The 2-back condition versus the 1-back condition comparison revealed activations in similar sites as observed in the previous experiment in the Awh et al. (1996) study. These activations were found in Broca's area (BA 44), the left SMA, the left premotor area (BA 6), the left posterior parietal (BA 40), the left superior parietal (BA 7), the right cerebellum, and the anterior cingulate area (BA 32). The unexplained activation of the thalamus and insular cortex that was seen in the previous experiment was not found with this contrast. There were however, additional activations to the previous experiment, which were found in areas of the right hemisphere which were homologous to those activated in the left. These additional areas of activation were the right superior parietal region (BA 7), the right premotor cortex and the right SMA. It should be noted that the activations found in these homologous right hemisphere regions were of a lower significance level, in respect to the areas of activation in the left hemisphere. Activation of the left cerebellum was also observed in this comparison. The observed sites of activation were thought to contribute both to phonological storage and subvocal rehearsal processes.

When the results of the 2-back condition versus the rehearsal control condition were examined, as the authors predicted, a loss of activation was observed in Broca's area and in the left premotor cortex. These areas were thought to be involved with subvocal rehearsal. As expected by the authors, activation was still found in the posterior parietal regions, which was hypothesised prior to the experiment to be due to the process of phonological storage. The authors predicted that activation in the SMA and right cerebellum would also be cancelled out in the comparison, as these activations were predicted to be due to the subvocal rehearsal processes. This was not the case however, and the activations in these areas remained. The researchers suggested that the cause of these activations might have been due to the control task not being demanding enough to remove all the activation due to subvocal rehearsal. The other explanation that the researchers offered was that the activations in these areas are due to processes that are not components of rehearsal e.g. error detection or practise learning. Activation of the thalamus re-emerged as in the earlier experiment, the reason behind which the authors offered no explanation. Finally, activation of the anterior cingulate disappeared in the comparison of the 2-back condition versus the rehearsal control condition. This result was unexpected as the anterior cingulate is thought to be an area involved with attentional processes as opposed to an area involved with subvocal rehearsal.

Schumacher et al. (1996) were interested in examining the prediction, that during, for example, a letter version of the 3-back working memory task, verbal information, although presented visually, is coded phonologically. The researchers tested this assumption using PET versions of both a visually presented 3-back task and an auditorily presented 3-back task. The 3-back tasks involved the participants responding every time a letter was displayed or heard, that was identical to a letter presented three letters earlier in the sequence. In the 3-back task the participant had to be able to hold three letters constantly in working memory as the last three letters defined the next three responses. The controls that were used were a visual search condition for the visual 3-back task and an auditory search condition for the auditorily presented 3-back task. In the control conditions three letters were presented initially at the beginning of each block of serially presented letters. These initial letters defined the targets that were to be searched for and responded to during the list of serially presented letters. The results of the experimental tasks versus the control tasks revealed activations in at least twelve areas. The activations were in very similar sites for both the visual 3-back versus the visual search and the auditory 3-back versus the auditory search e.g. Broca's area, the left DLPFC, the left SMA, the superior and posterior parietal regions bilaterally, the anterior cingulate and the right cerebellum. The visual 3-back versus the visual search compared to the auditory 3-back versus the auditory search did not reveal any significant areas of activation. The converse contrast i.e. the auditory 3-back versus the auditory search compared to the visual 3-back versus the visual search revealed significant left hemisphere activation only in a site in Broca's area.

The researchers also examined the signal changes in ten spherical (2cm in diameter) Voxels of Interest (VOI's) of activation and 10 VOI's of deactivation (identified from regions of activation found in the E. E. Smith et al. (1996) study). The results of this analysis showed that activations and deactivations were observed in the same areas as in previous working memory studies. Activation was found in left BA 10, left BA 46/10, right BA 46/10, left BA 46, left BA 6, right BA 6, left BA 40, right BA 40, right BA 7 and right BA 40/7. Deactivation was observed in left BA 10, midline BA 9, midline BA 32, midline BA 11, right BA 25, right BA 21, left BA 42, right BA 42, midline BA 23/31 and left BA 18. The results of this analysis also illustrated that very similar signal changes were found in the visual comparison and the

auditory comparison. The results of the Schumacher et al. (1996) experiment demonstrated that the underlying verbal working memory circuitry appears to be similar regardless of the input modality (E. E. Smith, Jonides, Marshuetz, & Koeppe, 1998).

Based on the observation that the same verbal working memory processes (identified by active areas) remain in the comparison images of both the visual and auditory 3-back conditions, it would appear that although the visual and auditory stimuli are initially encoded in different ways (Schumacher et al., 1996), the visually presented information appears to be coded phonologically.

All the participants in the Shumacher et al. (1996) study completed a questionnaire detailing the strategy that was used for the execution of both the auditory and visual memory tasks. Every participant reported that for both memory conditions, the letters were repeated subvocally, with the addition of each new letter and the deletion of each old letter. None of the participants reported any attempts to use contrasting strategies for the same task in the two modalities.

The use of subtraction designs in imaging studies (for example those used in the Awh et al. (1996) or Schumacher et al. (1996) studies) may raise possible problems concerning the specificity of the active versus baseline conditions (Friston et al. (1996); Sidtis, Strother, Anderson and Rottenberg (1999); E. E. Smith et al. (1998)).

The subtraction designs have produced many interesting results, but the method rests on the assumption of "pure insertion". This assumption consists of the assertion that when a certain processing stage is added to a task, other operations performed during the task are not affected (Sternberg, 1969). E. E. Smith et al. (1998) illustrate the potential problems of the assumption, talking about the use of a 3-back minus a search-control task (0-back). The supposed difference between the memory condition and the search-control condition would be in memory. The assumption of pure insertion would predict that the addition of the memory component would have no effect on other processes, for example, perception or response. However, this may not be the case. It has been suggested that when a memory component is added to a task it may be possible that a different type of perceptual analysis occurs. Therefore, when the search-control condition is subtracted from the memory condition, perceptual network differences may be present in addition to mnemonic ones (E. E. Smith & Jonides, 1998).

An alternative approach that has been suggested is using neuro-imaging experiments with parametric designs. In parametric designs an experimental factor is varied quantitatively in order to affect the operation of a single processing stage. An example using the parametric method would be to vary the number of items to be retained in a working memory task and to determine the effect (e.g. a monotonic or linear increase) due to memory load that may be observed to various regions of interest (E. E. Smith et al., 1998). Using this parametric method, qualitative changes between conditions should not be observed as the conditions have been altered quantitatively (E. E. Smith et al., 1998). Some researchers have used parametric designs in order to improve the specificity of the obtained results e.g. Braver et al. (1997); Jansma, Ramsey, Coppola and Kahn (2000); E. E. Smith et al. (1998); Veltman, Rombouts and Dolan (2003).

Braver et al. (1997) used an fMRI parametric version of the n-back task to investigate working memory function in a group of eighteen to twenty-five year old participants. The researchers carried out two experiments, the first examining activation of the frontal cortex only and the second involving whole brain scanning.

The first experiment tested working memory ability for 0, 1, 2 and 3 back conditions. The 0-back condition required the participants to respond every time that a predetermined letter was presented during a series of letters. The format of a 1-back task and a 2-back task was explained above in the Awh et al. (1996) study. The requirements of a 3-back task were also explained in the study by Schumacher et al. (1996). The results of the Braver et al. (1997) experiment revealed that load dependent activation was present in the middle frontal gyrus (MFG; BA 46/9) bilaterally, the left inferior frontal gyrus (LIFG; BA 44/45), another left inferior area which was more anterior (BA 47/10) and the anterior cingulate gyrus (BA 32). When examined for monotonical increases due to task load with a planned contrast method (Braver & Sheets, 1993), only the DLPFC and Broca's areas were activated. The activation of these areas was characterised by increments in the percentage signal obtained for each additional memory load item. The increases in percentage signal appeared to follow a linear trend. The activation of the anterior cingulate and the left anterior area was found to decrease across the load conditions. Reaction times were also investigated and increases in these were observed for each additional increase in task load.

Experiment 2, which was a shorter version of experiment 1, with a new set of participants, involved whole brain scanning. The experiment replicated the findings of experiment 1, finding the same pattern of monotonic load sensitivity in bilateral MFG and LIFG. The response function increased at a similar level as before in the MFG, but there was a lower level of increment in the LIFG. Activation was also observed in the left frontal operculum (insular cortex), right BA 44, a number of motor areas (e.g. the premotor, motor and supplementary motor regions; BA 4 and 6), the parietal cortex regions (BA 40/7) bilaterally and the left caudate nucleus of the basal ganglia.

These two experiments demonstrate the neuroanatomical areas that appear to be sensitive to increases of task load when performing an n-back task of up to 3 letters back. Activation levels of the MFG and LIFG were found to increase when WM load was increased.

Returning to the problematic assumption of "pure insertion," E. E. Smith et al. (1998) examined the differences between the Schumacher et al. (1996) subtractive experiment (3-back minus 0-back) and the Jonides et al. (1997) parametric 3-back experiment (0, 1, 2 and 3-back). Jonides et al. (1997) found that by using the parametric version (which includes the additional steps of 1 and 2-back) that strictly monotonic increases can be observed in 10 out of 11 regions of interest (defined from the Awh et al. (1996) and Schumacher et al. (1996) experiments). The strictly monotonic increases found in the regions of interest (right BA 6, left BA 6/32, left BA 44, left BA 40, right BA 7, right BA 9/46, right BA 46/10, right cerebellum, mid cerebellum and left cerebellum) can be taken as evidence that these regions are part of the neural network for verbal WM (E. E. Smith et al., 1998). The regions of activation that can be observed in both the Schumacher et al. (1996) and the Jonides et al. (1997) experiments appear to demonstrate "converging evidence" of the subtractive method n-back task and the parametric method n-back task.

From the results of the Jonides et al. (1997) experiment it appears that the left DLPFC (BA 46/10) was the one region of interest not to demonstrate an increase in activation through all n-back conditions. Therefore, the activation in the DLPFC was not strictly monotonic. Compared to a control condition, a large increase in activation was observed between the 1-back (1.34%) and the 2-back (3.44%), but not between the 0-back (1.39%) and the 1-back (1.34%). Significant DLPFC activation was also

observed in the 2-back and 3-back conditions, but not the 0-back or 1-back conditions. E. E. Smith et al. (1998) suggested that activation observed in the DLPFC may be caused by the temporal coding and/or inhibition of previous letters. The rationale behind this assumption is that temporal coding and inhibition processes are not required in the 0 or 1 back conditions, but are required in 2 and 3 back (E. E. Smith et al., 1998).

There was also a similar jump in activation for Broca's area between the 1-back (1.07%) and 2-back (4.40%). This finding is most likely because little rehearsal was needed in order to complete the 0 and 1 back, but rehearsal was required to a greater extent for the 1 and 2 back. This explanation is supported by the small change in activations between the 0-back (0.97%) and the 1-back (1.07%). A monotonic increase in activation was however, observed in Broca's area over all the n-back conditions (0, 1, 2 and 3-back).

E. E. Smith et al. (1998) predicted that DLPFC activation might occur whenever a working memory task involves processing as well as storage. DLPFC activation can be seen in a number of tasks that involve processing in addition to storage. However, the processing requirements may vary between experiments, for example, the additional processing may consist of temporal coding, inhibition, searching, checking for regular sequences and monitoring. It is difficult therefore, to ascertain whether the DLPFC is required for each and every one of these processes or if all these processes share a common feature that is housed within the DLPFC e.g. the need to divide attention (E. E. Smith et al., 1998).

Working memory has often previously been discussed in terms of the processes involved i.e. maintenance and manipulation during tasks. The process of maintenance has been described as the ability to transfer, maintain (which includes rehearsal) and match information in working memory (Veltman et al., 2003). It should also be noted that the process of maintenance is not always referred to as being identical in function to the phonological loop, as it can also include searching and matching WM processes (Veltman et al., 2003). The process of manipulation has been described as the reorganisation or updating of information in working memory (Veltman et al., 2003).

Veltman et al. (2003) examined the concepts of manipulation and maintenance in working memory using two tasks, an n-letter back task and the Sternberg task. The authors claim that the n-back task is primarily a manipulation task (although, the authors themselves have recognised that the n-back task also includes maintenance of the information), whereas, the Sternberg task is primarily a maintenance task. It is

difficult to dissociate maintenance and manipulation processes as working memory tasks often involve the use of both processes to some extent.

The Veltman et al. (2003) experiments involved young adults as the participant group. For the Sternberg task the participants had to memorize letter strings of varying lengths (2-7 letters) after which 15 single letters were presented. The participants had to respond to whether or not the single letters had been in the serially presented string of letters with the press of one of two buttons. For the n-back experiment the researchers used a similar paradigm to the Braver et al. (1997) study, which involved 0, 1, 2 and 3 back conditions. The participants had to respond with a button press every time a target letter was presented.

The researchers found that due to increased working memory load, both the tasks activated a number of areas in common. These were the dorsolateral prefrontal cortex (DLPFC) bilaterally, the ventrolateral prefrontal cortex (VLPFC) bilaterally, the left anterior prefrontal cortex, the parietal cortex bilaterally, the left inferior temporal cortex, the supplementary motor area (SMA) and the cerebellum (Veltman et al., 2003).

In response to an increase in working memory load, the areas activated during performance of the Sternberg task were bilateral DLPFC, left VLPFC, the left parietal cortex, the supplementary motor cortex and the cerebellum (Veltman et al., 2003).

In response to an increase in working memory load the n-back task activated the bilateral DLPFC, the bilateral VLPFC, the left anterior PFC, the bilateral parietal cortex, the left inferior temporal cortex, the SMA and the cerebellum (Veltman et al., 2003). These areas of activation can be seen in Figure 3.2.

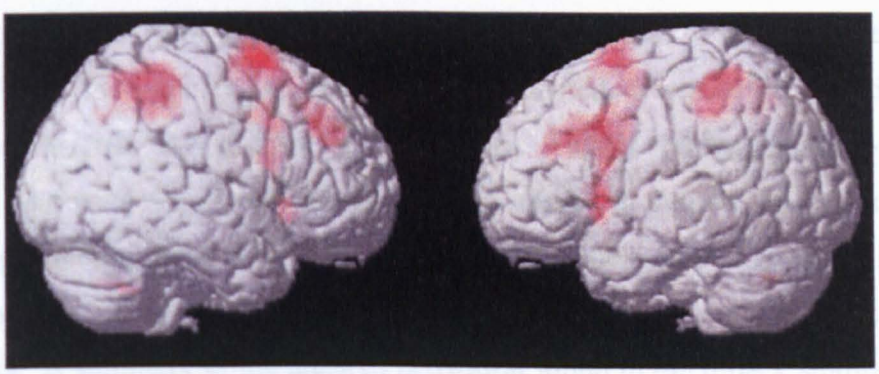

Fig 3.2: The areas that were activated during the n-back task in response to increases in WM load (from the Veltman et al. (2003) study). With kind permission of Elsevier.

The study by Veltman et al. (2003) also investigated the role of the DLPFC. Contrary to previous findings which imply that the DLPFC is most highly activated during manipulation tasks of encoding (e.g. Rypma, Prabhakaran, Desmond, Glover and Gabrieli (1999); Rypma & D'Esposito (1999)), the results of the Sternberg task when analysed separately for encoding and responding revealed that the greatest levels of bilateral middle DLPFC activation were found during the responding stage of the experiment (Veltman et al., 2003). The researchers commented that responding by itself appeared to correspond to DLPFC activation especially for high task loads.

Although some of the studies described above use subtractive designs and others use parametric designs there appears to be a large amount of converging evidence that identifies a number of common structures associated with verbal working memory. E. E. Smith (1997) commented that in order to identify the underlying neuroanatomical areas associated with particular processes e.g. working memory, "converging evidence" is required. E. E. Smith (1997) suggested that "converging evidence" should include four prerequisites. These are: 1) When a certain area "A" is lesioned, the patient should not be able to perform the hypothesized process "P". This is the "lesion site criterion". 2) When other tasks involving the same process "P" are examined, the difference image should again include area "A". This is the "other-positive-evidence" criterion. The less similar to the initial study that the subsequent studies are, the stronger the evidence that process "P" is mediated by areas "A". 3) When tasks that are not hypothesized to involve process "P" are studied, the difference image should not include area "A". This is the "negative-evidence" criterion. The more similar the tasks to the initial task that involved process "P" the stronger the evidence that process "P" is mediated by area "A". 4) When the need for process "P" is incremented, increases in activation should be observed in area "A", but not in other areas. This is the "incremental-increases" criterion. The studies reviewed in this chapter appear to demonstrate the criteria for converging evidence defined by E. E. Smith (1997). The evidence reveals a number of the components that are used by the verbal working memory system for the completion of the tasks. A summary of the areas of activation found in the n-back studies that have been reviewed in this thesis can be found in Table 3.1.

Table 3.1: Illustrates the areas of activation found in a number of n-back working memory tasks.

Authors and Experimental Design	Frontal					BA	Parietal		Cere-	Other
	IFG	BA44	DLPFC	SMA	Pre-motor BA6	32	BA40	BA7	bellum	
Awh et al (1996) 2 vs 1 back.		○		◆	◆	✱	○	◆	◆	□Cerebellar vermis
Awh et al (1996) 2 back vs rehearsal.				◆			○	◆	□	□Thalamus and □Cerebellar vermis
Schumacher et al (1996) 3 back minus visual search or auditory search.		○ and left BA45	○	◆		✱	◆	◆	□	
Schumacher et al (1996) 10 spheres of VOI's identified from Smith et al (1996).	left BA10 left BA46/10 left BA46 right BA46/10				◆		◆ and right BA40/7	□		
Braver et al (1997) Frontal analysis only Parametric design. 0, 1, 2 and 3 back.	LIFG BA44/45 and also BA47/10		bilateral MFG BA46/9			?				
Braver et al (1997) Whole brain analysis 0, 1, 2 and 3 back.	LIFG BA 44/6 and RIFG BA44		bilateral MFG		○ also left BA4 and right BA8/6		◆	◆		left frontal operculum (insular cortex) and the right caudate nucleus of the basal ganglia
Jonides et al (1997) 0, 1, 2 and 3 back. Parametric design. Monotonic increases in ROI's from Awh et al (1996) and Schumacher et al (1996)		○	right BA9/46 and right BA46/10		□ and left BA6/32		○	□	◆ ✱	
Veltman et al (2003) parametric 0, 1, 2 and 3 back.	bilateral VLPFC and left anterior PFC		◆	□			◆		□	left inferior temporal (BA37)

IFG: Inferior Frontal Gyrus
LIFG: Left Inferior Frontal Gyrus
RIFG: Right Inferior Frontal Gyrus
DLPFC: Dorsolateral Prefrontal Cortex
SMA: Supplementary Motor Area

Left ○
Right □
Bilateral ◆
Present but along the midline ✱
Present but lateralization not specified ?

In Summary, the verbal working memory system appears to be composed of a number of different components. These components seem to mediate various processes that are used for the completion of the tasks. The areas of the brain that are generally activated during the n-back working memory task are the left inferior frontal gyrus (including Broca's area, BA 44), the dorsolateral prefrontal cortex (BA 9 and 46), the SMA (BA 6), the superior and inferior parietal cortices (BA 7 and 40) bilaterally, the anterior cingulate cortex (BA 32) and the cerebellum.

3.8 Sustained Attention and Target Detection in Working Memory

N-back working memory tasks generally consist of a condition in which simple sustained attention and target detection is required, and working memory load is increased from this point. The theory behind the various working memory components and their corresponding underlying brain areas have already been discussed in detail. A few select studies on sustained attention, target detection and the orthographical processing of letters will now be described in order to provide a background for the initial experimental condition in this thesis. The first contrast in the first experiment involves the comparison of a vigilance task (which involves the identification of a target letter in a sequence distracter letters) to a baseline task (which involves the repeated presentation of a single symbol). Target detection, sustained attention and orthographical processing all play a role in the successful completion of the vigilance task. Experiments that have investigated these functions will be discussed in order to create a theoretical basis for some of the comparisons that are to be performed.

The first findings that will be examined are those from an fMRI experiment that was performed by Polk and Farah (1998). The experiment involved the presentation of sequences of single letter stimuli, single digit stimuli, geometric shapes, or fixation points. The results of the experiment (letter versus digit comparison) suggested that an area of the left inferior occipitotemporal cortex responded significantly more to letters than digits. Of the participants, three out of the five that were tested revealed activation in that area. One of these participants was also tested again six weeks after the initial testing. The results again revealed activation in the left inferior occipitotemporal area, consistent with the activation observed at the first time of testing. The authors

suggested that the findings from the experiment show that certain extrastriate visual areas respond more to letters than digits (at least in some literate participants).

Activation was also found in this area in five out of the six sessions (this included the results from the participant that had taken part in the experiment on the two separate occasions) for the letter versus fixation comparison. The area also tended to show activation in the digit versus fixation comparison, but to a lesser extent. For example, none of the digit versus fixation comparisons were significant when correcting for all the voxels in the brain, but three out of the six comparisons were significant when correcting only for the voxels that were activated in the letter versus fixation comparison.

A further experiment was carried out by Polk et al. (2002). In this additional experiment only letters, digits and fixation points were used. The letter stimuli that were used in this experiment were perceptually very similar to the digit stimuli (e.g. the number of curves and straight lines in the stimuli were similar). Active string matching of the stimuli was also tested in some participants and passive viewing in others (only passive viewing was examined in the initial experiment). Eight comparisons between letter stimuli and digit stimuli were made. These consisted of three passive viewing comparisons and five active string matching comparisons (one participant accounts for two of these comparisons as both the passive viewing and active matching tasks were performed by this participant). ROIs were specified for each participant, which covered the left fusiform gyrus, the left lingual gyrus and the left inferior temporal gyrus. The results revealed that in seven out of the eight letter stimuli versus digit stimuli comparisons, significant activation was observed in approximately the same area in the left inferior occipitotemporal cortex (within 9mm of Talairach coordinates -44, -49, -9), which was on or near the fusiform gyrus, except for the activation for one participant, which was more superior and appeared to be in a sulcus. The activity for the letter stimuli versus digit stimuli comparison that was found in the participant that did both the passive viewing and active string matching tasks appeared to be in approximately the same area. The examination of the letter stimuli versus fixation comparison revealed activation in the same left inferior sites as in the letter stimuli versus digit stimuli comparison.

In summary, the letter stimuli versus digit stimuli (and letter versus fixation) comparisons revealed activation in the left inferior occipito-temporal cortex, both

during passive viewing and during active string matching for seven out of the eight available comparisons. The experiments by Polk and Farah (1998) and Polk et al. (2002) led the authors to conclude that an area in the left inferior visual cortex appears to be specialised to process letters as opposed to digits (Polk et al., 2002).

Flowers et al. (2004) also carried out an experiment, this time using event related fMRI, in order to examine the brain areas involved with the identification of single letter stimuli. The stimuli consisted of an identical set. Each task required the participant to process the stimuli differently. Fifty percent of the stimuli consisted of letters and fifty percent of the stimuli were symbols (with similar forms to letters). Half of these stimuli were in black and the other half were in white. In the letter identification task the participant had to push a button every time a letter was presented (which was on 50% of the trials). In the non-letter identification (symbol) task the participants had to push a button every time a shape was presented (which was on 50% of the trials). Lastly in the colour identification task the participant had to push a button every time a black stimulus was presented (which was on 50% of the trials). All of these conditions were compared to control conditions in which the participants viewed a fixation cross.

The experimenters ran three different analyses. The first investigated the brain areas that were activated significantly on each of the three experimental tasks versus the control (fixation cross) condition. For the letter identification task versus the control task significant activation was observed in the fusiform gyrus (BA 19/37) bilaterally, the inferior frontal gyrus (BA 47) bilaterally and in the supplementary motor area (BA 6).

The second analysis identified the common areas that were activated in the letter identification vs control condition, the symbol identification vs control condition and the colour identification vs control condition. The area that was activated in all three comparisons was the fusiform gyrus bilaterally (BA 37/19). The activation in this region was greatest during the letter identification condition.

The third analysis that was performed was a conjunction analysis to reveal the areas specific to letter processing. The conjunction analysis consisted of the letter identification vs control condition > symbol identification vs control condition comparison and the letter identification vs control condition > colour identification vs control condition comparison. The analyses revealed activation of the left middle

occipital gyrus (lateral portion of BA 37) and the inferior frontal gyrus bilaterally (BA 47). The extrastriate cortex was not significantly activated during separate conjunction analyses of either the symbol identification or the colour identification conditions. It should be noted that the area of the left ventral extrastriate cortex (left middle occipital gyrus, BA 37) that was activated uniquely for letter identification (as revealed by the conjunction analysis) was observed to be more anterior and more lateral than the common activation that was shared by letter identification, symbol identification and colour identification (fusiform gyrus, bilaterally, BA 37/19).

Some explanations for the activation of the inferior frontal gyrus (BA 47) were offered by Flowers et al. (2004). The researchers suggested that the activation in these areas could possibly be due to the activation of working memory circuits or due to semantic processes that are engaged by the letter stimuli but not by the non-alphabetic stimuli.

In summary, during the letter identification task versus the control condition, significant activation was observed in the fusiform gyrus bilaterally, the inferior frontal gyrus bilaterally and the SMA. An important finding (revealed by the conjunction analyses) was that when the participant observed the same set of stimuli and attended to the letters rather than the non-alphabetic stimuli, activation was observed in the left middle occipital gyrus and the inferior frontal gyrus bilaterally. This activation of the left middle occipital gyrus was found to be more anterior and more lateral to the common activation that was observed in each of the three conditions (identification of letters, symbols and colours).

Lawrence, Ross, Hoffmann, Garavan and Stein (2003) carried out an experiment that employed fMRI to investigate sustained attention. The experimental condition involved the participant performing a rapid visual information processing (RVIP) task. The control condition involved the participant performing a sensorimotor task. The RVIP task involved the presentation of a sequence of digits for 90 seconds. The participant had to respond if there were three consecutive odd or three consecutive even numbers (these were regarded as targets). There were four targets every 30 seconds. The control task involved the participant responding every time a "0" was presented in a sequence of digits. The sequence of digits was identical to the experimental sequence of digits except that one digit in every target set was replaced by a "0". Twenty-nine clusters of activation were revealed that illustrated differences between the experimental

task and the control task. The largest clusters of increased activation included the inferior and superior parietal cortex, the inferior and middle frontal gyri, the pre-SMA, the thalamus and caudate, the anterior insula and the cerebellum, bilaterally. Areas of significant decreased activation were also observed. These included the anterior and posterior cingulate bilaterally, the left angular and middle temporal gyrus, the mid-insula, the left parahippocampal gyrus, in addition to several other smaller clusters in the medial and middle frontal gyrus.

Regression analyses of the BOLD response in these areas and performance (number of hits) were carried out on each of the participants. There were significant positive correlations of the left middle frontal gyrus, the right inferior and middle frontal gyri, the right superior frontal gyrus, the right medial frontal gyrus, bilateral pre-SMA, bilateral parietal cortex, and the left anterior insula. Significant negative correlations were also observed in the left medial frontal gyrus, the bilateral anterior and posterior cingulate, the left middle temporal gyrus, and the right insula.

Regression analyses of the BOLD response were also performed on the reaction times of the participants (faster reaction times were regarded demonstrating better performance). Significant correlations between increased BOLD signal and fast reaction times were observed in the right medial and right inferior/middle frontal gyrus, the pre-SMA bilaterally and the parietal cortex, bilaterally (these were much the same as the significant positive correlations found with the number of hits). Additional significant correlations were found for fast reaction times in the left middle and superior frontal gyri, the left occipital/inferior temporal gyrus, the cerebellum bilaterally and the right anterior insula/inferior frontal gyrus. The only significant correlation that was observed between decreased BOLD and faster reaction times was observed in the left medial frontal gyrus.

Factor analysis was used to examine the relationship between the significantly activated and deactivated regions in the twenty-five participants (29 clusters). The results of these analyses revealed that two separate networks (that are not correlated with each other) appear to be operating. In participants that had performed well on the task, it appeared that a number of alternatives may have been occurring, e.g. one of the networks was activated strongly and the other strongly deactivated, or one was strongly activated and the other weakly deactivated, or one was weakly activated but the other strongly deactivated. Weak activation and weak deactivation of the networks however, seemed to be related to lower performance.

Lawrence et al. (2003) posited that attention and working memory performance could possibly be modified by distinct neurobiological strategies e.g. by predominantly increasing activation in the prefrontal-parietal cortex regions, by primarily deactivating temporo-limbic circuitry, or by a combination of both these strategies.

The findings of the experiment are interesting as the RVIP task involves working memory and sustained attention (similar to the requirements of the n-back working memory task). The results show that two separate networks of activation and deactivation may be occurring (either together or predominantly by one or the other) in order to perform the task well. The findings are also informative, as the regions of deactivation seem to include the ventral medial frontal cortex and the anterior and posterior cingulate.

A PET experiment by Pardo et al. (1991) examined the differences in brain activation between a condition in which the participants had to concentrate on a dim spot and a condition in which the participants had their eyes closed. In the condition in which the participants had to attend to the dim spot, monitoring of the frequency of spot dimming was required. No dimming of the spot actually occurred in the experiment but false alarms occurred in most participants. The results of the comparison revealed activation of medial striate regions, which were attributed to the visual stimulation. Activation was again present in the right prefrontal and right superior parietal cortices (BA 7).

Another experiment by Pardo et al. (1991) was concerned with somatosensory vigilance for stimulation to either the left toe or the right toe. The comparison condition again involved the participants' eyes being closed. The results were similar to the dot dimming comparison and the prefrontal and superior parietal cortices were activated.

The prefrontal and superior parietal cortices were activated across both modalities, visual and somatosensory. The right laterality of this attentional system was unrelated to the side of the sensory input.

In a further experiment by Lewin et al. (1996) participants again had to concentrate on a small dim spot and this was compared to a condition in which the participants eyes were closed. The results revealed activation of the right middle frontal gyrus and the right parietal lobe. These tasks by Pardo et al. (1991) and Lewin et al. (1996) appear to demonstrate that right frontal and superior parietal regions are used in order to perform tasks which require sustained attention.

The task of target detection has been reported to activate the anterior cingulate gyrus (Posner & Raichle, 1997). The activation was observed when participants responded to animal names (targets) while reading a series of nouns. The level of activation in the cingulate area increased as the number of target words was expanded.

Stroop tasks have also been shown to produce activation in the anterior cingulate gyrus e.g. Pardo, Pardo, Janer and Raichle (1990). Stroop tasks induce conflict which requires effortful attentive processing to successfully complete the task. A stroop task involves for example, a congruent condition i.e. the word RED written in RED ink, and an incongruent condition i.e. the word RED written in BLUE ink. The participant finds it much more difficult to name the colour of the ink in the incongruent condition than in the congruent condition. The participant must inhibit the natural tendency to read the name of the word (Gazzaniga et al., 1998). The conflict is thought to be one of the reasons for the activation of the anterior cingulate gyrus.

In summary, the above studies have shown that orthographic processing seems to involve the left fusiform gyrus and the left middle occipital gyrus. The vigilance network appears to incorporate the right middle frontal gyrus and right parietal lobule. Deactivation of the anterior cingulate may be seen during tasks requiring sustained attention, whereas activation of this region may be observed during tasks that involve target detection or inhibition.

3.9 Experiment 1: The Effect of Age on Vigilance and Working Memory

It is interesting to examine the effect of age on working memory, as it is this memory system that is essential for everyday tasks which involve information to be retained temporarily for use in the present. Ageing seems to affect the working memory system in many ways. Age appears to contribute to slower processing ability in the elderly (Salthouse, 1991), impairments in choosing strategies (Lemaire, Arnaud, & Lecacheur, 2004), problems in switching attention (Verhaeghen & Basak, 2005), a tendency for perseverations to increase (Ridderinkhof, Span, & van der Molen, 2002), a

reduced capacity for inhibition (Hasher, Stoltzfus, Zacks, & Rypma, 1991), a less highly peaked attentional focus (Baddeley, 1996), and a drop in capacity thought to be due to a failing central executive and a deficiency of the frontal lobes (Stuart-Hamilton, 2000), amongst other effects. The drop in capacity of working memory in the elderly was reported by Stuart-Hamilton (2000) to be quantitative in nature. This means that the elderly appear to mostly use the same cognitive processes as the young, just not as effectively (Baddeley, 1986).

Braver and Barch (2002) suggested that many cognitive processes, including working memory, rely on the internal representation, maintenance and updating of contextual information. The researchers held that this contextual information can consist of any task relevant information that could bias the processing associated with task performance. A study by Satpute, Braver and Barch (2002) investigated the effect of age on the processing of contextual information. The researchers predicted that older adults would be impaired on an adapted version of the classic Continuous Performance Test (CPT), described by Beck, Bransome, Mirsky, Rosvold and Sarason (1956), when the length of delay was increased between the cue and target. The researchers suggested that poor context representation or maintenance deficits would account for this age related impairment. The modified CPT that was used involved trials in which "A" was the cue, and "X" was the target. When this order of events took place (which was known as the "AX" trial), the participant responded with a press of a button. Another condition consisted of the cue "A" followed by a false target "Y". For this "AY" trial the participant responded with a different button. "BX" trials were also presented. These "BX" trials consisted of a false cue "B" with the correct target "X". Typically, young participants that are presumed to have good context representations, have significantly more AY errors than BX errors.

The researchers split a group of old adults into two groups, younger old and older old. In both the older groups the advantage of BX over AY did not exist and the amount of BX errors were either greater or equal to AY errors. The authors suggested that this finding reflects a disturbance in context representation.

When the delay period between cue and target was altered (maintenance), performance in the group of younger old was not affected. In the older old, however, BX was significantly poorer with delay and AY performance was found to be significantly enhanced.

Braver and Barch (2002) commented that the results of the Satpute et al. (2002) experiment appeared to demonstrate that context representations are impaired in older participants. The researchers also suggested that context representation and maintenance may be dissociable cognitive control functions, as it was found that the older subdivision of the old group of adults were also impaired on maintenance.

Reuter-Lorenz et al. (2000) investigated the effects of age on working memory with PET using a verbal working memory task. The results of the experiment showed that the older participants (62-75 yrs old) had significantly slower response times in reaction to the stimuli, than the younger adults (18-30 yrs old). The use of reaction times in older adults however, may not be an accurate measure of cognitive processing if the results are confounded by factors which are not cognitive, i.e. the presence of arthritis or of essential tremor.

3.9.1 The Effect of Age on Working Memory - Neuroimaging Evidence

An fMRI study by Adler, Holland, Enseleit and Strakowski (2001) examined the levels of activation in young adults when performing both the 2-back task and the 0-back task. The researchers showed that activation for both the left and right hippocampi significantly increased with age. These age-related functional changes are revealed even when no behavioural working memory deficits are observed.

The results of the Reuter-Lorenz et al. (2000) PET study which investigated verbal working memory, were that the younger adults tended to be left lateralised for the verbal material, whereas the older adults tended to have a global pattern of bilateral activation. These researchers also divided the areas of the brain into posterior sites and anterior sites and carried out further analyses. In the posterior regions there was significant activation of the left hemisphere in both groups, but there was no significant difference between the young and old adults. The anterior sites however, revealed that the activations in the younger group tended to be asymmetrical, with significant left sided activation, but no significant activation on the right. On the other hand, the older adult group had significant activations in both hemispheres. The magnitude of the difference between young and old was also significant.

The researchers then split the brain into smaller subsections in order to examine the different areas of activation which contributed to the more holistic results. The results of this analysis showed certain similarities between the groups e.g. both groups activated the medial SMA bilaterally and both groups activated the left lateral SMA more than the right (although the older adults activation was more asymmetrical than the younger adults). There were also differences in the activation patterns of the young and older adults. The young significantly activated Broca's area and showed non-significant deactivation in the homologous region on the right, whereas the older adults had significant activation in these areas bilaterally. A further difference between groups was in the DLPFC (BA 46/9), in which the young significantly activated the left, whereas the older adults significantly activated the right and had only a weak tendency to activate the left.

Reuter-Lorenz et al. (2000) suggested that the activation of Broca's area and its homologue in the older adults was possibly a general compensatory mechanism to assist working memory processes. This hypothesis was based on the observations from neuroimaging experiments which investigated patients recovering language and patients with left-hemisphere damage (which sometimes included Broca's area, BA 44). In these patients activation of the right frontal operculum (BA 44/45) could be seen, which indicated the availability of this region to be recruited for language related processes e.g. Buckner, Corbetta, Schatz, Raichle and Petersen (1996).

Building on the finding in the Reuter-Lorenz et al. (2000) verbal WM study, that reaction times were slower in the older adults, the researchers split the older group into two using the median response time. Correlation analysis on the PET results revealed that the slower older adults activated the DLPFC more in the right than the left, and the faster older adults had bilateral DLPFC activation. This finding led the researchers to conclude that the paradoxical laterality that was observed in the older adult group (in which the right DLPFC more than the left was activated, which is contrary to the reported findings that verbal working memory components are usually housed in the left hemisphere) is less efficient than the bilateral activation of the DLPFC.

Braver and Barch (2002) suggested that the DLPFC is associated with the maintenance, the internal representation, and the updating of context information. An earlier experiment by Barch, Braver, Racine and Satpute (2001) investigated the role of the DLPFC, by using a CPT (that they created), under fMRI conditions. In the

experiment the length of time taken to maintain the context representation was manipulated to be either 1 second or 7.5 seconds. Barch et al. suggested that the older adults would be impaired on the longer delay condition because of possible context representation and/or maintenance deficits that were presumed to be present in this older population. fMRI enabled the researchers to investigate the levels of activation in the DLPFC for the shorter and longer delay periods and to compare them between groups of young and old participants. The results showed that with the short delay period, the older adults showed a greater increase than the young in left DLPFC activity. However, the older adults also revealed decreased activity in the left DLPFC during the longer delay condition (maintenance condition). During this decrease in the DLPFC which was associated with the long delay the older adults also had a general increase in task related brain activity elsewhere in the brain.

3.9.2 What factors may contribute to an age related decline in WM?

Braver and Barch (2002) proposed that the prefrontal cortex and the dopaminergic system are amongst the areas that are affected most by age. The authors suggested that dopaminergic projections from the midbrain that lead to the DLPFC become impaired with age. The authors also suggested that both phasic and tonic changes in dopaminergic activity may be occurring. Braver and Cohen (2000) proposed that the phasic activity may trigger the updating of context information in the PFC, whereas Braver and Barch (2002) stated that the tonic levels of dopamine activity might be important in the maintenance of the context representation. The researchers suggested that there may be a differential time-course for the impairment of both phasic and tonic dopaminergic activity. If two different time courses do exist, this might explain the results from the CPT study (Satpute et al., 2002), which found that older adults appeared to have impaired context representations (phasic activity), whereas only the older of the old adults were impaired on maintenance (tonic activity). However, Braver and Barch (2002) suggested that this theory of ageing requires further investigation.

The atrophy of regions associated with working memory functioning may also contribute to the differences that are observed between older and younger adults.

Volumetric analyses have demonstrated that age related changes in brain matter do exist. With Magnetic Resonance Imaging (MRI), Salat, Kaye and Janowsky (1999) investigated the differences in grey and white matter volumes between a group of young elderly (mean age 70) and a group of old elderly (mean age 90). The researchers showed that the old group had significantly less total prefrontal volume than the young group (approximately 15% less). Examining only the white matter, the old elderly group had a significantly lower volume than the young elderly (approximately 30% less). The old elderly group also had a significantly higher grey-white matter volume ratio than the young elderly group. The old elderly had significant negative correlations between both age and total prefrontal volume and between age and white matter volume. The results demonstrate that the white matter volume appears to decrease disproportionately faster than the grey matter volume as an effect of age.

A further study by Salat, Kaye and Janowsky (2001) examined the volumetric differences in prefrontal regions that exist between young elderly (mean age 71.7) and old elderly (mean age 88.9). The results revealed that the older group of elderly participants had less prefrontal white matter than the group of young elderly participants. The orbital frontal region appeared to be preserved in the old elderly group compared to the other prefrontal regions.

An additional study to investigate the effect of ageing on the volume of white matter in the brain was carried out by Bartzokis et al. (2003). The researchers used the transverse relaxation rate in order to indirectly measure the volume of frontal lobe white matter (FLWM). The participants that were studied (n = 252) were between the ages of 19 and 82. The results showed that the volume of FLWM appeared to increase up until the age of 38 and then decreased noticeably with age.

3.9.3 The Effect of Ageing on Working Memory - Theories

Ageing has been postulated to have many consequences for cognition. Some descriptions of the general effects of ageing were mentioned previously in the introductory chapter. Two models of the effects of ageing were described. These were the model of Hemispheric Asymmetry Reduction in Older Adults (HAROLD) (Cabeza, 2002) and the Right Hemi-Aging Model (Dolcos et al., 2002). The HAROLD model specifies that frontal activity becomes less lateralised in older adults when compared to

young adults. The Right Hemi-Aging Model states that the right hemisphere undergoes greater cognitive decline than the left due to the effects of age. These two models attempt to describe some of the effects that have been observed due to the process of ageing.

Other effects attributable to the ageing process, are under-activation, non-selective over-activation, the activation of different regions, a decrease in laterality, compensatory activations and the effect of dedifferentiation. Under-activation is seen when older adults tend to activate the regions that the younger activate but at lower levels, or when the older adults fail to activate these areas at all. The effect of non-selective over-activation is the result of older adults activating areas that the young do not activate. These activations may be detrimental to the functioning of cognitive mechanisms. This type of activation may be due to a breakdown in inhibitory processes, which in turn no longer prevent the activation of these irrelevant areas. The activation of different regions may occur due to compensation, different strategies, or differing neural networks. Decreases in the laterality of activations have been proposed to be due to the effects of ageing. Young adults often have strongly lateralised neural networks (Reuter-Lorenz et al., 2000), and for various reasons older adults exhibit a decrease in this laterality. Differences in patterns of activation have often been described to be due to compensatory attempts by the elderly in order to make up for the effects of, for example, atrophy, decreased blood flow, and changes in neural architecture which can occur with advances in age. Dedifferentiation is the term applied to a decrease in asymmetrical activation that is presumed to be due to an effect of age, in which older adults lose the ability to activate specialised functional mechanisms that are available to the young.

The various and wide-ranging effects described above are thought to be due to the effects of ageing. Of these effects, the specific consequences of ageing on the working memory system should be examined. An example of under-activation in older adults can be seen in the study by Jonides et al. (2000). The experiment consisted of a verbal working memory task that involved high and low conflicting response tendencies. In the young adult group during the higher conflicting response condition, an increase in activation of the LIFG (BA 44-45 boundary) was observed. However, the older adults did not recruit this IFG region and performed more poorly than the

younger group. It appears that the under-activation of this region in the older group contributed to the lower performance.

Reuter-Lorenz et al. (2000) used a verbal WM task with PET to investigate the effects of age. The task involved the presentation of four letters around a fixation point, then the letters would disappear during the delay and a target letter would be presented. The participant had to indicate whether or not the target letter was present in the presentation stage. As revealed by examining regions of interest, the young significantly activated regions of Broca's area, BA 6, BA 40/7 on the left and the anterior cingulate. The elderly group activated similar regions to the young, but also employed the homologous region of BA 44 and the right DLPFC.

Reuter-Lorenz et al. (2000) also carried out a spatial working memory experiment using PET, in which the participants had to observe the locations of three dots on a screen. A circle was then presented and the participant had to respond to whether the circle encompassed one of the locations of the previous dots or did not. Both the groups of young and old scored approximately 90% correct. The young and elderly groups activated regions of the right and left parietal cortex that were assumed to be associated with spatial processing. Both groups also activated right frontal regions assumed to be used in the rehearsal of spatial information, these were the ventral prefrontal cortex (BA 47), the DLPFC (BA 46/9) and the SMA (BA 6). However, in addition to the right hemisphere frontal regions the older group also activated the homologous frontal regions on the left. This result showed that the older adults were recruiting more brain regions in order to perform the same task.

Looking at the findings from the verbal WM experiment by Reuter-Lorenz et al. (2000) the older adults appeared to recruit the homologous frontal regions on the right (in addition to the regular left frontal regions) to perform optimally, whereas in the spatial WM task the complementary result was observed, in which the older adults recruited the homologous frontal regions on the left (in addition to the regular right frontal regions). The bilateral activations that were observed in the tasks may be examples of compensatory efforts employed by older adults to perform at their best.

It is possible that in some circumstances the differences in activation that are observed between older adults and younger adults may be due to the application of different strategies between the groups. However, debriefing reports and patterns of

error do not suggest that the elderly tend to engage alternative strategies to the young (Reuter-Lorenz, 2002).

The n-back working memory task will be used in the first experiment in this thesis in order to examine the effects of age on the verbal working memory network. Previous research that has been outlined above suggests that verbal working memory is sensitive to the ageing process. It is expected that differences will exist in the areas that are activated during the n-back working memory task, between young and elderly individuals.

The n-back working memory task is well documented in the literature. A number of neuroimaging experiments have been outlined above, that investigated which areas of the brain were activated when engaging in the n-back working memory task e.g. Awh et al. (1996); Schumacher et al. (1996); Braver et al. (1997); Jonides et al. (1997); Veltman et al. (2003). The experiments sometimes vary in different stimulus timings or use slightly different paradigms, but the evidence appears to converge on a number of brain structures which are used in order to carry out this verbal working memory task. The areas that are most commonly activated during the n-back working memory task are the left inferior frontal gyrus (including Broca's area), the dorsolateral prefrontal cortex, the SMA, the inferior and superior parietal cortices bilaterally, the anterior cingulate cortex and regions of the cerebellum.

3.9.4 N-Back Working Memory Task

An n-back working memory task consists of a number of conditions. Each of the conditions in the n-back tasks comprises a different working memory load. A useful feature of the n-back task is that WM load can be systematically increased, and using fMRI, the brain regions used to complete the task for each WM load can be identified. This method can be used investigate whether the same areas are used as WM load increases, or if additional areas are activated.

The n-back task consists of the maintenance of the letters to be remembered and also the manipulation of the letters. As in the animal studies that have been described, associative information is not sufficient to perform the n-back task. The letters to be remembered constantly change and WM must be updated constantly.

It should be noted that although the n-back task involves visual presentation of letters, these stimuli will most likely be transferred into phonological code. Hitch, Woodin and Baker (1989) suggested that a preference exists for phonological coding after carrying out an experiment that showed older children could use either visual or phonological coding, but tended to use phonological codes whenever possible unless they were pressed to use visual coding (i.e. when under articulatory suppression).

The n-back task involves subvocal rehearsal, phonological storage and central executive processing. The n-back working memory task (adapted for fMRI) may be useful for examining the effect of ageing on brain activation as older adults tend to have lower working memory spans than younger adults (Stuart-Hamilton, 2000) and this decrement presumably has a biological basis. It might be possible to observe differences between the young and elderly participants by using fMRI.

3.9.5 Experiment 1: Hypotheses

3.9.5.1 Experiment 1a: Vigilance Hypotheses

For the young adults:

1) Areas of significant activation will include the letter discrimination areas of the left fusiform gyrus and left middle occipital gyrus.
2) Areas of activation will incorporate the right DLPFC and regions of the cingulate cortex.
3) Activation is also expected in the inferior parietal lobule (BA 40), bilaterally.

For the elderly:

1) Areas of significant activation will include the letter discrimination areas of the left fusiform gyrus and left middle occipital gyrus.
2) Areas of activation will also include the right DLPFC and regions of the cingulate cortex.
3) Activation is expected in the inferior parietal lobule (BA 40), bilaterally.

4) In concordance with the HAROLD a more bilateral pattern of activation will be seen in the elderly group compared to the young group.
5) The inferior parietal lobule (BA 40) will have reduced activation in the right hemisphere compared to the left (hypothesised in concordance with the right hemi-ageing hypothesis).

Note: For the elderly hypotheses, numbers 1, 2 and 3 concern the same areas of activation that are expected for the young. Hypotheses 4 and 5 concern the effects that might be produced due to effects of age.

3.9.5.2 Experiment 1b: Light Working Memory Load Hypotheses

For the young adults:

1) The working memory network will be made up of a frontal/parietal network.
2) The areas in the frontal lobes proposed to be activated significantly are: the left anterior PFC (Broca's area, BA 44), bilateral DLPFC, bilateral VLPFC and the SMA.
3) Parietal areas BA 7 and BA 40 will also be significantly activated bilaterally.

For the elderly:

1) The working memory network will be made up of a frontal/parietal network.
2) The areas in the frontal lobes that will be activated significantly are: the left anterior PFC (Broca's area, BA 44), bilateral DLPFC, bilateral VLPFC, and the SMA.
3) Parietal areas BA 7 and BA 40 will be significantly activated bilaterally.
4) A more bilateral pattern of activation is expected in the elderly group than the young group (hypothesized in concordance with the HAROLD).
5) Parietal areas (BA 7/40) will have reduced activation in the right hemisphere compared to the left hemisphere (hypothesized in concordance with the right hemi-ageing hypothesis).

Note: For the elderly hypotheses, numbers 2 and 3 concern the same areas of activation that are expected for the young. Hypotheses 4 and 5 concern the effects that might be produced due to the consequences of ageing.

3.9.5.3 Experiment 1c: More Demanding Working Memory Load Hypotheses

Similar areas of activation are expected in the 2-back versus 1-back comparison as in the 1-back versus 0-back comparison. The 2-back task involves a higher working memory load, however. This means that higher levels of activation may be expected in the areas associated with working memory. The task required the constant maintenance in memory of two letters, constantly updating these letters, and inhibiting the irrelevant letters that were presented previously in the sequence. The higher working memory load may be more taxing on mechanisms of phonological rehearsal. The 1-back condition was considered to be a working memory task which was less demanding e.g. only one letter had to be maintained in working memory (in addition to the processes of updating the letter and inhibiting the irrelevant letters that were presented previously).

For the young adults:

1) The working memory network will be made up of a frontal/parietal network.
2) The areas in the frontal lobes proposed to be activated significantly are: the left anterior PFC (Broca's area, BA 44), the bilateral DLPFC, the bilateral VLPFC and the SMA.
3) Parietal areas BA 7 and BA 40 will also be significantly activated bilaterally.

For the elderly:

1) The working memory network will be made up of a frontal/parietal network.
2) The areas in the frontal lobes that will be activated significantly are: the left anterior PFC (Broca's area, BA 44), bilateral DLPFC, bilateral VLPFC, and the SMA.

3) Parietal areas BA 7 and BA 40 will be significantly activated bilaterally.
4) A more bilateral pattern of activation is expected in the elderly group than the young group (hypothesized in concordance with the HAROLD).
5) Parietal areas (BA 7/40) will have reduced activation in the right hemisphere compared to the left hemisphere (hypothesized in concordance with the right hemi-ageing hypothesis).

Note: For the elderly hypotheses, numbers 2 and 3 concern the same areas of activation that are expected for the young. Hypotheses 4 and 5 concern the effects that might be produced due to the consequences of ageing.

3.9.5.4 Experiment 1d: Parametric Design Hypotheses

A parametric method of analysis was applied to investigate the brain areas that are engaged as working memory load is incremented. This method of analysis was used because of the potential drawbacks of using a subtractive method.

For the young adults:

1) The working memory network will be made up of a frontal/parietal network.
2) The areas in the frontal lobes proposed to be activated significantly are: the left anterior PFC (Broca's area, BA 44), bilateral DLPFC, bilateral VLPFC and the SMA.
3) Parietal areas BA 7 and BA 40 will also be significantly activated bilaterally.

For the elderly:

1) The working memory network will be made up of a frontal/parietal network.
2) The areas in the frontal lobes that will be activated significantly are: the left anterior PFC (Broca's area, BA 44), bilateral DLPFC, bilateral VLPFC, and the SMA.
3) Parietal areas BA 7 and BA 40 will be significantly activated bilaterally.

4) A more bilateral pattern of activation is expected in the elderly group than the young group (hypothesized in concordance with the HAROLD).
5) Parietal areas (BA 7/40) will have reduced activation in the right hemisphere compared to the left hemisphere (hypothesized in concordance with the right hemi-ageing hypothesis).

Note: For the elderly hypotheses, numbers 2 and 3 concern the same areas of activation that are expected for the young. Hypotheses 4 and 5 concern the effects that might be produced due to the consequences of ageing.

3.9.6 Methods

3.9.6.1 Participants

The participant groups were 9 young participants and 8 elderly participants. The young controls were 3 males and 6 females within the ages of 21 and 28. The mean age of the young participants was 23.33 (SD 2.18). The elderly controls were 2 males and 6 females within the ages of 72 and 77. The mean age of the elderly participants was 75 (SD 1.69). The participants were all British and English was their first language. All the participants recruited for the study were right handed. Ethical approval was granted by the joint Grampian Health Board and the University of Aberdeen Ethics Committee.

3.9.6.2 Materials

The software "Presentation" for Windows was used to create the experiment program and control the stimuli timings. fMRI was performed on a 1.5 Tesla GE MRI system equipped with echo-planar imaging capabilities using a standard head coil. The stimuli where presented onto a screen viewable with a mirror attached to the head coil with the use of a PC via LCD projector. The participants were equipped with a fibre optic response device in the left and right hand.

3.9.6.3 fMRI Paradigm

An n-back paradigm was used to create a version of the task in which a series of letters were presented. This version of the task was created in order to ensure compatibility with fMRI. The task consisted of four conditions. In each of the conditions the presentation screen was white and the letters or symbols were presented in a black "Times New Roman" font. The first condition was the baseline (see Fig 3.3). This consisted of the baseline instructions which lasted for five seconds, after which came the test stimuli. Eighteen hash symbols were presented serially (in the centre of the screen), for 2000ms each, with a blank screen interstimulus interval of 500ms. The participant had to observe the hash symbols and push a response button every time the hash symbol was presented. This condition made up the baseline task.

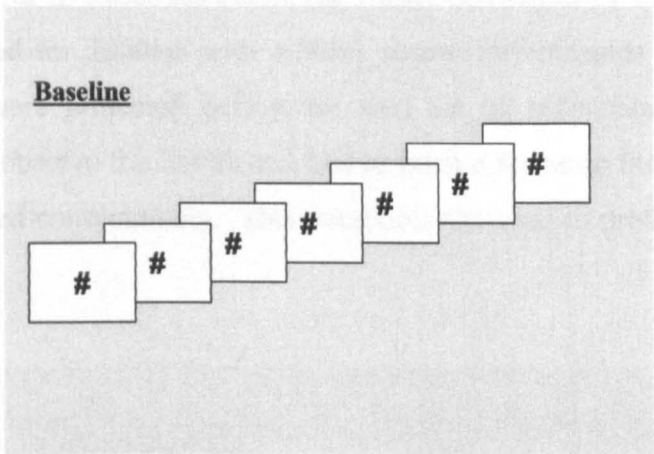

Fig 3.3: Demonstrates what was required for completion of the baseline condition.

The second condition was the 0-back (see Fig 3.4). The 0-back instructions lasted for five seconds after which the 0-back test sequence was presented. Each letter was presented for 2000ms with a blank screen interstimulus interval of 500ms. In total eighteen letters were projected before the beginning of the next condition. The participant's task in this condition was to observe the letters and push a response button, whenever the letter X was presented. It should be noted that this is the only condition in which the letter X was displayed. This condition was used to test the vigilance of the participant.

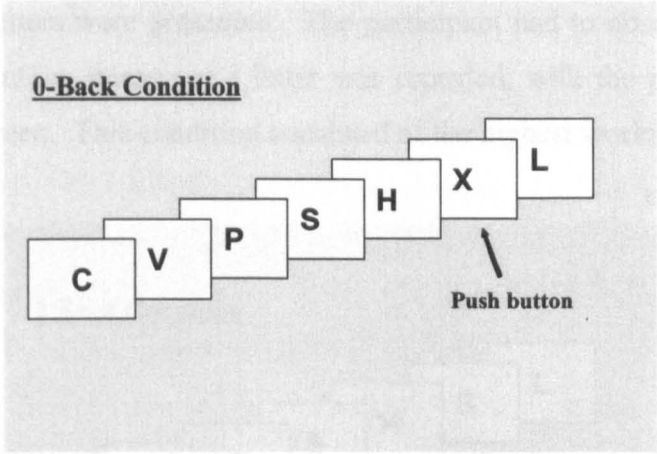

Fig 3.4: Demonstrating what was required for completion of the 0-back condition.

The third condition was the 1-back condition (see Fig 3.5). The 1-back instructions lasted for five seconds before the 1-back test sequence was presented. Each letter was presented for 2000ms with a blank screen interstimulus interval of 500ms. Eighteen letters were projected before the next set of instructions appeared. The participant had to observe the letters and had to push a response button every time the same letter appeared consecutively. This condition was used to produce a low working memory load.

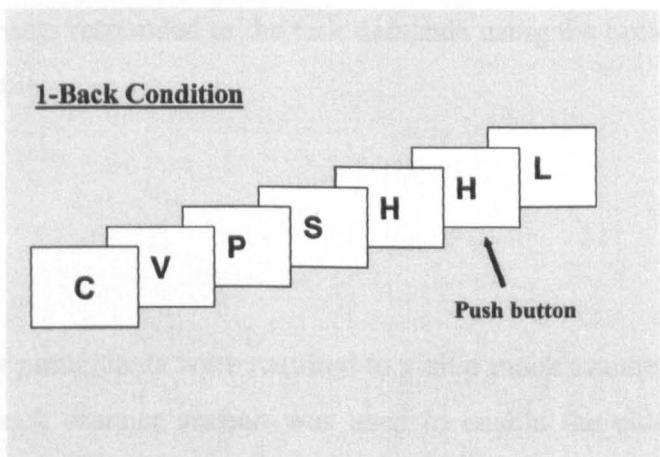

Fig 3.5: Demonstrating what was required for completion of the 1-back condition.

The fourth condition was the 2-back condition (see Fig 3.6). The 2-back instructions lasted for five seconds before the 2-back test sequence was presented. Each letter was presented for 2000ms with a blank screen interstimulus interval of 500ms. A

total of eighteen letters were presented. The participant had to observe the letters and push a response button, whenever a letter was repeated, with the presentation of one other letter in between. This condition consisted of the highest working memory load.

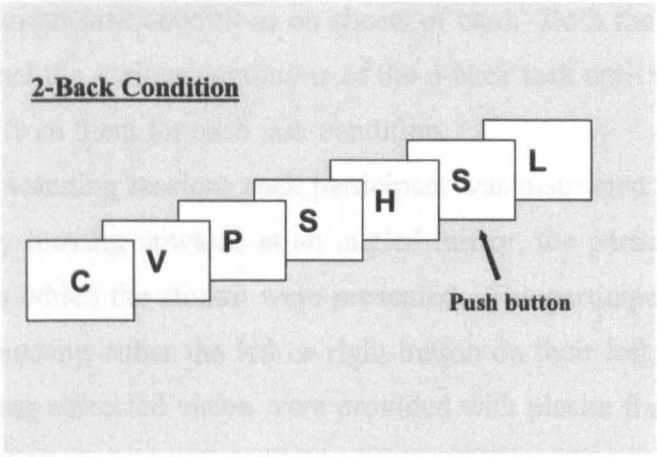

Fig 3.6: Demonstrating what was required for completion of the 2-back condition.

In all the letter conditions only consonants were used. There were no vowels and the letter Y was absent from the presentations. The exception of the vowels and the letter Y was to prevent the participants using syllables to remember the letters. The participants had a button positioned for response with the left hand and one for the right hand. The participants responded to the task demands using the button with which they felt most comfortable.

3.9.6.4 Procedure

The elderly participants were required to visit a mock scanner one week prior to scanning. The mock scanner session was used to enable the elderly participants to familiarise themselves with the experimental procedure. During this session the elderly that were too claustrophobic to be scanned were identified and excluded from enrolment for the fMRI study. Instructions were presented verbally to the participants along with visual examples of the various task conditions on sheets of card. The participants were allowed to practice the different conditions of the n-back task while in the mock scanner until they were familiar with each variant of the task.

Immediately prior to scanning both the young and elderly participants were subjected to a practice session in which the elderly participants were reminded of the differing conditions and the young participants learnt what would be required of them in the scanning session. The instructions were presented verbally along with visual examples of the various task conditions on sheets of card. Both the young and elderly participants practiced the various conditions of the n-back task until they were aware of what was required from them for each task condition.

During the scanning sessions each participant was instructed to lie on their back in the scanner. By looking upwards at an angled mirror, the participants could see a projector screen on which the stimuli were presented. The participants had to respond to the stimuli by pushing either the left or right button on their left or right hand. All participants requiring corrected vision were provided with plastic framed glasses which fitted their prescription.

The first part of the scanning procedure consisted of four dummy scans, the duration of which (10 seconds in total) allowed the scanner to reach equilibrium. The order that the conditions were presented was, baseline, 0-back, 1-back and finally 2-back. This completed the first complete run of all the conditions. All the conditions were repeated two more times, meaning that the participant performed three baseline test phases, three 0-back test phases, three 1-back test phases and three 2-back test phases. This completed the first test session. In total, the first test session consisted of 135 seconds of baseline scanning, 135 seconds of 0-back scanning, 135 seconds of 1-back scanning and 135 seconds of 2-back scanning. The entire test session was also repeated by each participant, in order to strengthen the statistical power of the data analysis.

The number of targets in each condition for session 1 consisted of 18, 18 and 18 for the baseline runs 1, 2, and 3 respectively. There were 5, 5 and 6 targets for the 0-back runs 1, 2 and 3, respectively. There were 3, 4 and 4 targets for the 1-back runs 1, 2 and 3, respectively. There were 3, 3 and 3, for the 2-back runs 1, 2 and 3, respectively.

The number of targets was the same for session two. It should be noted that different stimuli and target positions were used in session 2.

3.9.6.5 fMRI Methods

The fMRI acquisition was carried out on a 1.5 Tesla GE MRI system that was equipped with echo-planar imaging capabilities using a standard head coil. The following parameters were used: TE = 35ms, TR = 2.5s, in plane resolution $2x2mm^2$, 5mm slice thickness.

3.9.6.6 fMRI Data Analyses

This was a between groups comparison. Both the young and elderly groups performed the conditions of baseline, 0-back, 1-back and 2-back. This enabled the effect of ageing to be examined for both the vigilance and the working memory conditions.

Many different analyses can be performed comparing these conditions. The experimental conditions can be compared with each other as well as to the baseline. In addition, combinations of the conditions can also be compared. All the conditions that were used in the experiment had similar perceptual and motor requirements.

The fMRI data were analysed using Statistical Parametric Mapping (SPM99) imaging analysis software (Wellcome Department of Imaging Neuroscience, London). Images were re-aligned with a double pass procedure, first creating a mean image and then realigning to this. The data were then normalised into standard stereotactic space and smoothed using a Gaussian filter set at 8mm. The comparisons between conditions were performed on each voxel using t-test statistics. Further analyses were carried out using one sample t-tests with a random effects analysis procedure. The chosen height threshold of significance was $p < 0.01$.

3.9.7 Results

3.9.7.1 Analysis of Behavioural Performance

Initially the behavioural results for the young and elderly groups were investigated. Analysis of variance (ANOVA) was used to compare the mean proportion of scores correct for the young and elderly groups on the 0-back, 1-back and 2-back conditions. The mean scores of the groups on each condition are displayed in Table 3.2. The within-subjects factor was condition (0-back, 1-back and 2-back) and the between-subjects factor was group (young and elderly). The degrees of freedom for the within-subject F-ratios were corrected using Greenhouse-Geisser. There was no main effect of condition, $F(1.32,19.74) = 2.119$; p = ns, or group, $F(1,15) = .014$; p = ns, nor was there an interaction between the factors, $F(1.32,19.74) = .502$; p = ns.

Table 3.2

The mean 0, 1 and 2 back behavioural scores for the groups of young and elderly.

Condition	Group	N	Mean (SD)
0-back scores	Young	9	31.56 (1.33)
	Elderly	8	31.88 (0.35)
1-back scores	Young	9	22.00 (0.00)
	Elderly	8	21.75 (0.71)
2-back scores	Young	9	17.56 (1.01)
	Elderly	8	17.50 (0.76)

Note: The maximum score of the 0-back is 32.
The maximum score of the 1-back is 22.
The maximum score of the 2-back is 18.

The reaction times of the young and elderly groups were also examined for each of the experimental conditions i.e. 0back, 1back and 2back. One of the young participants was excluded from the analysis because their reaction times were more than four standard deviations above the mean reaction times of the group (for all three of the conditions). Figure 3.7 shows that the mean reaction times appeared to increase for

both the young and elderly groups through each condition, i.e. reaction times were longer in the 1-back than the 0-back, and longer in the 2-back than the 1-back. ANOVA was carried out to examine whether condition (0-back, 1-back and 2-back) or group (young and elderly) influenced the reaction times. The within-subject factor was condition (0-back, 1-back and 2-back) and the between-subject factor was group (young and elderly). Correction of the degrees of freedom for the within-subject F-ratios was made using Greenhouse-Geisser. The analysis showed a significant main effect of condition, $F(1.31,18.39) = 43.95$; $p < 0.001$. There was no main effect of group, $F(1,14) = .269$; p = ns, neither was there an interaction between condition and group, $F(1.31,18.39) = .340$; p = ns.

Planned within-subject contrasts showed that the reaction times were significantly longer for the 1-back compared to the 0-back, $F(1,14) = 18.31$; $p < 0.01$, and for the 2-back compared to the 1-back, $F(1,14) = 35.32$; $p < 0.001$.

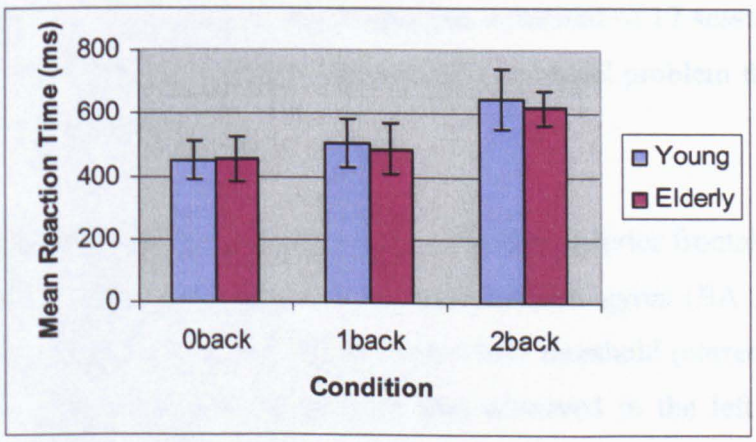

Fig 3.7: The mean reaction times for the young and elderly groups on each experimental condition (error bars of the standard deviations are provided).

It should be noted that none of the participants were explicitly instructed to perform the tasks as quickly as possible. The participants were told to respond as soon as they saw the target (with no emphasis on the speed of response).

3.9.7.2 fMRI Experiment 1a: Detection of Areas Used in Sustained Attention, Target Detection and Visual Discrimination

The first comparison that was carried out using the fMRI data was the 0-back condition versus the baseline condition. The 0-back task was considered to be predominantly a vigilance task, that involved the recognition of a single predetermined letter (the letter X) during a sequence of non-target letters (as well as remembering which condition they were being tested on, in addition to the rules of the condition). The baseline condition was considered to involve similar levels of perceptual input and motor operations as the 0-back task. The comparison of the 0-back to Baseline was predicted to illustrate the brain areas that are required for vigilance.

Young Group: For each young participant all of the 0-back conditions versus Baseline contrasts were modelled session by session, after which a random effects analysis of the data was carried out. The random effects analysis consisted of 17 sessions (Note: One of the 18 sessions had to be removed because of a technical problem that arose during the acquisition of the data).

Significant activations were observed in the right inferior frontal gyrus (BA 45), the right middle frontal gyrus (BA 46), the left fusiform gyrus (BA 37) and the left middle occipital gyrus (BA 18 and 37), at the $p < 0.01$ threshold (corrected for multiple comparisons). Significant activations were also observed in the left inferior frontal gyrus (BA 47), the left middle frontal gyrus (BA 10), the left superior frontal gyrus (BA 10), the right superior frontal gyrus (BA 8), the right medial frontal gyrus (BA 8 and 9), the left superior parietal lobule (BA 7), the left precuneus (BA 7), the right precuneus (BA 19), the right angular gyrus (BA 39), the right middle temporal gyrus (BA 21 and 39), the right superior temporal gyrus (BA 22, 39 and 41), the right inferior occipital gyrus (BA 18), the left middle occipital gyrus (BA 18), the left lentiform nucleus (putamen), the hypothalamus and the left subthalamic nucleus (midbrain), at the $p < 0.01$ threshold (uncorrected for multiple comparisons). Table 3.3 shows the areas of significant activation.

Table 3.3

Lists the sites of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the 0-back versus Baseline contrast in the young group.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Middle Occipital Gyrus	37	6.47	4.47	971	0.005	-36	-62	-2
	18	4.96	3.8			-44	-83	2
Left Fusiform Gyrus	37	4.37	3.49			-44	-63	-9
Right Middle Frontal Gyrus	46	4.25	3.43	887	0.008	44	32	21
Right Inferior Frontal Gyrus	45	4.16	3.38			53	24	6
b)					p-value uncorrected			
Left Superior Frontal Gyrus	10	5.11	3.88	196	0.041	-20	60	1
Left Middle Frontal Gyrus	10	3.06	2.67			-28	51	5
	10	2.92	2.58			-36	54	-4
Left Inferior Frontal Gyrus	47	4.66	3.65	420	0.005	-30	19	-18
Left Lentiform Nucleus		3.88	3.21			-22	13	-7
Left Middle Occipital Gyrus	18	4.55	3.59	516	0.002	-28	-79	6
	18	4.33	3.47			-24	-89	4
	18	4.04	3.31			-32	-93	1
Left Precuneus	7	3.93	3.24	348	0.009	-24	-68	40
Left Superior Parietal Lobule	7	3.7	3.1			-32	-60	42
	7	3.47	2.95			-28	-50	45
Hypothalamus		3.86	3.2	229	0.029	2	-3	-13
Left Subthalamic Nucleus		3.24	2.8			-6	-12	-6
Right Middle Temporal Gyrus	21	5.93	4.25	581	0.001	55	-28	-12
Right Superior Temporal Gyrus	41	4.26	3.49			42	-31	2
	22	4.16	3.37			50	-21	3
Right Cerebellum		5.34	3.99	299	0.014	6	-61	-17
		3.85	3.19			22	-58	-24
		3.75	3.13			14	-55	-19
Right Inferior Occipital Gyrus	18	4.4	3.51	593	0.001	48	-78	1
Right Middle Temporal Gyrus	39	4.06	3.32			40	-71	15
Right Angular Gyrus	39	4.36	3.49	393	0.006	30	-60	34
Right Superior Temporal Gyrus	39	4.15	3.37			42	-53	30
Right Precuneus	19	2.79	2.44			30	-70	42
Right Superior Frontal Gyrus	8	3.49	2.97	230	0.028	8	32	50
Right Medial Frontal Gyrus	9	3.38	2.9			10	46	29
	8	3.36	2.88			10	39	40

Note: * BA refers to Brodmann's Areas.

The significant clusters of activation have been superimposed upon a 3D rendering of the brain see Figure 3.8.

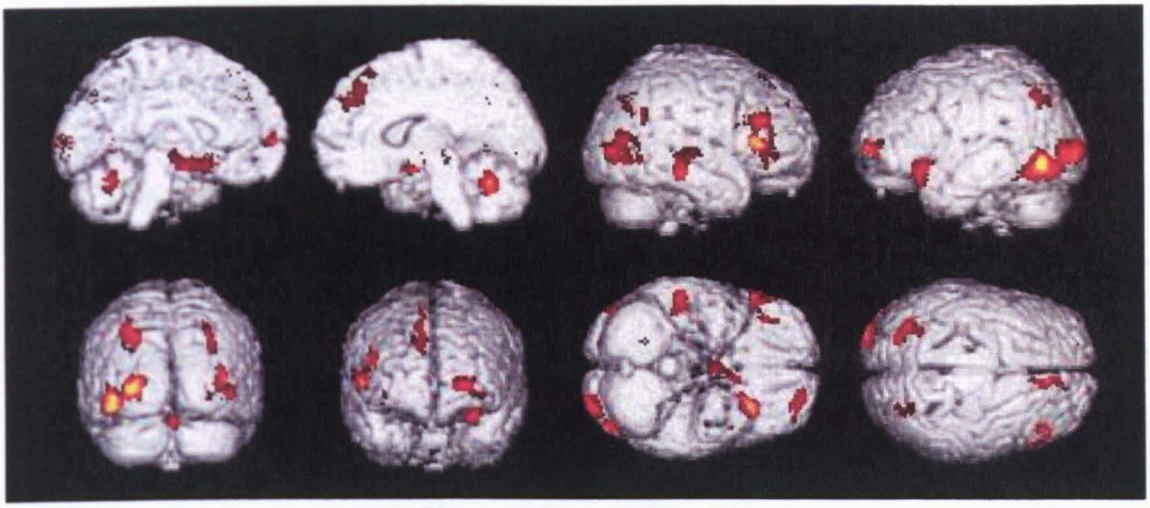

Fig 3.8: Illustrates the sites of significant activation found for the 0-back versus Baseline contrast in the young group (areas activated at the corrected and uncorrected level of significance are shown).

Elderly Group: The group of elderly participants was analysed in the same fashion as the young. The analysis of each individual was performed session by session, after which a random effects analysis of the data was carried out. The random effects analysis was composed of 16 sessions. Table 3.4 shows the areas of activation that are portrayed in Figure 3.9.

At the $p < 0.01$ threshold (corrected) no significant activations were observed. At the $p < 0.01$ threshold (uncorrected) significant activations were observed in the left cingulate gyrus (BA 23), the right cingulate gyrus (BA 24), the left posterior cingulate (BA 24), the left precuneus (BA 19), the left lingual gyrus (BA 18) and the right cuneus (BA 17).

Table 3.4

The sites of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values (uncorrected), for the 0-back versus Baseline contrast in the elderly group.

Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Precuneus	19	5.32	3.93	155	0.035	-30	-68	40
Left Lingual Gyrus	18	4.56	3.55	142	0.042	-4	-72	2
Right Cuneus	17	3.66	3.04			2	-77	11
Right Cingulate Gyrus	24	10.87	5.65	401	0.002	6	-20	34
Left Cingulate Gyrus	23	5.33	3.93			0	-34	26
Left Posterior Cingulate	23	5.26	3.9			-8	-36	24

Note: * BA refers to Brodmann's Areas.

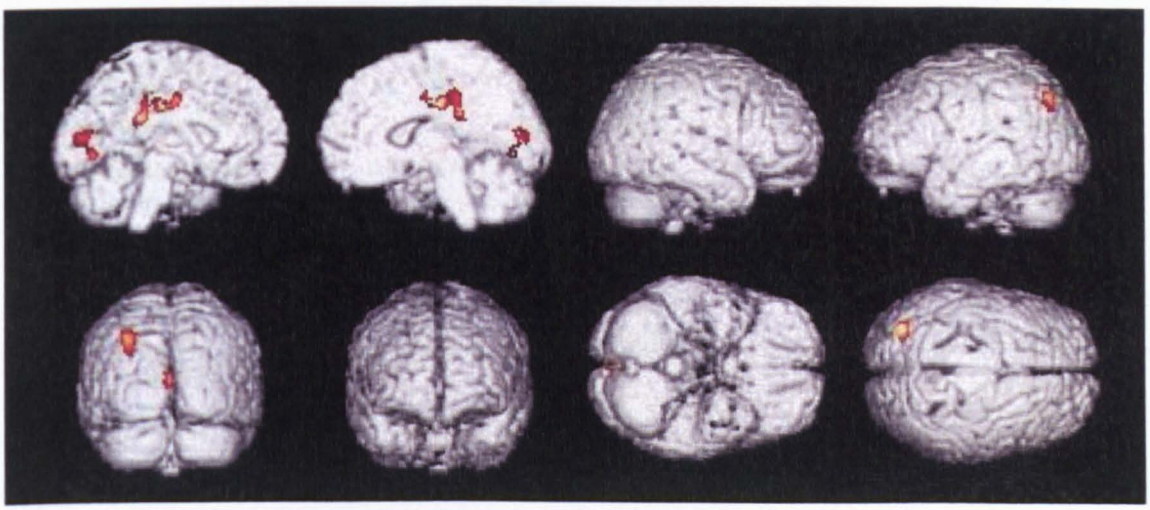

Fig 3.9: The sites of significant activation found for the 0-back versus Baseline contrast in the elderly group.

The elderly group were also investigated at the $p < 0.05$ level of significance in order to examine whether or not these aged individuals tended to activate similar areas to the young, but at decreased levels of activation. At this more liberal threshold, additional activations were observed in the left fusiform gyrus (BA 37), the right fusiform gyrus (BA 19), the left inferior occipital gyrus (BA 19), the right lingual gyrus (BA 17), the left precuneus (BA 7), the left cuneus (BA 19) and the right posterior

cingulate (BA 30). All the areas of activation found at this threshold are listed in Table 3.5 and displayed in Figure 3.10.

Table 3.5

The sites of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values (uncorrected), for the 0-back versus Baseline contrast in the elderly group ($p < 0.05$).

Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Precuneus	19	5.32	3.93	513	0.048	-30	-68	40
	7	2.38	2.16			-22	-64	31
Left Cuneus	19	2.32	2.11			-20	-82	35
Left Fusiform Gyrus	37	3.67	3.05	761	0.019	-42	-49	-9
	37	3.2	2.75			-38	-61	-14
Left Inferior Occipital Gyrus	19	3.16	2.72			-40	-72	-6
Left Lingual Gyrus	18	4.56	3.55	654	0.028	-4	-72	2
Right Cuneus	17	3.66	3.04			2	-77	11
Right Lingual Gyrus	17	3.21	2.76			8	-86	-1
Right Cingulate Gyrus	24	10.87	5.65	1316	0.003	6	-20	34
Left Cingulate Gyrus	23	5.33	3.93			0	-34	26
Left Posterior Cingulate	23	5.26	3.9			-8	-36	24
Right Posterior Cingulate	30	5.48	4	798	0.017	12	-64	11
Right Fusiform Gyrus	19	5.11	3.83			28	-59	-12
	19	3.72	3.08			38	-65	-9

Note: * BA refers to Brodmann's Areas.

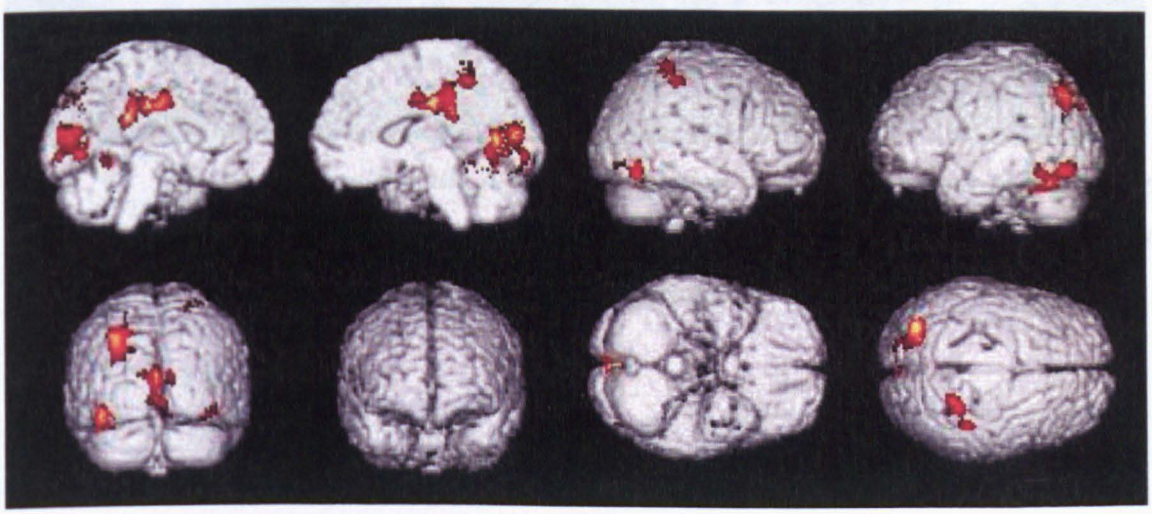

Fig 3.10: The sites of significant activation found for the 0-back versus Baseline contrast in the elderly group ($p < 0.05$).

Young Group versus Elderly Group Comparison: Analysis was carried out in the form of a t-test in order to compare the young group to the elderly group on the 0-back versus Baseline contrast. The 17 sessions of the young participants were compared to the 16 sessions of the elderly participants. The significant differences in activation can be seen in Table 3.6 and in Figure 3.11.

The comparison of the young group to the elderly group revealed significantly different levels of activation in the left inferior frontal gyrus (BA 47), the right superior temporal gyrus (21 and 22), the left hippocampus, the left middle occipital gyrus (BA 37), the left lentiform nucleus (medial globus pallidus) and the right lentiform nucleus (putamen), at the $p < 0.01$ level of significance (corrected). Significant differences between the groups were also detected at the uncorrected level of significance in the right middle temporal gyrus (BA 39), the left middle occipital gyrus (BA 18) and the left anterior cingulate (BA 32).

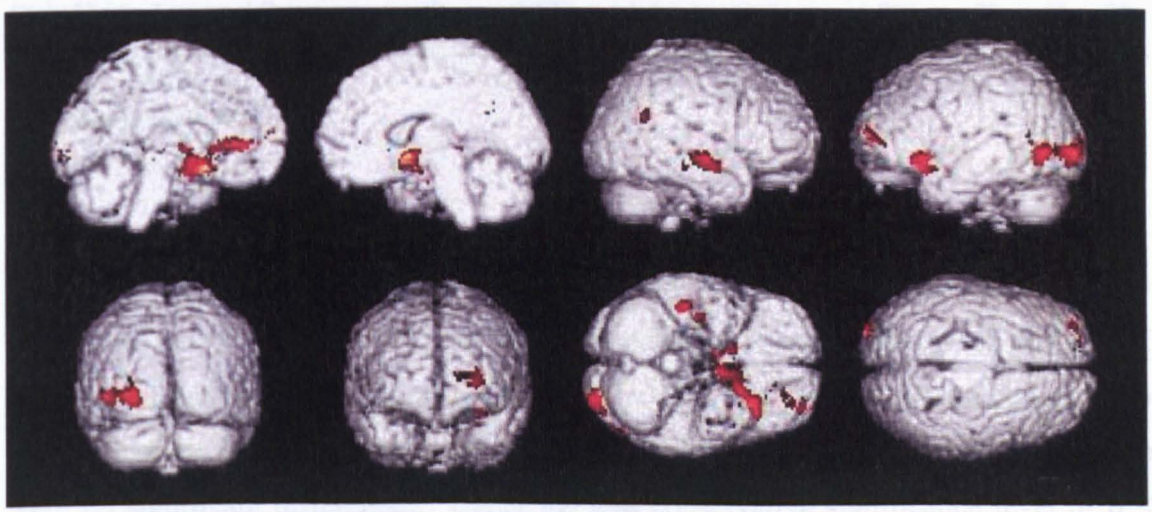

Fig 3.11: The sites of significantly different activation in the comparison of the young group to the elderly group on the 0-back versus Baseline contrast (the differences at both the corrected and uncorrected level of significance are shown).

Table 3.6

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the comparison of the young group to the elderly group on the 0-back versus Baseline contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Lentiform Nucleus		4.3	3.78	757	0.019	-26	-20	-4
Left Middle Occipital Gyrus	37	3.99	3.56			-38	-66	0
Left Hippocampus		3.99	3.56			-34	-46	10
Left Inferior Frontal Gyrus	47	5.31	4.44	1022	0.004	-30	21	-13
Right Lentiform Nucleus		4.68	4.04			10	2	-7
Right Superior Temporal Gyrus	22	5.56	4.59	617	0.050	48	-16	-4
Right Superior Temporal Gyrus	21	3.81	3.42			46	-29	-7
b)					p-value uncorrected			
Left Middle Occipital Gyrus	18	4.57	3.97	269	0.021	-24	-89	3
	18	3.45	3.15			-30	-95	3
	18	3.17	2.93			-32	-85	3
Left Anterior Cingulate	32	3.39	3.1	470	0.004	-16	45	0
Right Middle Temporal Gyrus	39	3.77	3.4	216	0.036	32	-55	29
	39	3.51	3.19			42	-55	25

Note:
* BA refers to Brodmann's Areas.

Elderly Group versus Young Group Comparison: The converse t-test was also performed in order to compare the elderly group to the young group on the 0-back versus Baseline contrast. The 16 sessions of the elderly participants were compared to the 17 sessions of the young participants. At the $p < 0.01$ level of significance, there were no significant differences. Using the less conservative significance level of $p < 0.05$ (uncorrected), significant differences in activation were observed in the two groups, with the elderly activating the right precentral gyrus (BA 6), the right postcentral gyrus (BA 43), the cingulate gyrus bilaterally (BA 24) and the right insula (BA 13) more than the young (see Table 3.7 and Figure.3.12).

Table 3.7

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values for the elderly group versus the young group comparison on the 0-back versus Baseline contrast.

Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Right Cingulate Gyrus	24	4.86	4.16	697	0.045	6	-22	36
	24	4.34	3.81			6	13	29
Left Cingulate Gyrus	24	3.59	3.26			-2	-8	35
Right Postcentral Gyrus	43	3.56	3.23	712	0.043	59	-9	15
Right Insula	13	2.89	2.7			51	-28	18
Right Precentral Gyrus	6	2.57	2.43			50	-7	22

Note: * BA refers to Brodmann's Areas.

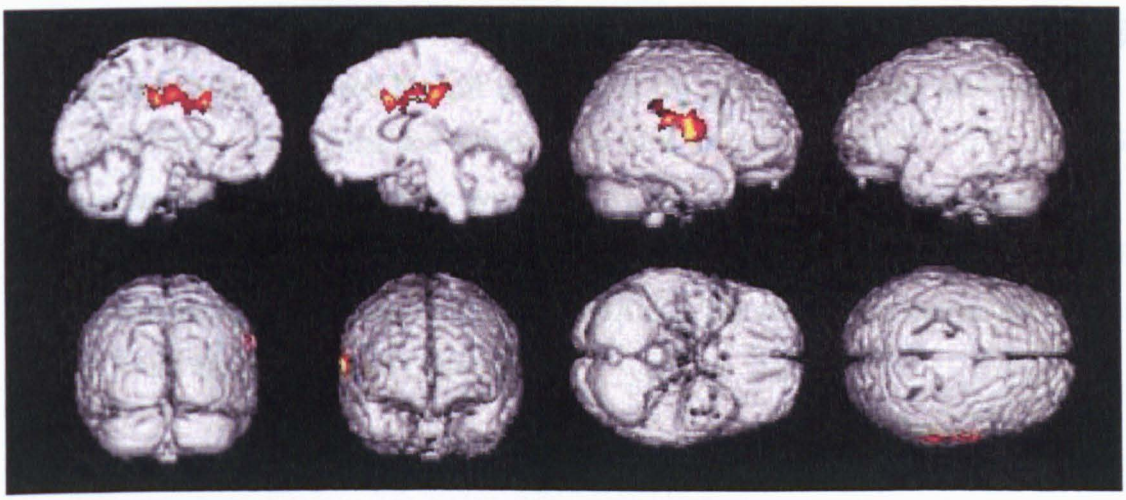

Fig 3.12: Significant differences in activation for the elderly group versus young group comparison on the 0-back versus Baseline contrast.

3.9.7.3 fMRI Experiment 1b: Detection of Areas Involved with a Light Working Memory Load

The second comparison that was performed with the fMRI data was that of the 1-back condition versus the 0-back condition. The 1-back task was considered to consist of a light working memory load e.g. the participant had to always maintain one letter in memory. Note that additional processes were required i.e. constantly updating this letter, inhibiting the letters presented previous to this in the sequence and

remembering what was required during the task (e.g. which condition they were being tested on). The 0-back task was the vigilance condition that was described above.

Young Group: For each participant all of the 1-back conditions versus 0-back conditions were modelled session by session. This contrast compared the 1-back (light working memory load) condition to the 0-back (vigilance task). This comparison was predicted to highlight the areas used in order to perform a working memory task with a light load. A random effects analysis of the 17 available sessions was again carried out.

Significant activation was observed in the left inferior frontal gyrus (BA 47), the inferior parietal lobule bilaterally (BA 40), the left superior parietal lobule (BA 7), the right postcentral gyrus (BA 40), the right middle temporal gyrus (BA 21), the left superior temporal gyrus (BA 22), the right superior temporal gyrus (BA 13), the right fusiform gyrus (BA 20), and the left insula (BA 13) when a threshold was used of $p < 0.01$ (corrected). Additional activations were also observed at the $p < 0.01$ threshold (uncorrected) in the left precentral gyrus (BA 6), the right inferior frontal gyrus (BA 13, 45 and 47), the right middle frontal gyrus (BA 10), the middle frontal gyrus bilaterally (BA 6), and the right superior frontal gyrus (BA 6). The sites of activation are listed in Table 3.8 and are displayed in Figure 3.13.

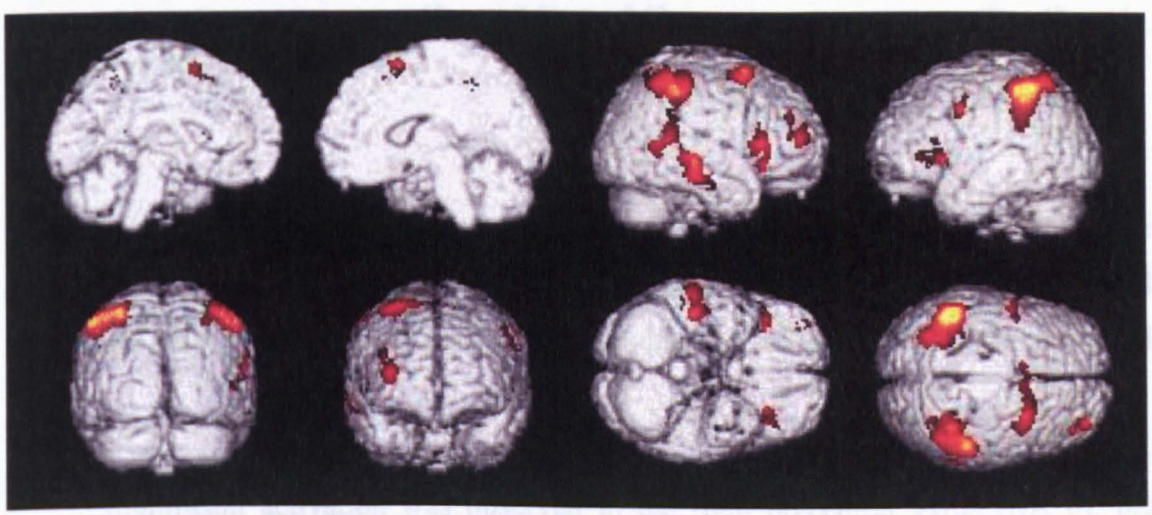

Fig 3.13: The sites of activation found for the 1-back versus 0-back contrast in the young group (corrected and uncorrected levels of significance).

Table 3.8

The sites of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the 1-back versus 0-back contrast in the young group.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Insula	13	7.52	4.85	555	0.030	-30	18	12
Left Superior Temporal Gyrus	22	4.7	3.67			-48	13	-4
Left Inferior Frontal Gyrus	47	3.84	3.18			-30	27	-5
Left Superior Parietal Lobule	7	6.66	4.55	2193	0.000	-30	-55	60
Left Inferior Parietal Lobule	40	6.54	4.5			-42	-44	50
	40	6.59	4.5			-50	-36	48
Right Postcentral Gyrus	40	6.37	4.43	1586	0.000	53	-31	48
Right Inferior Parietal Lobule	40	5.61	4.11			34	-36	48
	40	5.05	3.85			48	-48	56
Right Middle Temporal Gyrus	21	5.41	4.02	1233	0.000	59	-26	-5
Right Fusiform Gyrus	20	5.12	3.89			44	-26	-14
Right Superior Temporal Gyrus	13	4.59	3.61			59	-40	19
b)					p-value uncorrected			
Left Precentral Gyrus	6	3.95	3.25	136	0.05	-44	4	37
Left Middle Frontal Gyrus	6	3.46	2.94			-51	2	39
Left Precentral Gyrus	6	3.3	2.84			-57	5	31
Right Middle Frontal Gyrus	6	6.22	4.37	466	0.001	30	13	58
	6	4.9	3.77			38	11	55
Right Superior Frontal Gyrus	6	3.64	3.06			12	15	60
Right Inferior Frontal Gyrus	13	5.56	4.09	447	0.001	42	24	8
	45	4.85	3.75			50	20	5
	47	3.89	3.22			40	23	-8
Right Middle Frontal Gyrus	10	5.48	4.05	231	0.014	36	53	8
	10	3.49	2.92			40	44	24
	10	2.86	2.59			42	43	11

Note: * BA refers to Brodmann's Areas.

Elderly Group: The group of elderly participants were again analysed using the same method as that used for the young. The analysis of each individual was performed session by session, after which a random effects analysis of the 16 sessions was carried out.

Significant activation was observed in the right precentral gyrus (BA 6), the right middle frontal gyrus (BA 13) and the right insula (BA 13), at the $p < 0.01$ threshold (corrected). Additional activations were also observed at the uncorrected

level of significance in the left middle frontal gyrus (BA 9), the left inferior parietal lobule (BA 40), the left superior parietal lobule (BA 7), the left precuneus (BA 7), the left inferior temporal gyrus (BA 37), the left middle occipital gyrus (BA 19) and the right lentiform nucleus (medial globus pallidus, lateral globus pallidus and putamen). The areas of activation are shown in Table 3.9 and in Figure 3.14.

Table 3.9

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the 1-back versus 0-back contrast in the elderly group.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Right Precentral Gyrus	6	6.29	4.34	1215	0.000	48	1	28
Right Insula	13	5.02	3.79			32	23	3
Right Middle Frontal Gyrus	9	4.79	3.64			36	11	25
b)					p-value uncorrected			
Left Inferior Parietal Lobule	40	7.98	4.91	190	0.026	-50	-36	50
	40	3.16	2.72			-44	-43	39
Left Middle Frontal Gyrus	9	5.83	4.15	144	0.048	-38	13	32
	9	5.11	3.89			-36	27	26
Left Inferior Temporal Gyrus	37	4.53	3.54	209	0.021	-50	-72	2
Left Middle Occipital Gyrus	19	4.11	3.31			-50	-60	-5
Left Fusiform Gyrus	19	3.91	3.2			-40	-72	-12
Left Superior Parietal Lobule	7	4.09	3.3	211	0.02	-30	-52	45
Left Precuneus	7	4.07	3.29			-22	-56	51
Left Superior Parietal Lobule	7	3.67	3.05			-34	-66	44
Right Lentiform Nucleus		4.34	3.44	298	0.007	12	-6	-5
		4.16	3.34			14	2	-5
		3.82	3.14			26	-3	11

Note: * BA refers to Brodmann's Areas.

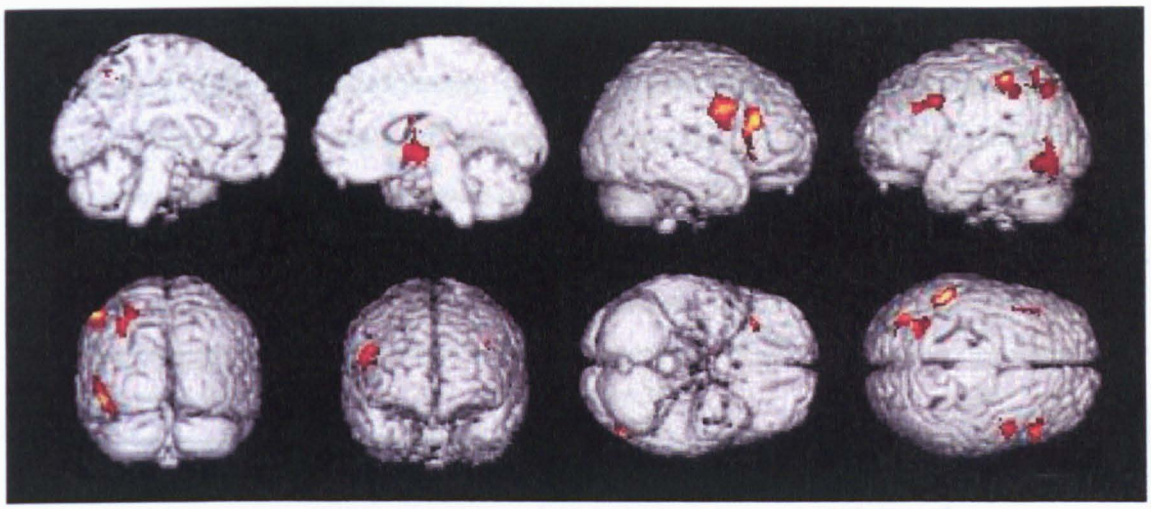

Fig 3.14: The sites of activation found in the elderly for the 1-back versus 0-back contrast (activated areas at the corrected and uncorrected levels of significance are displayed).

At the $p < 0.05$ level of significance additional activation was observed in the right parahippocampal gyrus (BA 27) and the right cerebellum (culmen).

Young Group versus Elderly Group Comparison: Statistical analysis was again carried out using a t-test in order to compare the young group to the elderly group on the 1-back versus 0-back contrast. The 17 sessions of the young participants were compared to the 16 sessions of the elderly participants. The areas of significant activation can be seen in Table 3.10 and in Figure 3.15.

Significant differences in activation were revealed in the right inferior parietal lobule (BA 40) and the right postcentral gyrus (BA 3 and 5) when the $p < 0.01$ threshold was used (corrected). Additional activations were also observed in the left postcentral gyrus (BA 3), the left inferior parietal lobule (BA 40), the right middle temporal gyrus (BA 21 and 22) and the right superior temporal gyrus (BA 22 and 39) when an uncorrected level of significance was employed.

Table 3.10

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the young group versus the elderly group comparison on the 1-back versus 0-back contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Right Inferior Parietal Lobule	40	5.1	4.31	910	0.005	55	-31	46
Right Postcentral Gyrus	5	3.77	3.39			38	-42	61
	3	3.74	3.37			30	-38	46
b)					p-value uncorrected			
Left Postcentral Gyrus	3	4.02	3.58	581	0.001	-32	-32	51
Left Inferior Parietal Lobule	40	3.72	3.36			-38	-39	39
Right Middle Temporal Gyrus	22	4.96	4.22	493	0.002	53	-35	0
Right Superior Temporal Gyrus	22	4.91	3.79			55	-13	3
Right Middle Temporal Gyrus	21	3.41	3.12			61	-24	-4
Right Superior Temporal Gyrus	39	4.15	3.67	204	0.035	50	-56	6

Note: * BA refers to Brodmann's Areas.

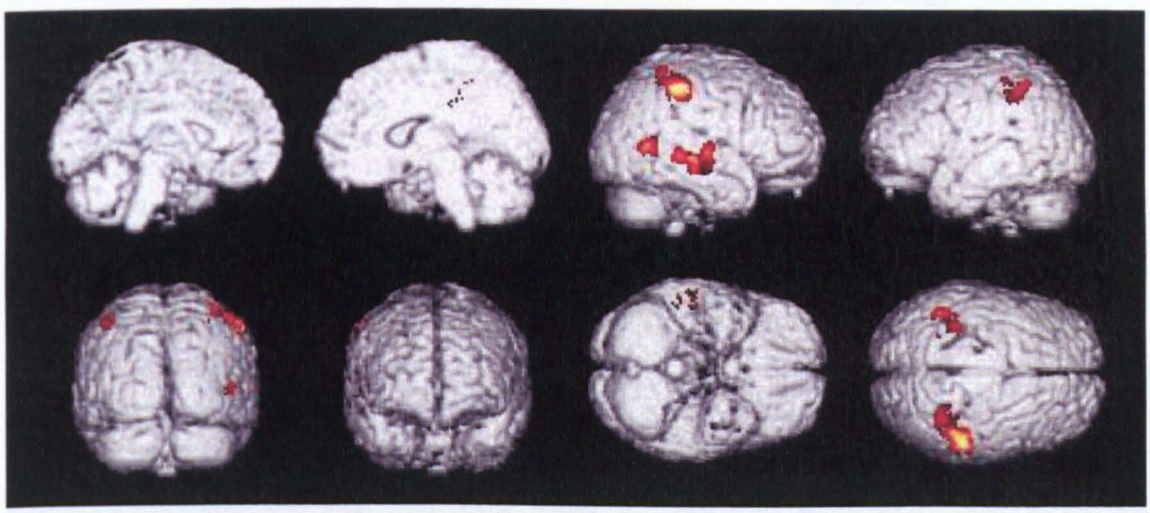

Fig 3.15: The areas that differed significantly in the comparison of the young group to the elderly group on the 1-back versus 0-back contrast (the differences at the corrected and uncorrected level of significance can be seen).

Elderly group versus Young group Comparison: The elderly group were also compared to the young group on the 1-back versus 0-back contrast. A t-test was used to compare the 16 sessions of the elderly participants to the 17 sessions of the young participants.

At the $p < 0.01$ threshold (corrected) the right lingual gyrus (BA 18/19) and the right parahippocampal gyrus (BA 30) were activated. At the uncorrected level, activations included the right inferior frontal gyrus (BA 47) and the right lentiform nucleus (medial globus pallidus). The areas of activation are listed in Table 3.11 and are shown in Figure 3.16.

Table 3.11

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the elderly group versus the young group comparison on the 1-back versus 0-back contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Right Lingual Gyrus	19	6.78	5.27	3364	0.000	20	-66	-7
	18	4.69	4.05			6	-72	0
Right Parahippocampal Gyrus	30	4.41	3.86			-10	-43	4
b)					p-value uncorrected			
Right Lentiform Nucleus		4.3	3.78	220	0.029	14	0	-3
Right Inferior Frontal Gyrus	47	3.08	2.86			18	9	-14

Note: * BA refers to Brodmann's Areas.

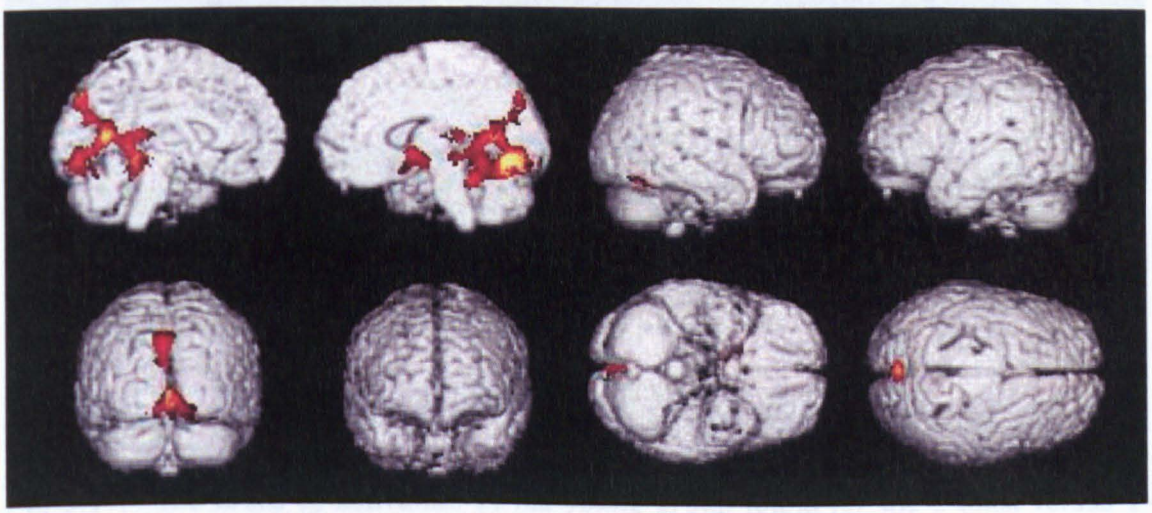

Fig 3.16: Differences in activation for the comparison of the elderly group to the young group on the 1-back versus 0-back contrast (the differences at the corrected and uncorrected level of significance are displayed).

3.9.7.4 fMRI Experiment 1c: Detection of Areas Associated with a More Demanding Working Memory Task

This comparison was predicted to reveal those areas which are used to cope with more demanding working memory loads. For each participant all of the 2-back conditions versus 1-back conditions were modelled session by session.

Young Group: A random effects analysis of the 17 sessions was carried out. The activations can be seen in Table 3.12 and in Figure 3.17. Significant activation was seen in the left inferior frontal gyrus (BA 9, 10 and 44), the left middle frontal gyrus (BA 10 and 47), the right middle frontal gyrus (BA 6), the middle frontal gyrus bilaterally (BA 9), the right superior frontal gyrus (BA 10), the superior frontal gyrus bilaterally (BA 6 and 8), the left inferior parietal lobule (BA 40), the precuneus bilaterally (BA 7), the fusiform gyrus bilaterally (BA 37), the right lingual gyrus (BA 18), the left cingulate gyrus (BA 32), the left thalamus (medial dorsal nucleus) and the left caudate body ($p < 0.01$, corrected). Activation also occurred in the right inferior frontal gyrus (BA 47) at the uncorrected level of significance.

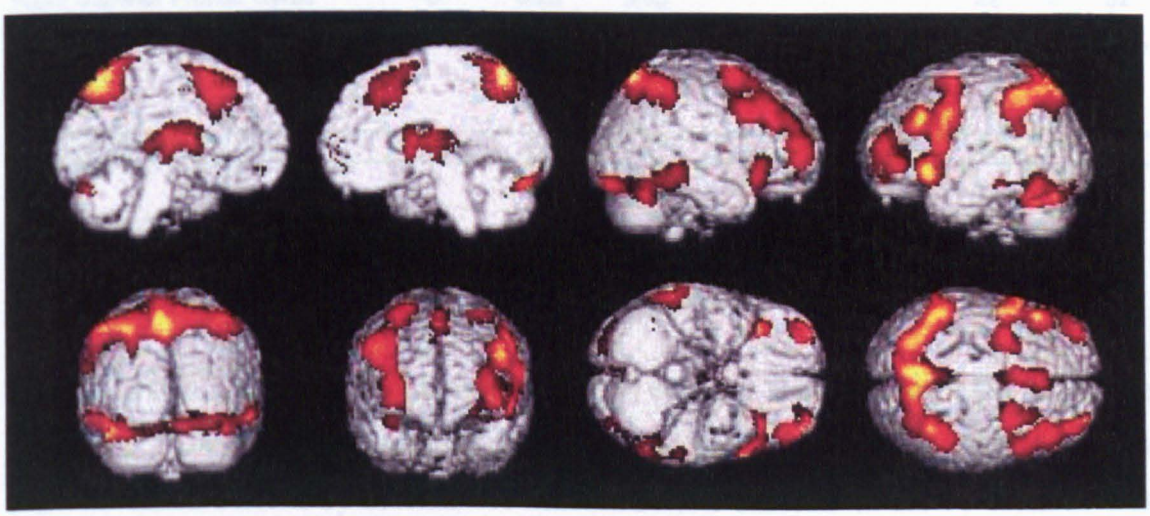

Fig 3.17: The areas of activation in the young group found for the 2-back versus 1-back comparison (the sites of activation are shown for both the corrected and uncorrected levels of significance).

Table 3.12

The sites of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the young group on the 2-back versus 1-back contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Middle Frontal Gyrus	9	9.17	5.35	4163	0.000	-44	27	28
Left Inferior Frontal Gyrus	9	7.99	5			-46	7	27
	44	7.74	4.92			-55	12	16
Left Thalamus		7.2	4.74	1666	0.000	-4	-15	12
Left Caudate Body		6.4	4.45			-14	-13	21
		5.54	4.08			-8	0	9
Left Cingulate Gyrus	32	6.44	4.46	1448	0.000	-2	20	41
Left Superior Frontal Gyrus	6	6.39	4.44			-6	12	51
	8	5.1	3.87			4	30	46
Left Middle Frontal Gyrus	47	6.05	4.3	967	0.000	-40	41	-5
Left Inferior Frontal Gyrus	10	5.37	4			-40	54	-1
Left Middle Frontal Gyrus	10	5.3	3.97			-36	53	7
Left Fusiform Gyrus	37	11.35	5.86	2487	0.000	-46	-55	-19
Right Fusiform Gyrus	37	6.58	4.52			42	-59	-19
Right Lingual Gyrus	18	6.26	4.39			12	-78	-15
Right Precuneus	7	9.88	5.53	6456	0.000	12	-63	62
Left Inferior Parietal Lobule	40	9.04	5.31			-48	-42	50
Left Precuneus	7	8.14	5.05			-4	-63	57
Right Superior Frontal Gyrus	10	5.94	4.26	2459	0.000	36	53	18
Right Middle Frontal Gyrus	9	5.32	3.98			51	13	34
Right Middle Frontal Gyrus	6	5.25	3.95	750	0.020	36	9	55
Right Superior Frontal Gyrus	6	5.25	3.95			22	9	62
	8	3.7	3.1			30	22	52

b)					p-value uncorrected			
Right Inferior Frontal Gyrus	47	5.4	4.02	455	0.004	36	21	-11

Note:
* BA refers to Brodmann's Areas.

Elderly Group: The elderly data were analysed with the same method used to analyse the young. For each participant all of the 2-back conditions versus 1-back conditions were modelled session by session. A random effects analysis of the 16 sessions was carried out.

The left inferior frontal gyrus (BA 45), the left middle frontal gyrus (BA 9), the left supramarginal gyrus (BA 40), the right inferior parietal lobule (BA 40), the left

superior parietal lobule (BA 7) and the left claustrum were activated to a significant level at the $p < 0.01$ threshold (corrected). Activation was also seen in the right inferior frontal gyrus (BA 47), the middle frontal gyrus bilaterally (BA 6 and 10), the right superior frontal gyrus (BA 6 and 8), the right medial frontal gyrus (BA 8), the right insula (BA 13), the right thalamus and the right lentiform nucleus (putamen), when an uncorrected threshold was used. See Table 3.13 for the details of the activations and Figure 3.18 for a visual presentation of the activated areas.

Table 3.13

The areas of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the elderly group on the 2-back versus 1-back contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Supramarginal Gyrus	40	5.89	4.17	1856	0.000	-42	-47	36
Left Superior Parietal Lobule	7	5.28	3.91			-12	-59	58
	7	5.02	3.79			-38	-68	46
Left Claustrum		5.5	4.01	1596	0.000	-28	25	1
Left Middle Frontal Gyrus	9	5.33	3.93			-53	15	32
Left Inferior Frontal Gyrus	45	5.08	3.82			-48	25	4
Right Inferior Parietal Lobule	40	4.39	3.46	682	0.000	42	-39	39
	40	4.32	3.43			50	-50	41
	40	4.08	3.29			44	-50	49
b)					p-value uncorrected			
Left Middle Frontal Gyrus	6	8.18	4.98	450	0.002	-24	-2	46
	6	3.89	3.18			-30	13	58
	6	3.1	2.68			-36	5	51
Left Middle Frontal Gyrus	10	4.35	3.44	174	0.034	-22	59	6
	10	4.3	3.42			-34	55	5
	10	3.55	2.98			-44	49	7
Right Middle Frontal Gyrus	6	8.85	5.16	354	0.004	34	14	53
	6	5.4	3.96			30	1	59
Right Inferior Frontal Gyrus	47	5.41	3.97	366	0.004	36	31	0
Right Insula	13	4.45	3.5			32	23	-3
Right Middle Frontal Gyrus	10	3.8	3.13			38	53	5
Right Thalamus		5.3	3.92	295	0.008	4	-9	15
Right Lentiform Nucleus		4.25	3.39			18	3	13
Right Thalamus		3.54	2.97			18	-7	15
Right Superior Frontal Gyrus	8	5.23	3.89	464	0.001	4	31	43
Right Medial Frontal Gyrus	8	4.89	3.72			0	22	47
Right Superior Frontal Gyrus	6	4.28	3.41			10	16	47

Note: * BA refers to Brodmann's Areas.

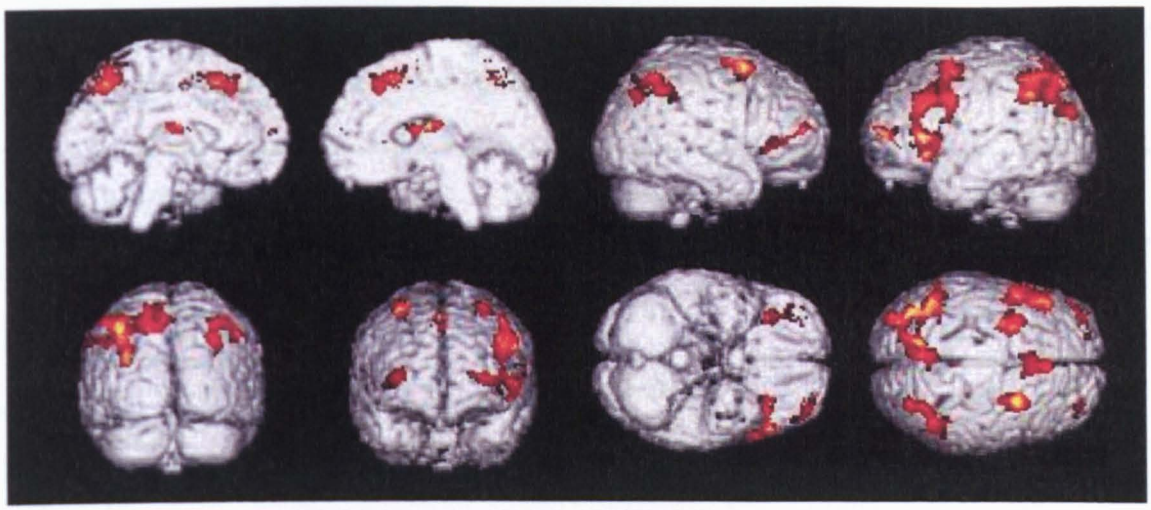

Fig 3.18: The sites of activation found in the elderly for the 2-back versus 1-Back comparison (both for the corrected and uncorrected activations).

Young Group versus Elderly Group Comparison: A t-test was again used to compare the young group to the elderly group on the 2-back versus 1-back contrast. The 17 sessions of the young participants were compared to the 16 sessions of the elderly participants.

At the $p < 0.01$ level of significance (uncorrected), significant differences in activation were seen in the left inferior frontal gyrus (BA 47), the left inferior parietal lobule (BA 40), the left postcentral gyrus (BA 7), the superior parietal lobule bilaterally (BA 7), the right precuneus (BA 7), the cingulate gyrus bilaterally (BA 32), the left anterior cingulate (BA 32) and the left lentiform nucleus (putamen). See Table 3.14 and Figure 3.19 for details of the differences.

Table 3.14

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the young group versus the elderly group on the 2-back versus 1-back contrast.

Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Inferior Parietal Lobule	40	4.63	4	442	0.006	-38	-39	39
Left Superior Parietal Lobule	7	3.42	3.13			-26	-62	51
Left Inferior Parietal Lobule	40	3.15	2.91			-46	-42	48
Left Lentiform Nucleus		3.48	3.18	239	0.034	-30	0	-3
Left Inferior Frontal Gyrus	47	3.29	3.02			-36	15	-11
Right Precuneus	7	4.56	3.96	323	0.016	10	-61	64
Left Postcentral Gyrus	7	4.08	3.62			-6	-53	62
Right Superior Parietal Lobule	7	3.95	3.53			18	-65	62
Right Cingulate Gyrus	32	3.85	3.46	279	0.023	6	12	36
Left Cingulate Gyrus	32	3.46	3.16			-4	12	42
Left Anterior Cingulate	32	3.11	2.88			-12	23	26

Note: * BA refers to Brodmann's Areas.

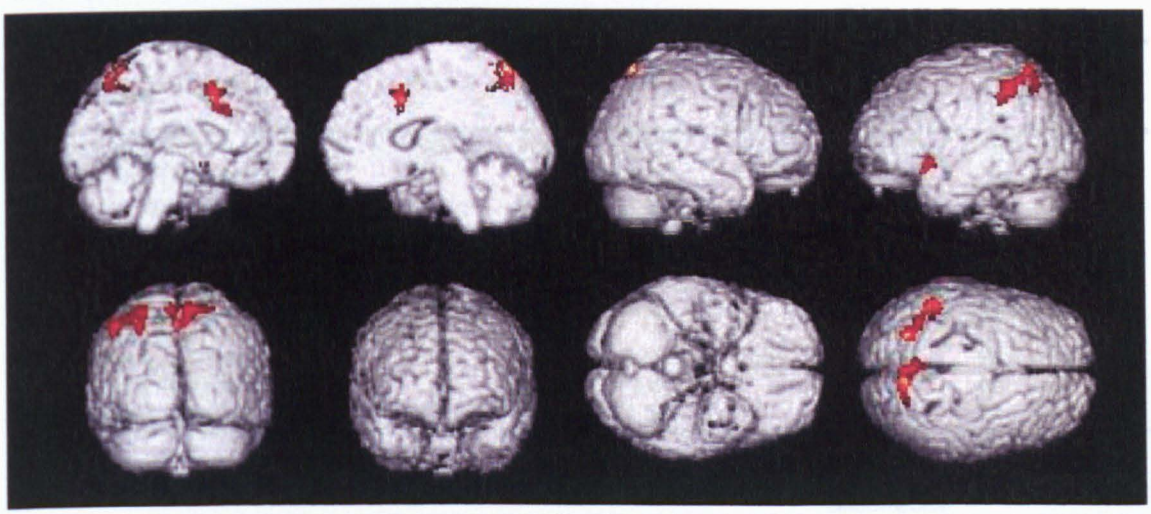

Fig 3.19: The sites showing significant differences in activation for the comparison of the young group to the elderly group on the 2-back versus 1-back contrast.

Elderly Group versus Young Group Comparison: The converse t-test was applied in order to compare the elderly group to the young group on the 2-back versus 1-back contrast. The 16 sessions of the elderly participants were compared to the 17 sessions of the young participants.

The results of this comparison revealed significant differences in activation in the left inferior parietal lobule (BA 39), the right middle temporal gyrus (BA 39), the left superior temporal gyrus (BA 39), the right fusiform gyrus (BA 37), the left parahippocampal gyrus (BA 19), the left middle occipital gyrus (BA 19), the left posterior cingulate (BA 29) and the left caudate tail ($p < 0.01$, corrected). Further activations were observed in the left lingual gyrus (BA 18), the left inferior occipital gyrus (BA 17), the left cuneus (BA 17), the right insula (BA 13) and the caudate head bilaterally (uncorrected). The areas that differed significantly are listed in Table 3.15 and can be seen in the rendering shown in Figure 3.20.

Table 3.15

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the elderly group versus the young group comparison on the 2-back versus 1-back contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Inferior Parietal Lobule	39	4.49	3.91	919	0.010	-36	-62	38
Left Superior Temporal Gyrus	39	4.2	3.71			-34	-57	30
Left Middle Occipital Gyrus	19	3.85	3.46			-46	-73	9
Left Caudate Tail		3.82	3.43	766	0.025	-26	-40	15
Left Posterior Cingulate	29	3.77	3.39			-10	-50	8
Left Parahippocampal Gyrus	19	3.56	3.23			-26	-41	-3
Right Fusiform Gyrus	37	5.62	4.63	5554	0.000	40	-45	-10
Right Middle Temporal Gyrus	39	5.24	4.4			48	-63	27
Right Fusiform Gyrus	37	4.59	3.98			28	-40	-15
b)					p-value uncorrected			
Left Cuneus	17	3.61	3.27	323	0.016	-18	-73	11
Left Lingual Gyrus	18	3.11	2.88			-22	-76	-3
Left Inferior Occipital Gyrus	17	3.09	2.86			-20	-90	-7
Right Caudate Head		4.79	4.11	557	0.003	14	25	1
Left Caudate Head		4.44	3.87			-14	27	2
Right Insula	13	3.71	3.35	223	0.040	36	-3	17
Right Insula	13	3.25	3			36	-17	14
Right Insula	13	2.99	2.78			34	-8	24

Note:
* BA refers to Brodmann's Areas.

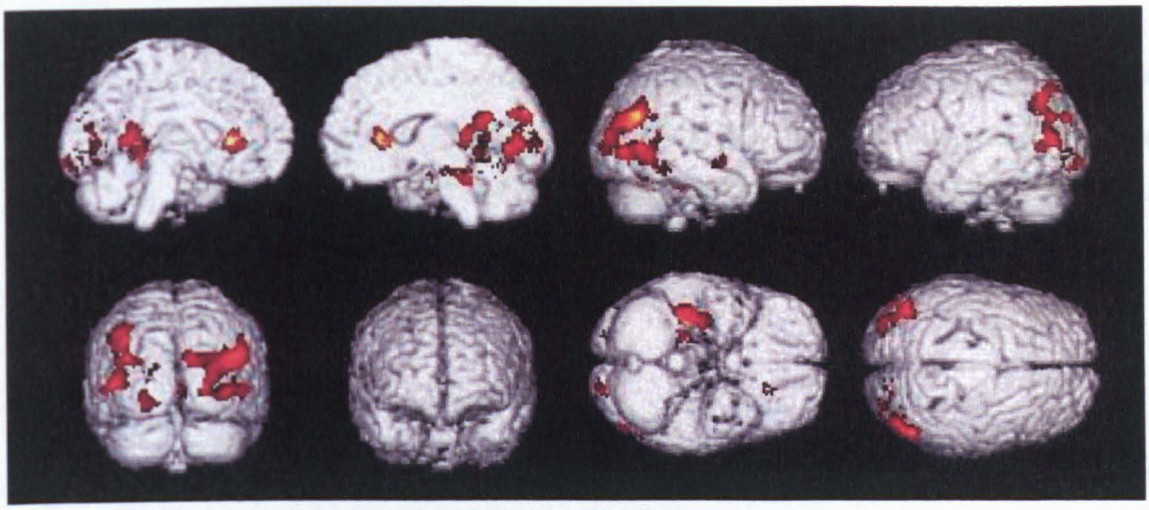

Fig 3.20: The areas showing significant differences in activation for the comparison of the elderly group to the young group on the 2-back versus 1-back contrast (both corrected and uncorrected thresholds are displayed).

3.9.7.5 fMRI Experiment 1d: Detection of the Areas Used as Working Memory Load is Increased

The fourth comparison that was performed with the fMRI data was the parametric design, which incorporated the 2-back, 1-back and 0-back. The 2-back condition was the more demanding of the working memory conditions, the 1-back was the condition that consisted of a light working memory load and the 0-back condition was the vigilance task. For each participant all of the parametric comparisons were modelled session by session. This comparison was predicted to expose the areas that would be activated in response to increments in working memory load (i.e. the relatively simple vigilance task to the light working memory load, and the light working memory load to the more demanding working memory load).

Young Group: A random effects analysis of the 17 sessions was carried out. Activation was detected in the left superior frontal gyrus (BA 6), the right superior frontal gyrus (BA 8 and BA 10), the right middle frontal gyrus (BA 6), the middle frontal gyrus bilaterally (BA 9), the left precentral gyrus (BA 6), the left inferior parietal lobule (BA 40), the right precuneus (BA 7), the right middle temporal gyrus (BA 20), the fusiform

gyrus bilaterally (BA 37), the left caudate body and the left thalamus ($p < 0.01$, corrected). Additional activations were also seen in the right inferior frontal gyrus (BA 47) and the right superior temporal gyrus (BA 38), when investigated with an uncorrected threshold. Table 3.16 shows the details of each of the clusters of activation. These can be viewed in Figure 3.21.

Table 3.16

The sites of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the young group on the parametric design.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Fusiform Gyrus	37	11.28	5.85	2441	0.000	-48	-59	-21
Right Middle Temporal Gyrus	20	6.88	4.63			63	-41	-11
Right Fusiform Gyrus	37	6.04	4.3			44	-61	-19
Left Middle Frontal Gyrus	9	8.1	5.04	5471	0.000	-44	27	26
Left Precentral Gyrus	6	7.66	4.9			-44	0	31
	6	7.52	4.85			-50	2	37
Left Caudate Body		7.45	4.83	1541	0.000	-14	-13	21
		5.94	4.26			-16	5	18
Left Thalamus		5.77	4.18			-2	-15	12
Left Superior Frontal Gyrus	6	6.6	4.52	1630	0.000	-8	12	51
Left Cingulate Gyrus	32	6.13	4.34			-4	20	41
Right Superior Frontal Gyrus	8	5.23	3.94			4	30	46
Right Precuneus	7	10.93	5.77	7024	0.000	12	-63	62
Left Inferior Parietal Lobule	40	9.84	5.52			-48	-42	50
	40	8.31	5.1			-40	-39	39
Right Middle Frontal Gyrus	6	6.14	4.34	3691	0.000	36	7	57
	9	5.92	4.25			51	13	34
Right Superior Frontal Gyrus	10	5.86	4.22			36	53	16
b)					p-value uncorrected			
Right Inferior Frontal Gyrus	47	5.59	4.1	623	0.001	38	23	-10
Right Superior Temporal Gyrus	38	4.38	3.5			53	15	-6

Note: * BA refers to Brodmann's Areas.

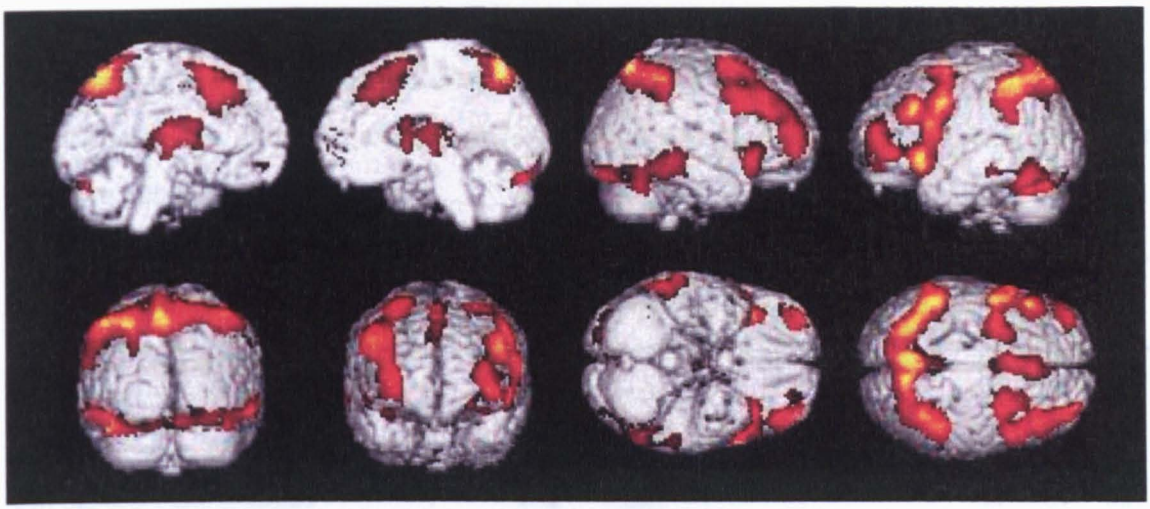

Fig 3.21: The areas of activation found in the young group for the parametric comparison (both corrected and uncorrected activations can be seen).

Elderly Group: The elderly were analysed using the same methods as that used for the young. The parametric contrasts were modelled for each participant session by session, after which a random effects analysis was carried out on the 16 sessions. The results can be seen in Table 3.17 and Figure 3.22.

The areas of activation included the left inferior frontal gyrus (BA 45), the right inferior frontal gyrus (BA 47), the left middle frontal gyrus (BA 6 and 9), the right superior frontal gyrus (BA 8), the right medial frontal gyrus (BA 8), the inferior parietal lobule bilaterally (BA 40), the left superior parietal lobule (BA 7), the right postcentral gyrus (BA 7), the right precuneus (BA 19), and the right insula (BA 13), when the $p < 0.01$ level of significance was used (corrected). An uncorrected threshold revealed additional activation in the left middle frontal gyrus (BA 6 and 10), the caudate head bilaterally, the right caudate body, the right medial dorsal nucleus (thalamus) and the pulvinar (thalamus) bilaterally.

Table 3.17

The areas of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the elderly group on the parametric design.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Middle Frontal Gyrus	6	7.4	4.73	2669	0.000	-24	0	46
Left Inferior Frontal Gyrus	45	5.68	4.09			-46	27	6
Left Middle Frontal Gyrus	9	5.65	4.07			-46	29	32
Left Inferior Parietal Lobule	40	6.43	4.39	2359	0.000	-38	-49	37
Left Superior Parietal Lobule	7	5.42	3.97			-14	-61	60
	7	5.25	3.9			-36	-68	46
Right Insula	13	5.35	3.94	555	0.038	32	23	1
Right Inferior Frontal Gyrus	47	4.88	3.72			36	31	0
Right Superior Frontal Gyrus	8	4.93	3.74	605	0.025	4	31	43
Right Medial Frontal Gyrus	8	4.79	3.67			0	22	47
	8	4.58	3.57			8	20	49
Right Inferior Parietal Lobule	40	4.71	3.63	957	0.002	50	-50	41
Right Precuneus	19	4.48	3.51			32	-64	38
Right Postcentral Gyrus	7	4.46	3.5			6	-55	65
b)					p-value uncorrected			
Left Middle Frontal Gyrus	6	7.95	4.91	353	0.005	32	12	53
	6	5.08	3.82			30	1	59
Left Middle Frontal Gyrus	10	5.39	3.96	190	0.03	-20	59	6
	10	4.71	3.63			-34	55	5
	10	3.83	3.15			-42	45	-2
Left Caudate Head		5.53	4.02	152	0.048	-14	27	2
Right Caudate Head		3.88	3.18			12	23	1
		3.43	2.9			2	20	3
Right Thalamus		4.24	3.39	149	0.05	2	-31	7
Left Thalamus		3.51	2.95			-6	-25	3
Right Thalamus		6.58	4.44	481	0.001	4	-11	15
Right Caudate Body		4.39	3.47			16	3	13
Right Thalamus		3.79	3.12			20	-9	12

Note:

* BA refers to Brodmann's Areas.

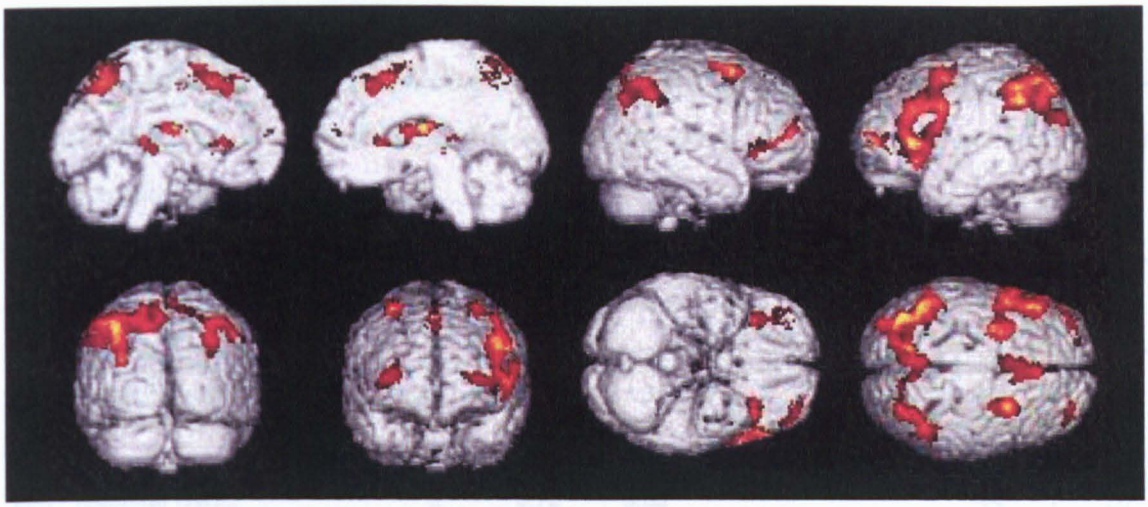

Fig 3.22: The sites of significant activation found in the elderly group for the parametric comparison (both corrected and uncorrected activations can be observed).

Young Group versus Elderly Group Comparison: A t-test was used in order to compare the results of the young group to the elderly group on the parametric contrast. The 17 sessions of the young participants were compared to the 16 sessions of the elderly participants.

When using a level of significance of $p < 0.01$ (uncorrected), the sites of differential activation included the left inferior frontal gyrus (BA 47), the left precentral gyrus (BA 6 and 44), the left middle frontal gyrus (BA 6), the inferior parietal lobule bilaterally (BA 40), the left superior parietal lobule (BA 7), the left superior temporal gyrus (BA 22 and 38), the right superior temporal gyrus (BA 13) and the cingulate gyrus bilaterally (BA 32). Table 3.18 provides details of the areas that differed significantly and Figure 3.23 portrays these differences.

Table 3.18

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the young group versus the elderly group on the parametric contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Inferior Parietal Lobule	40	5.13	4.33	634	0.002	-38	-39	39
Left Inferior Parietal Lobule	40	3.68	3.33			-46	-42	48
Left Superior Parietal Lobule	7	3.53	3.21			-26	-62	51
Left Middle Frontal Gyrus	6	4.3	3.78	244	0.035	-48	0	39
Left Precentral Gyrus	6	3.75	3.38			-44	1	28
Left Precentral Gyrus	44	2.78	2.61			-46	10	12
Left Superior Temporal Gyrus	22	3.86	3.46	228	0.041	-55	9	-7
Left Superior Temporal Gyrus	38	3.44	3.14			-50	17	-13
Left Inferior Frontal Gyrus	47	3.31	3.04			-36	15	-11
Right Cingulate Gyrus	32	3.81	3.42	312	0.019	4	13	36
Left Cingulate Gyrus	32	3.62	3.28			-4	12	42
Left Cingulate Gyrus	32	3.12	2.89			-12	21	28
Right Superior Temporal Gyrus	13	3.57	3.24	259	0.031	57	-42	15
Right Inferior Parietal Lobule	40	3.86	3.46	492	0.005	40	-40	55
Right Inferior Parietal Lobule	40	3.55	3.22			38	-38	48
Right Inferior Parietal Lobule	40	2.92	2.72			50	-38	53

Note:
* BA refers to Brodmann's Areas.

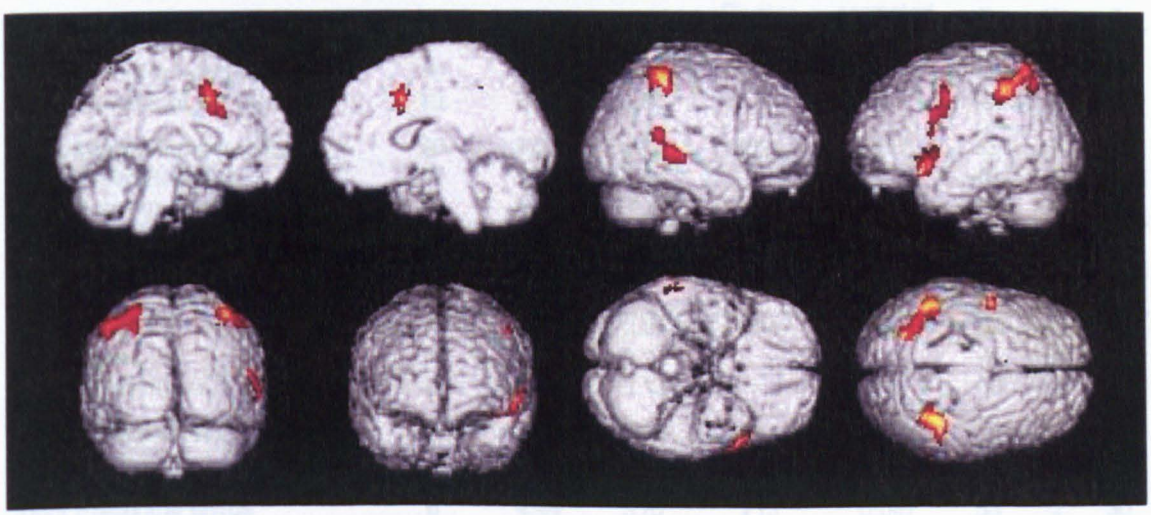

Fig 3.23: The areas of differential activation in the comparison of the young group to the elderly group on the parametric contrast.

Elderly Group versus Young Group Comparison: A t-test was again used, this time to compare the elderly group to the young group on the parametric contrast. The 16 sessions of the elderly participants were compared to the 17 sessions of the young participants.

Differences in activation were seen in the left inferior parietal lobule (BA 39), the left angular gyrus (BA 39), the right middle temporal gyrus (BA 39), the right fusiform gyrus (BA 37), the left middle occipital gyrus (BA 19) and the right superior occipital gyrus (BA 19), at the $p < 0.01$ level of significance (corrected). At an uncorrected threshold, further differences were observed in the right precentral gyrus (BA 4 and 6), the left lingual gyrus (BA 18), the left cuneus (BA 17 and 19) and the caudate head bilaterally.

Table 3.19

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the elderly group versus the young group comparison on the parametric contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Angular Gyrus	39	5.46	4.54	1162	0.003	-36	-60	36
Left Inferior Parietal Lobule	39	4.11	3.65			-42	-66	42
Left Middle Occipital Gyrus	19	3.99	3.56			-42	-71	9
Right Middle Temporal Gyrus	39	5.69	4.68	8031	0.000	53	-63	29
Right Fusiform Gyrus	37	5.5	4.56			40	-45	-10
Right Superior Occipital Gyrus	19	4.77	4.1			38	-71	22
b)					p-value uncorrected			
Left Cuneus	17	3.61	3.27	604	0.002	-18	-73	13
Left Cuneus	19	3.52	3.21			-8	-88	27
Left Lingual Gyrus	18	3.41	3.12			-18	-95	-4
Right Caudate Head		5.16	4.35	584	0.002	12	23	1
Left Caudate Head		4.88	4.17			-14	27	2
Right Precentral Gyrus	6	4.44	3.87	213	0.047	53	-2	30
Right Precentral Gyrus	6	3.1	2.87			59	-14	39
Right Precentral Gyrus	4	2.52	2.39			50	-12	36

Note:

* BA refers to Brodmann's Areas.

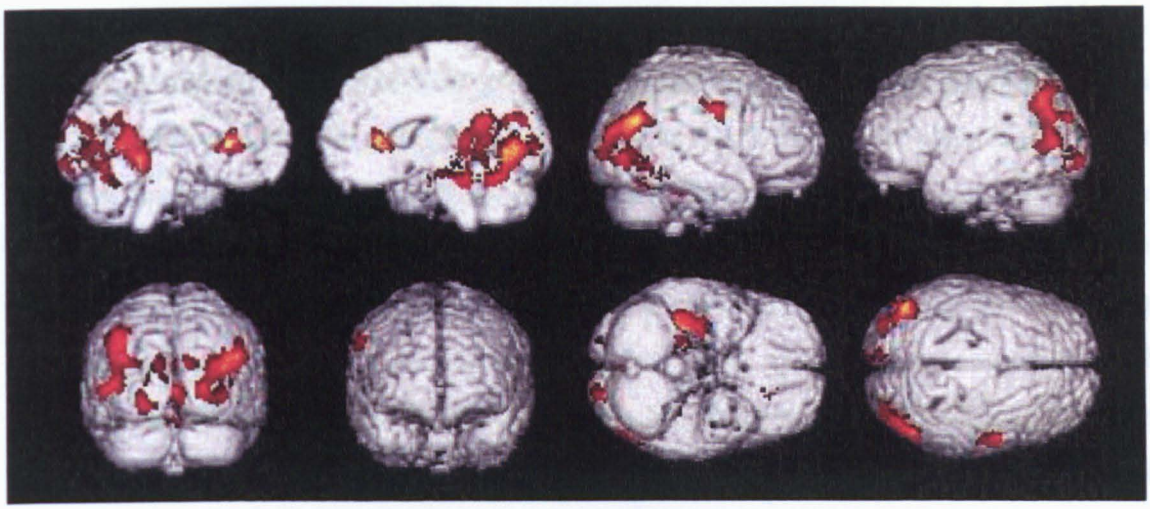

Fig 3.24: The areas that differed significantly in activation for the comparison of the elderly group to the young group on the parametric contrast (both corrected and uncorrected thresholds are displayed).

3.9.8 Discussion

3.9.8.1 fMRI Experiment 1a: Regions Involved in Sustained Attention, Target Detection and Visual Discrimination

In the 0-back versus baseline contrast (vigilance comparison), although similar levels of perceptual input was presented, for example, in both conditions the same size of black coloured font was used on a white background in order to portray the stimuli, the tasks did vary in a number of important ways. The 0-back task involved the participant responding with a button press every time an "X" was present in a sequence of letters (vigilance). The Baseline task simply involved the participant viewing a sequence of "#" symbols and responding (presumably more automatically) with a button press on every presentation. It would therefore, be expected that the statistical comparison would reveal the activation corresponding to vigilance and attention (discriminating the letter X from the other letter stimuli). Activation would also be expected in the areas used for the perception of letters, as this process would be needed in the 0-back condition but not the Baseline condition.

As central executive processes have not been mapped onto the underlying neuro-anatomical regions as successfully as the other working memory components and as central executive demands tend to vary considerably between various tasks it is difficult to predict exactly which areas will be activated in response to the vigilance task. Some processes that occur during the task can be predicted, however, and the activations found in previous studies compared. Examples of some central executive processes that may be used in order to complete the vigilance task may be, the maintenance of attention on the regularly changing stimuli, the inhibition of responses to the distracter letters (which were not targets), the recognition of the target letter and the subsequent response. The baseline task may be viewed as being more automated and less demanding of attentional resources.

Young Group: The 0-back (vigilance) task was more demanding of central executive resources, compared to the baseline task, and activation of the right middle frontal gyrus (BA 46) was observed in the young group of participants in the present study. Pardo et al. (1991) stated that vigilance appears to be one component of attention which is right-lateralised. The right middle frontal gyrus has previously been activated in response to increases in attentional task demands, for example, in the rapid visual information processing task of Lawrence et al. (2003), the visual dot dimming tasks of Lewin et al. (1996) and Pardo et al. (1991), and the parametric n-back designs of Braver et al. (1997), Jonides et al. (1997) and Veltman et al. (2003).

The attention tasks of, for example, Lawrence et al. (2003), Lewin et al. (1996) and Pardo et al. (1991) methodologically vary from the vigilance task used in the present study, but activation can nonetheless be seen in the right middle frontal gyrus in all the tasks. The parametric n-back tasks of the Braver et al. (1997), Jonides et al. (1997) and Veltman et al. (2003) are much more similar to the paradigm used in the current study and again reveal activation of the right middle frontal gyrus. The observed activation in the middle frontal gyrus in the present study may therefore, be due to the processes that are required for sustained attention which lead to the successful completion of the vigilance task.

The 0-back task although requiring the inhibition of responses to letters that were not the letter "X", did not seem to activate frontal regions as reported in the literature involving inhibitive processes. For example, the left inferior frontal gyrus,

BA 45, found in the working memory interference studies by D'Esposito, Postle, Jonides and Smith (1999) and Jonides, Smith, Marshuetz, Koeppe and Reuter-Lorenz (1998), or the bilateral frontal areas, BA 44 and 45, found in the go/no-go study by Konishi et al. (1999). Nor did it activate the right frontal areas, BA 9 and 10, which were found in the go/no- go study by Garavan, Ross and Stein (1999). Many studies of inhibition (especially those concerning stroop tasks) generally report a more distributed pattern of activation than in the frontal areas alone.

It is possible that the 0-back task did not require high enough levels of inhibition to provide a signal change in the frontal areas that would be large enough to survive the statistical thresholds. Another explanation could be that as the areas activated in studies of inhibition appear to differ substantially depending on what task and material is used, it is difficult to compare areas of activation found in other studies to the present 0-back study. Inhibitive processes are thought to be active in the 0-back study and may be showing up on the activation maps but it is difficult to say with confidence that the distributed areas that are activated in the experiment are due to inhibition or to one of the other processes that are taking place.

In summary, although it is difficult to interpret the exact cause of the activations due to executive processes, as most studies have more than one executive function which co-occur for the completion of the tasks, the studies mentioned above appear to lend support to the interpretation of the activation of the right middle frontal gyrus (BA 46) in the present study as reflecting demands of executive processes such as sustained attention.

No activation of the cingulate region was observed at the $p < 0.01$ level of significance in young group in the present study (when either corrected or uncorrected for multiple comparisons). Pardo et al. (1991) proposed that the vigilance network encompasses both frontal and superior parietal regions, which can operate independently of midline anterior attentional systems. This appears to be the case as the young group do not seem to activate the anterior cingulate region, at least to a high enough level to show up on the activation maps as significant.

Deactivation of the anterior cingulate region has been thought to occur during sustained attention (Posner & Raichle, 1997). Activation of this region may occur instead during target detection, i.e. as the number of targets in a stimulus set increases,

the activation of the anterior cingulate increases (Posner & Raichle, 1997). It is possible that the young deactivated the anterior cingulate for the majority of the duration of the task and only activated it during the presentation of the target stimulus. Due to the nature of the block design in the current experiment it may be that the activation of the anterior cingulate (during the presentation of the targets) did not reach statistical significance, because of the more lengthy periods of deactivation that were occurring in this region during sustained attention (the presentation of the non-target stimuli).

The results of the young group in the current experiment revealed activation of the left middle occipital gyrus (BA 37). An area in the left middle occipital gyrus (BA 37) was also activated in the study by Flowers et al. (2004), and was suggested to be used in the processing of letters. Flowers et al. (2004) reported that the area of the left extrastriate cortex (the left lateral portion of the middle occipital gyrus, BA 37), that was activated in their study, was used uniquely for alphabetic processing, whereas a more posterior area, namely the left fusiform gyrus (BA 37/19) was commonly activated when identifying either letters, shapes or colour from the same stimulus set.

Other studies also support the role of the ventral extrastriate cortex in letter processing, for example, Polk et al. (2002) proposed that an area on or near the left fusiform gyrus is involved in letter processing. The findings from the Garrett et al. (2000) study also revealed that the left ventrolateral inferior temporal occipital cortex (BA 37) was related to letter recognition. It has been suggested that the left lingual/fusiform gyrus may not be as related as much to lexicality as it may be to visual complexity (Indefrey et al., 1997). The left fusiform gyrus (BA 37) was activated by the young group in the present experiment.

In summary, in the present experiment the young group activated the left middle occipital gyrus (BA 37) and the left fusiform gyrus (BA 37/19). These activations appear to be due to the processing of the letters. The activation of the right middle frontal gyrus (BA 46) seems to be due to the function of the central executive in maintaining alertness (vigilance).

Elderly Group: The activation observed in the elderly participants differed from the activation observed in the young participants. Activation was observed in the left cingulate region (BA 23) and the right cingulate region (BA 24). The cingulate activation observed in the elderly participants might indicate that the elderly were recruiting a midline attentional system in order to complete the task. The young do not appear to recruit this midline attentional system (at least to a level which reaches significance), but rather seem to rely on a central executive component of the attentional network, which appears to be housed in the right middle frontal gyrus.

The activation of the midline region might signify that greater levels of attention are needed to perform the task in the elderly participants. The elderly may be compensating for regions that cannot be activated to the same levels as in the young, by activating the midline attentional region in order to attempt to perform the task as well as possible. An alternative, but less likely explanation, could be that the elderly are voluntarily employing a different behavioural strategy which is equally effective or superior, in comparison to the strategy used by the young participants. It is difficult to decide with absolute certainty which explanation is most appropriate. Compensation appears the most likely explanation however, as previous studies, for example, that of Pardo et al. (1990) have shown that attentionally demanding tasks, such as the stroop, involve activation of the cingulate cortex. The elderly may be activating the cingulate areas because increased effort is needed to inhibit irrelevant information (due to the detrimental effects of ageing). There is also no obvious reason for the elderly adults to attempt to voluntarily use a different strategy than the young adults.

Activation was also observed in the elderly in three areas used for visual discrimination and processing, the left precuneus (BA 19), the right cuneus (BA 17) and the left lingual gyrus (BA 18). Of these regions, the young only activated the left precuneus significantly. It should be noted however, that in the young, the focus of activation in the left precuneus was in Brodmann's area 7, whereas the focus of activation in the elderly was in Brodmann's area 19.

To test whether the elderly were activating other areas that the young activated only at a decreased level, the activations obtained at a more liberal threshold ($p < 0.05$) were also determined in the elderly. The areas of activation that were found in the elderly at this threshold were more similar to the areas of activation observed in the

young. The areas that were activated in the elderly were the left precuneus (BA 7 and 19). Activation in Brodmann's area 7 on the left, has previously been shown to be involved in working memory networks (The vigilance task demands a light working memory load in which the participants must remember to push only when the letter "X" is presented. Amongst other areas that were activated by the elderly participants, the left fusiform gyrus (BA 37), the right fusiform gyrus (BA 19) and the left inferior occipital gyrus (BA 19) were activated. The left fusiform gyrus (BA 37) was also activated in the young and as described above, is involved with the visual discrimination of letters. Additional activation was also found in the right posterior cingulate (BA 30). The right middle frontal gyrus (BA 46) was not activated to a significant level in the elderly.

In summary, the elderly appeared to activate midline regions generally associated with attention, i.e. regions of the cingulate (BA 23, 24 and 30). The elderly also activated regions associated with visual letter discrimination, e.g. the left fusiform gyrus (BA 37). It should be noted however, that the activation in the left fusiform gyrus was only observed at a liberal threshold of significance.

3.9.8.2 fMRI Experiment 1a: The Effect of Ageing on Sustained Attention, Target Detection and Visual Discrimination

Young Group versus Elderly Group Comparison: In the two sample t-test of the young versus the elderly, the young differentially activated the left middle occipital gyrus (BA 37 and BA 18). This may indicate that the young are activating specialised areas used for letter discrimination to a higher level than the elderly.

The young participants also appeared to activate the left inferior frontal gyrus (BA 47) to a higher level than the elderly participants. It may be that this area is being activated due to the selection of response i.e. only to the letter "X". In the literature on semantic memory, activation of the left inferior frontal gyrus occurs during tasks which require selection amongst competing alternatives (e.g. Thompson-Schill, D'Esposito, Aguirre and Farah (1997)). It is possible that the left inferior frontal gyrus may have a more general function concerning selection, than for semantic memory alone (Zhang, Feng, Fox, Gao, & Tan, 2004). An overlap of the function concerning selection

amongst competing alternatives, between memory domains and tasks, might explain the activation that is observed in the present experiment. The young activated this region to a higher level than the elderly.

A significant difference in activation was observed in the left anterior cingulate region (BA 32) during the young versus elderly t-test comparison. A likely explanation may be that for most of the duration of the experiment (i.e. when no targets are present), both the young and the elderly were deactivating the anterior cingulate. Deactivation of the anterior cingulate would be expected during sustained attention and alertness (Posner & Raichle, 1997). Target detection on the other hand is associated with the activation of the anterior cingulate (Posner & Raichle, 1997), and is presumed to be a necessary requirement of the vigilance task. It is therefore likely that the young and indeed the elderly were both periodically activating the anterior cingulate during the presence of a target stimulus and that the difference arose because the young activated this region (when it was called upon) to a greater extent than the elderly. Note that in the random effects analysis of the young group alone, the periodical activation of the anterior cingulate did not reach significance. This may have been because of a prolonged period of deactivation that occurred during the alert state i.e. when no targets were present. The significant difference in activation between the young and the elderly groups in the t-test comparison may have arisen because the level of deactivation was greater in the elderly than in the young (the young were presumed to activate the anterior cingulate to a greater extent than the elderly when targets were present). The anterior cingulate may have been somewhat dysfunctional in the elderly group and they might have under-activated this region when the targets were presented.

Significant differences in activation were found in the right superior temporal gyrus (BA 21 and 22), the right middle temporal gyrus (BA 39) and the left hippocampus in the present study. Paulesu et al. (1993) suggested that the bilateral superior temporal cortex (BA 22) is involved in phoneme processing. Further differences were seen in the lentiform nucleus, bilaterally (left putamen and right medial globus pallidus), showing that the young activated these structures to higher levels than the elderly. These areas of the lentiform nucleus are connected to other brain structures. For example, the putamen projects to both the thalamus and the cortex; and the medial globus pallidus projects to the putamen and the subthalamic nucleus, receiving input from the thalamus (Crossman & Neary, 2000). The connectivity of these structures may

explain the activation in this area (but it does not explain why the young are activating the regions to higher levels than the elderly). Thalamic (and brain stem) activity has however, been suggested to control the transition from relaxed wakefulness to high levels of concentration (Kinomura, Larsson, Gulyas, & Roland, 1996).

No significant differences occurred in the right middle frontal gyrus (BA 46), between the young and the elderly. This finding suggests that comparable levels of activation might be occurring between the young and the elderly groups and that the elderly may be activating the region at a sub-threshold level (which is why no activation was observed in the random effects analysis of the elderly group).

In summary, the young group appeared to activate a number of areas to a higher level than the elderly. Significant differences in activation were found in the visual processing areas of the left middle occipital gyrus (BA 37 and 18). The young also showed higher activation of the left inferior frontal gyrus (BA 47) which may play a role in selecting between competing alternatives. A significant difference was observed in the left anterior cingulate (BA 32) region, perhaps due to the elderly having stronger deactivation in this region than the young. This difference may exist due to a greater rise in the level of activation in the young group that occurs when a target is detected, even though for the majority of the task, the young are likely to be deactivating the anterior cingulate region.

Elderly Group versus Young Group Comparison: No activation was observed at the $p < 0.01$ level of significance for this comparison, but when a less conservative threshold was used ($p < 0.05$) the elderly participants activated the cingulate region (BA 24) bilaterally, to a higher level than the young participants. Although it is not clear exactly what process is taking place in the cingulate region (BA 24), we can be reasonably confident that the significant difference that is observed in this region (via the t-test comparison), is due to the elderly activating to a higher level than the young. The random effects analysis of the elderly group by themselves, confirms that they are activating the right cingulate (BA 24). The elderly group may be activating the cingulate gyrus (BA 24) bilaterally in an attempt to compensate for regions that are not operating as efficiently as those found in the young. It may be the activation of this region that is sustaining the performance of the elderly group. Cingulate regions have

been shown to be active in studies which require high levels of attention e.g. Pardo et al. (1990).

Activation was observed in the right insula (BA 13). This area has been associated with the programming of speech (Dronkers, 1996). Activation was also observed in the right precentral gyrus (BA 6). This area on the motor strip may be involved with controlling voluntary movements. It could be that this area was activated for the planning of language without actual overt speech as proposed by Paulesu et al. (1993). The right postcentral gyrus (BA 43) was also activated, which is a sensory area that receives feedback from joints and tendons. The elderly may be activating these sensorimotor areas as they are devoting more resources to the planning of their responses (and the feedback about these) than the young require. It appears that in addition to recruiting extra attentional areas e.g. the bilateral cingulate cortex (BA 24), the elderly are activating right sided regions to a higher level than the young e.g. the right insula (BA 13), the right postcentral gyrus (BA 43) and the right precentral gyrus (BA 6). It is possible that this finding could fit with the HAROLD hypothesis proposed by Cabeza et al. (2002), but it is difficult to tell if there is a reduction in asymmetry (through the recruitment of right sided areas) because even when using a liberal threshold, no significant activation of the frontal areas can be seen in the random effects analysis of the elderly. The right sided activation can only be seen in the elderly versus young statistical comparison. The only conclusion that can be drawn with some confidence from this comparison (elderly versus young), is that the elderly group activated right sided regions to a higher levels than the young.

In summary, the elderly activated the cingulate cortex (BA 24) bilaterally to higher levels than the young. The elderly may be activating this region, which is associated with attention, in order to compensate for dysfunctional areas that are normally available to the young. The elderly also activated right sensorimotor areas (precentral gyrus, BA 6, and postcentral gyrus, BA 43) to a higher level than the young. The differential activation of these areas might indicate that the elderly are planning their response (and receiving feedback about this) to a greater extent than the young. The right insula (BA 13) was also activated to a higher level in the elderly than the young.

Conclusions: The behavioural scores of the young and the elderly groups did not differ significantly from one another and both groups scored very highly. The young and the elderly could complete the task very well, but the reasons for the differences in the underlying brain activation patterns are not known for certain. Compensation in the elderly may be needed because of a number of possible deficits associated with aging, which may make distinguishing the letter "X" from the sequence of other letters, a more demanding task than for the young participants. The different activation patterns might have occurred because the elderly were unknowingly using a different strategy. For example, the areas of the young brains used for the visual discrimination of letters may be more highly activated than in the elderly, whereas the elderly brains may adopt a strategy which activates additional areas involved in attentional networks, for example regions of the cingulate. The reason for the cingulate activation in the elderly group may be in order to compensate for the lower levels of activation found in the areas involved with visual discrimination. Alternatively, the elderly may have activated the attentional areas along the midline due to a need to compensate for deficits in the frontal executive control of attention.

Evidence for HAROLD cannot be confirmed as the frontal cortex regions of the elderly group were not activated significantly in the random effects analysis. It is therefore, difficult to tell if asymmetry reduction is taking place (compared to the young group). The t-test comparison of the elderly versus the young group showed that the elderly activated the right precentral gyrus (BA 6), the right postcentral gyrus (BA 43) and the right insula (BA 13), to greater levels than the young (note also that all participants were right-handed). This finding suggests that asymmetry reduction may be occurring in the elderly. The suggestion is supported by the observation from the t-test comparison that the young did not activate these frontal regions to a greater extent on the left-side than the elderly, which suggests comparable levels of activation between the young and elderly groups are occurring in these regions. It appears therefore that the young and elderly groups were activating the left precentral gyrus, the left postcentral gyrus and the left insula to somewhat comparable levels, but the elderly group were activating the right homologues of these regions to higher levels than the young.

The right hemi-ageing hypothesis was not supported by the vigilance comparisons. The working memory conditions may require greater bilateral involvement of the hemispheres, which would provide better tests of the hemi-ageing hypothesis than the relatively simple vigilance task.

If convincing evidence of the proposed theories of ageing are to be observed it may be on the more demanding n-back working memory conditions as opposed to the relatively low demands of the vigilance task. Certain effects of ageing on the brain can, however be seen in the vigilance task. These effects of ageing are under-activation and compensation. Under-activation can be seen in two areas, the right middle frontal gyrus (BA 46) and the left middle occipital gyrus (BA 37).

Additional areas of activation that may be employed as mechanisms of compensation can also be observed in the elderly when compared to the young, for example, the posterior cingulate (BA 24) bilaterally. This region may be used to attempt to compensate for dysfunctional areas found in the elderly. Other areas of activation used by the elderly are the right precentral gyrus (BA 6), the right postcentral gyrus (BA 43) and the right insula (BA 13). It should be noted that we do not observe activation that is more diffuse in the elderly group than the young group. The tendency for elderly people to exhibit widespread patterns of activation has been described in other studies of ageing, for example, Reuter-Lorenz (2002).

In summary, during the vigilance task we see no evidence for the hemi-ageing hypothesis. Evidence for HAROLD has been suggested but is not entirely convincing as the conclusions have been based on inferences. Further investigation using the more demanding n-back working memory conditions may provide more compelling evidence in favour of the theories of ageing. Effects of ageing have been observed for the vigilance task however, and these have taken the form of under-activation in regions available to the young, and the activation of regions not recruited by the young, which may be compensatory.

3.9.8.3 fMRI Experiment 1b: Regions Associated with a Light Working Memory Load

When the 1-back condition was compared to the 0-back condition, the activation of various regions associated with a light verbal working memory load would be expected.

Young Group: Significant activation was detected in the left superior parietal lobule (BA 7) of the young group. Studies such as that of Steffener et al. (2001) found that an increase in WM load led to an increase of activation in the superior parietal lobe (BA 7). Alternative fMRI working memory paradigms using the n-back also showed activation of the left superior parietal lobule (BA 7), for example, Awh et al. (1996); Schumacher et al. (1996); Braver et al. (1997).

Activation was observed in the inferior parietal lobule (BA 40) bilaterally and the right postcentral gyrus (BA 40). Activation of left BA 40 has been observed using other n-back working memory paradigms, for example, Awh et al. (1996); Jonides et al. (1997); Veltman et al. (2003). Bilateral activation of BA 40 has also occurred in n-back paradigms, for example, those of Schumacher et al. (1996) and Braver et al. (1997). The left inferior parietal lobule has been suggested to be the neuro-anatomical correlate of the phonological store (Awh et al., 1996). Activation of the right inferior parietal lobule has been proposed to be associated with increased alertness (Posner & Raichle, 1997).

The left inferior frontal gyrus (BA 47) was activated. This area has been activated in other n-back tasks, e.g. Braver et al. (1997). As Broca's area incorporates a portion of BA 47 the activation of the left inferior frontal gyrus (BA 47) could possibly be due to rehearsal processes, or as mentioned previously the activation of this area could be due to a mechanism of selecting between competing alternatives.

Activation was present in the left insula (BA 13). The insular cortex has been activated in other working memory tasks, e.g. Paulesu et al. (1993) and Braver et al. (1997). Paulesu et al. (1993) suggested that the insula is used in phonological processing. The left superior temporal gyrus (BA 22), the right middle temporal gyrus (BA 21) and the right superior temporal gyrus (BA 13) were also activated. Paulesu et al. (1993) suggested that the left superior temporal gyrus (BA 22) is used in phoneme processing.

Contrary to the expectations of the hypotheses, activation was observed in the right fusiform gyrus (BA 20). This activation could reflect greater visual processing of the stimuli that is occurring in the 1-back condition compared to the 0-back condition.

Activation of the right middle frontal gyrus (BA 6 and 10) also occurred. Activation in the right middle frontal gyrus has been suggested to be associated with the vigilance network (Posner & Raichle, 1997). A number of other areas in the PFC were also activated. These were the left precentral gyrus (BA 6), the left middle frontal gyrus (BA 6), the right superior frontal gyrus (BA 6) and the right inferior frontal gyrus (BA 13, 45 and 47). The left precentral gyrus has been implicated in the planning of speech (Dronkers, 1996). The right inferior frontal gyrus (BA 47) has been suggested to be activated during the inhibition of erroneous responding (Arrington, Carr, Mayer, & Rao, 2000; Garrett et al., 2000).

In summary, the young group appeared to activate those areas that would be expected when engaging in an n-back working memory task. The young activated components of the vigilance network (i.e. the right middle frontal gyrus and the right inferior parietal lobule) and the working memory components of the phonological loop and store, for example, the left inferior parietal lobule, the left superior parietal lobule and the left inferior frontal gyrus. Additional activation was also observed in areas associated with phonological processing (e.g. the left insula and the left superior temporal gyrus) and in the planning of speech (e.g. the left precentral gyrus).

Elderly Group: Like the young group, the elderly activated the left inferior parietal lobule (BA 40), which is associated with phonological storage. Note that the young also activated the right inferior parietal lobule (BA 40), significant activation of this area was absent in the elderly, however. The elderly group activated the left superior parietal lobule (BA 7) and the left precuneus (BA 7). Similarly, activation of the left superior parietal lobule (BA 7) was observed in the young group.

The middle frontal gyrus (BA 9) was activated bilaterally in the elderly group. Bilateral activation of the middle frontal gyrus was also seen in the young group, but was found in Brodmann's area 6, with additional activation in the right middle frontal gyrus (BA 10).

Right precentral gyrus (BA 6) activation was observed in the elderly group. As mentioned previously, the precentral gyrus has been suggested to be associated with the planning of movement, possibly for speech as proposed by Paulesu et al. (1993). The left precentral gyrus (BA 6) was activated in the young group. The right insula (BA 13) was also activated in the elderly group, whereas, the left insula (BA 13) was activated in the young group. The elderly group appear to be activating a number of homologous sites to the activation found in the young group.

The left inferior temporal gyrus (BA 37) was activated in the elderly group. This area has also been activated in other verbal working memory tasks, for example, the parametric n-back task by Veltman et al. (2003).

The elderly group activated the right parahippocampal gyrus (BA 27). The right parahippocampal gyrus is associated, for example, in the encoding and retrieval of topographical information (Maguire, 1997) and the retrieval of spatial information (Johnsrude, Owen, Crane, Milner, & Evans, 1999). In addition, bilateral parahippocampal activation has been observed during the encoding of photographs of faces (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998) and during the encoding of film footage of an urban environment (Maguire, Frackowiak, & Frith, 1996). A study by Wagner et al. (1998) demonstrated that the left parahippocampal gyrus was associated with the learning of verbal material. The parahippocampal gyri appear to be involved in the encoding (and retrieval) of a wide range of information. The activation of the right parahippocampal gyrus may be aiding the elderly group to complete the task. Note that the young group did not activate this region.

Activation was observed in areas believed to be associated with visual discrimination e.g. the left fusiform gyrus (BA 19) and the left middle occipital gyrus (BA 19). It appears that the elderly are employing areas related to visual discrimination to greater levels in the 1-back task than the 0-back task. This was assumed to also be true of the young group who activated the right fusiform area (BA 20). The elderly also activated the right cerebellum (culmen) and the right lentiform nucleus (medial globus pallidus, lateral globus pallidus and putamen).

In summary, the elderly appeared to activate mainly the same areas as the young. The elderly activated regions associated with vigilance i.e. the right middle frontal gyrus. It should be noted that significant activation was absent in the right

inferior parietal lobule, however. The elderly also activated areas associated with working memory i.e. the left inferior and superior parietal lobules. No significant left inferior frontal activation was observed in the elderly group. The elderly appeared to activate homologous sites to various areas activated by the young i.e. the insula and the precentral gyrus.

3.9.8.4 fMRI Experiment 1b: The Effect of Ageing on a Light Working Memory Load

Young Group versus Elderly Group Comparison: The young group activated the inferior parietal lobule (BA 40) bilaterally, to a significantly higher level than the elderly group. In the random effects analysis of the elderly group, activation was observed in the left inferior parietal lobule (BA 40). The elderly group, therefore, appear to be activating the left inferior parietal lobule substantially, but the activation of this area in the young group is significantly higher. Activation in the right inferior parietal lobule (BA 40) was absent in the random effects analysis of the elderly. The elderly seemed to lack significant activation in this area (which is associated with vigilance) compared to the young group.

Differential activation was observed in the right postcentral gyrus (BA 5) and the postcentral gyrus (BA 3) bilaterally, when the young group was compared to the elderly group. Brodmann's area 3 was suggested by Paulesu et al. (1993) to be a primary sensorimotor area of the mouth and/or larynx. Brodmann's area 5 is part of the secondary somatosensory cortex, which is thought to coordinate somatosensory information from the primary somatosensory cortex (Joseph, 1996). The postcentral gyrus may therefore, have a role in the monitoring and/or the feedback of the sub-vocal rehearsal mechanism.

The right middle temporal gyrus (BA 22 and 21) and the right superior temporal gyrus (BA 22 and 39) were also activated to significantly higher levels in the young than in the elderly. Activation of the superior temporal gyri (BA 22) have been suggested to be associated with phonological processing (Paulesu et al., 1993). The elderly group appear to lack significant activation in these areas, however.

In summary, the lack of significant activation in right hemisphere areas exhibited by the elderly compared to the young (demonstrated by the observation of greater activation by the young in these areas), for example, in the right inferior parietal lobule (BA 40), the right middle temporal gyrus (BA 22 and 21), the right superior temporal gyrus (BA 22 and 39) and the right postcentral gyrus (BA 5), appears to be consistent with the right hemi-ageing hypothesis proposed by Dolcos et al. (2002), that the right hemisphere is more vulnerable to ageing than the left.

Elderly Group versus Young Group Comparison: The elderly group activated the right lingual gyrus (BA 19 and 18) significantly more than the young group. The left lingual gyrus has been shown to be related to the processing of letters (Paulesu et al., 1993). The elderly may be activating this right hemisphere region to aid in the discrimination and processing of the letter stimuli.

Differential activation was observed in the right parahippocampal gyrus (BA 30). Activation of the right parahippocampal gyrus has been demonstrated to occur during the learning of new information (Squire et al., 1992). The significantly higher level of activation of the right parahippocampal gyrus (BA 30) in the elderly group compared to the young group might reflect a method of compensation that is being used by the elderly group (for example, to make up for other areas that have been subjected to effects of ageing). A significant difference in activation was also observed in the right lentiform nucleus (medial globus pallidus) when the elderly group was compared to the young group.

The right inferior frontal gyrus (BA 47) was activated to a significantly higher level in the elderly than the young. The activation of this region was suggested previously to occur during the inhibition of a response to an incorrect stimulus (Arrington et al., 2000) (Garrett et al., 2000). The elderly might be activating this area to a higher level than the young group because more effort may be required in order to inhibit responses to non-target stimuli. Compared to young controls, elderly participants have been shown to be impaired on tasks involving inhibition, for example, the stroop task (Langenecker, Nielson, & Rao, 2004). Similar to the present experiment, the study by Langenecker et al. also showed that older adults had greater

activation of the right inferior frontal gyrus (BA 47) when compared to younger adults on the incongruent versus neutral condition.

In summary, the elderly group appeared to recruit the right lingual gyrus to higher levels than the young, possibly to aid discrimination and/or encoding of the stimuli. The elderly group may also have activated the right parahippocampal gyrus to a higher level than the young in order to assist in the completion of the 1-back task. These areas might have been recruited by the elderly group in order to compensate for regions that have undergone detrimental effects through ageing. The greater activation of the right inferior frontal gyrus (BA 47), in the elderly group than the young group, might reflect problems the elderly have with inhibiting incorrect responses to non-target stimuli.

Conclusions: The behavioural scores of the young and elderly groups did not differ significantly on either the 1-back or the 0-back conditions. Turning now to the fMRI data, the young group appeared to activate the areas that would be expected from a working memory task of this nature i.e. bilateral inferior parietal cortex (BA 40), the left superior parietal lobule (BA 7), the left inferior frontal gyrus (BA 47) and the DLPFC bilaterally. Similarly, the elderly group activated a number of regions closely associated with tasks of verbal working memory i.e. the left inferior parietal lobule (BA 40), the superior parietal lobule (BA 7) and the DLPFC bilaterally. Note that activation was not observed in the LIFG in the elderly group at the chosen threshold of significance.

The elderly group seemed to activate a number of homologous regions to that observed in the young, for example, the right precentral gyrus and the right insula. The activation of these right hemispheric regions may be a method that is available to the elderly to compensate for the effects of normal ageing and to sustain performance on the task. This result might suggest the presence of HAROLD (Cabeza, 2002), but the elderly group did not activate these regions on the left, which means that the evidence for this model of ageing is not conclusive. The elderly group may have further compensated by activating the right lingual gyrus and the right parahippocampal gyrus to higher levels than the young group.

The elderly group appeared to under-activate the left inferior parietal lobule (BA 40). Furthermore, a lack of significant activation was observed in the right inferior parietal lobule (BA 40) in the elderly compared to the young group.

The right hemi-ageing hypothesis (Dolcos et al., 2002) appears to hold for certain areas of the cortex, but not for limbic structures e.g. the elderly group under-activated the right inferior parietal lobule (BA 40), the right middle temporal gyrus (BA 22 and 21), the right superior temporal gyrus (BA 22 and 39) and the right postcentral gyrus (BA 5) compared to the young group. The elderly group activated the right insula and the right parahippocampal gyrus to significantly higher levels than the young group, however.

In summary, the effects of ageing on this task of light working memory load, appear to incorporate, underactivations e.g. in the left inferior parietal lobule and a lack of significant activation e.g. in the LIFG and right inferior parietal lobule. Compensatory effects may also be present i.e. the activation of homologous areas to those activated in the young e.g. the right precentral gyrus and insula and the activation of other additional areas e.g. the right lingual gyrus and the right parahippocampal gyrus. Evidence also appeared to support the right hemi-ageing hypothesis (Dolcos et al., 2002). For example, the elderly group seemed to under-activate a number of right hemispheric regions that were activated by the young group.

3.9.8.5 fMRI Experiment 1c: Regions of Activation Involved with a More Demanding Working Memory Task

The 2-back condition was compared to the 1-back condition, in order to reveal the areas associated with a more demanding working memory load.

Young Group: In the young group, activation was observed in the left inferior parietal lobule (BA 40) and the precuneus (BA 7) bilaterally. Activations in the left parietal lobule (BA 40) and in the parietal cortices (BA 7) bilaterally, have been observed in other n-back working memory experiments using an n-back paradigm, for example, the 2-back vs 1-back comparison by Awh et al. (1996). The activation of the left

hemisphere areas, in particular the left inferior parietal lobule, appears to be used in phonological storage (Awh et al., 1996).

Activation was observed in a number areas in the prefrontal cortex, e.g. the superior frontal gyrus (BA 6 and 8) bilaterally, the right superior frontal gyrus (BA 10), the middle frontal gyrus (BA 9) bilaterally, the left middle frontal gyrus (BA 10 and 47), the right middle frontal gyrus (BA 6) and the left inferior frontal gyrus (BA 10). The higher working memory load found in the 2-back condition appears to be causing higher levels of activation in the DLPFC, than the lower working memory load found in the 1-back condition. An increase in DLPFC activation was expected for this comparison as a number of previous working memory studies, for example, Rypma & D'Esposito (1999) and D'Esposito, Postle, Ballard and Lease (1999) have shown that DLPFC activation increases as working memory load increases.

Another feature of the present experiment which is likely to contribute to the increase in DLPFC activation is the requirement for the manipulation of the letters (i.e. as the task continues, irrelevant letters must be discarded from memory and responses to them inhibited, and the memory set must be updated with the new letters). The results of a study by Honey et al. (2001) showed that when manipulation demands are added to maintenance demands activation of the DLPFC increases.

Activation was seen in the left inferior frontal gyrus (BA 44). This area is thought to be used in subvocal rehearsal (Paulesu et al., 1993). The activation of this region was not observed in the 0-back versus baseline or 1-back versus 0-back contrasts. The activation of this area could reflect the greater demand for phonological rehearsal that is being added by the higher working memory load (2-back condition).

Activation was seen in the left cingulate gyrus (BA 32). This area was also activated in the n-back study by Awh et al. (1996). The authors attributed the activation to greater attentional demand in the 2-back task than the 1-back. Activation of the caudate body was observed in the present contrast. The activation of this structure may reflect the effort of the participants in searching for rules or strategies that could aid them to perform the 2-back working memory task. The caudate is thought to play an important role in procedural learning (Mesulam, 2000). In the present study activation

was found in the left thalamus. The 2-back versus rehearsal comparison by Awh et al. (1996) also revealed thalamic activation.

Bilateral activation of the fusiform gyri (BA 37) was detected. The activation of these areas may reflect deeper processing of the letters. Activation of the left fusiform gyrus was seen in the letter discrimination studies of Polk et al. (2002) and Flowers et al. (2004). An alternative explanation may be that some kind of mental imagery is being attempted by the participants. Activation of the fusiform gyri can be seen for example, in the mental imagery study of D'Esposito et al. (1997).

The activation of the right lingual gyrus (BA 18) may have occurred due to the visual processing of the letters. Activation of the left lingual gyrus has been suggested to be involved with this process (Paulesu et al., 1993).

The right inferior frontal gyrus (BA 47) was also activated. The activation in this area may be due to the inhibition of erroneous responses (Arrington et al., 2000; Garrett et al., 2000).

In summary, the young group activated a number of the areas that were predicted for the 2-back task. Activation could be seen in the left inferior frontal gyrus (Broca's area, BA 44), which is thought to be used in subvocal rehearsal. The left parietal lobule (BA 40) and the bilateral parietal cortices (BA 7) were activated. The roles of these areas are thought to be in phonological storage. The DLPFC was also activated to higher levels in the 2-back condition than in the 1-back. The activation of the DLPFC was considered to be due to increased working memory load and increased demand of central executive functions (i.e. manipulation of letters).

The Elderly: Activation occurred in the left supramarginal gyrus (BA 40). This area was predicted by Paulesu et al. (1993) to be the main neuroanatomical substrate of phonological storage. For the present contrast, activation was also observed in the left superior parietal lobule (BA 7).

The right inferior parietal lobule (BA 40) was activated. This area is homologous to the left hemisphere region thought to be used in phonological storage. The activation of the right parietal cortex (BA 40) was observed with the n-back paradigms of Braver et al. (1997) and Schumacher et al. (1996). Note that the young

group in the 2-back versus 1-back contrast did not activate the right inferior parietal lobule (BA 40).

The left inferior frontal gyrus (BA 44) was not activated in the elderly group. The left inferior frontal gyrus (BA 45) was activated, however, which may reflect mechanisms of subvocal rehearsal. Similar to the young group, the elderly activated the right inferior frontal gyrus (BA 47).

Other areas of the prefrontal cortex were also activated e.g. the right superior frontal gyrus (BA 6 and 8), the middle frontal gyrus (BA 6 and 10) bilaterally, the left middle frontal gyrus (BA 9) and the right medial frontal gyrus (BA 8). Like in the young group, the extra DLPFC activation seen in the elderly group for the 2-back versus 1-back contrast may reflect central executive functioning in response to the higher working memory load and the extra demand for the manipulation of the letter stimuli.

Activation was observed in the right insula (BA 13). The activation of this region may be due to phonological processing, as proposed by Paulesu et al. (1993). The insular cortex has been activated in other studies involving verbal working memory e.g. Awh et al. (1996) and Braver et al. (1997). Further activations were seen in the right putamen and the left claustrum. The putamen may be used in procedural learning, as suggested by Mesulam (2000). The right thalamus was also activated by the elderly. Activation of the thalamus was seen in the young group (however, it was left-sided).

In summary, the elderly activated areas of the brain associated with phonological storage, for example, the left supramarginal gyrus (BA 40) and the left superior parietal lobule (BA 7). Activation was also present in the right inferior parietal lobule (BA 40). Activation of the DLPFC was observed, which as thought for the young group, may reflect the central executive processing of the higher working memory load and the increased need for the manipulation of the stimuli. No activation occurred in the left inferior frontal gyrus in Brodmann's area 44, but activation did occur in Brodmann's area 45, which is likely to be associated with subvocal rehearsal.

3.9.8.6 fMRI Experiment 1c: The Effect of Ageing on a More Demanding Working Memory Task

Young Group versus Elderly Group Comparison: When the young group were compared to the elderly group on the 2-back versus 1-back contrast, greater levels of activation were observed in the left inferior parietal lobule (BA 40), the left postcentral gyrus (BA 7), the right precuneus (BA 7) and the superior parietal lobule (BA 7) bilaterally. Examination of the images of the random effects analyses of the young group (Fig 3.17) and the elderly group (Fig 3.18) show similar patterns of parietal activation in the groups. It seems, therefore, that when the young group was compared to the elderly group statistically, the higher levels of activation found in the parietal areas (BA 7 and 40), generally appear to reflect quantitative differences in activation rather than qualitative differences. For example, it appears mostly to be the levels of activation that are different rather than the areas of activation. Looking also at the areas of activation that occurred in the random effects analysis of the elderly group, activations can be seen in the left supramarginal gyrus (BA 40), the left superior parietal lobule (BA 7) and the right inferior parietal lobule (BA 40).

The young group appeared to activate the left inferior frontal gyrus (BA 47) to a higher level than the elderly group. This area may be used to select amongst competing stimuli. Zhang et al. (2004) suggested that the left inferior frontal gyrus may be used as a general mechanism for selection rather than specifically for semantic information. The young also activated the left putamen to a higher level than the elderly group. The random effects analysis of the elderly group showed that activation occurred in the right putamen.

Differential activation occurred in the cingulate gyrus (BA 32) bilaterally. Activation of the cingulate cortex (BA 32) has been associated with target detection and attention (Posner & Raichle, 1997).

In summary, a number of differences existed between the young and elderly groups. The young group activated regions of the parietal cortices (BA 7 and 40) to higher levels than the elderly group, but the random effects analysis of the elderly group also showed activation in the parietal cortices which implies that some of the differences may be quantitative in nature. A higher level of activation was seen in the

left inferior frontal gyrus (BA 47) of the young group, which may reflect mechanisms of selection. The cingulate cortex (BA 32) was also activated to a higher level in the young. This region is thought to be related to target detection and attentional processes (Posner & Raichle, 1997).

Elderly Group versus Young Group Comparison: Significantly different levels of activation occurred in the left inferior parietal lobule (BA 39). Differential activation was also observed in the left superior temporal gyrus (BA 39) and the right middle temporal gyrus (BA 39). The random effects analyses of the young group did not show activation of these regions. The temporo-parietal junction (BA 39) appears to be associated with lexical processes (Collette et al., 2001). The greater activations of the left inferior parietal lobule (BA 39), the left superior temporal gyrus (BA 39) and the right middle temporal gyrus (BA 39) in the elderly group may be due to compensatory mechanisms that are in effect.

Significant differences in activation were seen in areas associated with visual processing e.g. the left cuneus (BA 17), the left middle occipital gyrus (BA 19), the left inferior occipital gyrus (BA 17), the left lingual gyrus (BA 18) and the right fusiform gyrus (BA 37). Durgerian et al. (2001) found that during the maintain condition in their verbal working memory task, load dependent increases in activation occurred in the striate cortex (BA 17). The authors proposed that the primary visual cortex contained a visual image of the stimuli to be retrieved and that the DLPFC played a role in maintaining this image. Note that young participants were used in the Durgerian et al. (2001) study. The elderly participants in the present study may be using a process such as this however, to aid the successful completion of the 2-back task.

Higher levels of activation were seen in the right insula (BA 13). The involvement of the insular cortex in visual attention has been proposed by Corbetta, Miezin, Dobmeyer, Shulman and Petersen (1991). The greater activation of the right insula (BA 13) by the elderly participants may be due to increased demands on visual attention, compared to the young.

A significant difference between the groups was also observed in the left parahippocampal gyrus (BA 19). Activation of this area has been reported when

participants attempt to learn verbal material (Wagner et al., 1998). A further significant difference occurred in the left posterior cingulate (BA 29). The higher levels of activation in this region by the elderly group may be compensatory. Alternatively the difference in activation may reflect non-selective over-activation on behalf of the elderly. Differential activation was also observed in the left caudate tail and the caudate head bilaterally. The caudate has been implicated in procedural learning (Mesulam, 2000).

In summary, the elderly participants appeared to recruit a number of areas that were not activated significantly by young participants. Examples of these areas are the left middle occipital gyrus (BA 19), the left inferior occipital gyrus (BA 17), the left cuneus (BA 17), the posterior cingulate (BA 29), the right middle temporal gyrus (BA 39), the left parahippocampal gyrus (BA 19), and the right insula (BA 13). The differential activation of these regions could be in compensation for detrimental effects of ageing.

Conclusions: Behaviourally, the young and the elderly groups did not differ significantly on either the performance scores or the reaction times of the 2-back or 1-back conditions. In response to the higher working memory load found in the 2-back condition compared to the 1-back condition, the young group activated those areas that were predicted in the experimental hypotheses. For example, activation was detected in Broca's area (BA 44), the left inferior parietal lobule (BA 40) and a number of areas in the DLPFC. The young group also activated the left cingulate gyrus (BA 32). The activation of this region was considered to be due to increased demands on attention.

The elderly group activated a number of regions that were similar in location to those of the young, for example, the left supramarginal gyrus (BA 40), the left superior parietal lobule (BA 7), numerous areas in the DLPFC, and the right inferior frontal gyrus (BA 47). Examination of the images showing the random effects analyses of the young group (Fig 3.17) and the elderly (Fig 3.18) illustrate the similarities in the patterns of activation between the groups. Dissimilar to the young group, the elderly group activated the right inferior parietal lobule (BA 40). This activation may have

been due to an increased demand for attention in the elderly group (that was not required in the young group).

When statistically comparing the activation of the young group to the elderly group, a number of differences in activation occurred. Some of these differences appeared to be quantitative rather than qualitative in nature e.g. both groups activated regions in the left parietal cortices (BA 7 and 40), but the young activated these areas to higher levels. Note that quantitative differences between the young and elderly groups might be expected due to the literature on ageing which details effects of underactivation. Other significant differences between the groups did exist in certain areas, however. The young activated the left inferior frontal gyrus (BA 47) and the cingulate gyrus (BA 32) bilaterally, to significantly higher levels than the elderly.

The results suggest that the elderly group tended to activate similar areas to the young group, (e.g. the young group did not activate a large number of areas that were different in location to the elderly). When comparing the elderly group to the young group, however a larger range of differences occurred. The elderly activated a number of regions to significantly higher levels e.g. the right insula, the left parahippocampal gyrus, the left posterior cingulate (BA 29) and certain areas associated with visual processing. The results suggest that the elderly group use some brain regions differently to the young group. These differences may arise due to the consequences of ageing, which may cause additional processing demands in the elderly group.

No evidence for the theories of ageing (HAROLD and the hemi-ageing hypothesis) appears to be clear for this comparison. The HAROLD model (Cabeza, 2002) would predict an increase in bilateral activation in the elderly group compared to the young group. This was not observed in the 2-back versus 1-back contrast. If anything the images show the pattern of activation to be more bilateral in the frontal areas of the young group than the elderly (see Figure 3.17 for the random effects analysis of the young group and Figure 3.18 for the elderly group). The hemi-ageing hypothesis (Dolcos et al., 2002) predicts that the right hemisphere is more vulnerable to the effects of ageing than the left hemisphere. The hypothesis would envisage a lack of activation in the right hemisphere compared to the left. This did not appear to be the

case, however and the elderly activated some regions in the right hemisphere that the young did not e.g. the right inferior parietal lobule (BA 40).

In summary, the patterns of activation in the elderly group and the young group seem to look quite similar. The young may have activated regions in the parietal cortices to higher levels than the elderly group, but these differences seemed mainly to be quantitative in nature. The elderly did use certain brain regions differently to the young group, however, when performing the 2-back working memory task. The differences in the patterns of activation between the elderly group and the young group e.g. in the visual processing areas, the caudate and the posterior cingulate, are considered to be due to compensatory means. An alternative explanation, however, could be that specific regions may be undergoing non-selective over-activation by the elderly group.

3.9.8.7 fMRI Experiment 1d: Regions of Activation Associated with Increased Working Memory Load

Young Group: The parametric design showed activation of the left inferior parietal lobule (BA 40) in the young group. The parametric design is specified to identify the brain areas that increase in activation as working memory load increases. The left inferior parietal lobule (BA 40) is thought to be used in phonological storage (Awh et al., 1996). The activation in this region appears to increase as working memory load is incremented. Activation was also present in the right precuneus (BA 7) of the young group.

Activation occurred in a number of regions in the prefrontal cortex. The activated areas included the left superior frontal gyrus (BA 6), the right superior frontal gyrus (BA 8 and 10), the right middle frontal gyrus (BA 6) and the middle frontal gyrus (BA 9) bilaterally. Increased DLPFC activation has been described in other studies on working memory, for example, when working memory load is increased (Rypma & D'Esposito, 1999), and when manipulation of the material to be remembered is required (Honey et al., 2001). Activation was observed in the right inferior frontal gyrus (BA

47). As described, the activation of this region may be due to the processes of inhibiting incorrect responses (Arrington et al., 2000; Garrett et al., 2000).

The left cingulate gyrus (BA 32) was activated. The cingulate gyrus (BA 32) is thought to be used in attentional processes and in target detection (Posner & Raichle, 1997). The results of a verbal working memory study by Steffener et al. (2001) showed that activation occurred in the anterior cingulate (BA 32), due to increases in the time that the target stimuli had to be remembered.

Activation of Broca's area (BA 44), which was observed in the 2-back versus 1-back contrast, was not seen in the parametric design. This finding shows that the activation of Broca's area does not increase significantly through the conditions of 0-back, 1-back and 2-back. This may suggest that subvocal rehearsal mechanisms that involve Broca's area are recruited only when the more demanding 2-back task is attempted. Activation did occur in the left precentral gyrus (BA 6), however. The activation of this region may reflect increased motor planning for speech through the working memory conditions (without actual vocalisation) as proposed by Paulesu et al. (1993).

The fusiform gyrus (BA 37) was activated bilaterally. The activation of these areas may have been due to deeper processing of the letter stimuli. Activation of the left fusiform gyrus has been described in studies which concern the discrimination of letter stimuli, for example, Polk et al. (2002) and Flowers et al. (2004). Alternatively, the activation of these regions may reflect the increased use of mental imagery as working memory load increases. Activation of the fusiform gyri were reported by D'Esposito et al. (1997), in response to mental imagery. Activation of the left inferior temporal cortex (fusiform gyrus, BA 37) was described in the Veltman et al. (2003) working memory study, which used a parametric design that included the conditions of 0-back, 1-back, 2-back and 3-back.

The left caudate body was activated. The caudate is considered to be used in procedural learning (Mesulam, 2000). The young participants may be searching for rules or strategies that could aid in task completion. Alternatively, the caudate activation may illustrate increased levels of motivation as the conditions become more taxing. Patients that have caudate lesions may present severe losses of motivation

(Mesulam, 2000). Activation of the caudate was also found in the Braver et al. (1997) study which used a parametric design that included the 0-back, 1-back, 2-back and 3-back. The left thalamus was activated in the parametric contrast in the present study. Activation of the thalamus has been observed in other working memory studies, for example, Awh et al. (1996) and Durgerian et al. (2001). A study by Kinomura et al. (1996) showed that thalamic activation occurred during the transition from relaxed wakefulness to an attentionally demanding state.

In summary, load related activation was observed, for example, in the left inferior parietal lobule (BA 40), the right precuneus (BA 7), the DLPFC bilaterally, the left cingulate gyrus (BA 32), and the caudate body. The pattern of activation appeared to be very similar to other n-back studies that used a parametric design e.g. Braver et al. (1997) and Veltman et al. (2003). The image of the activations found in young group from the present comparison (Fig 3.21) may be compared to the image of the activation found in the Veltman study (Fig 3.2). Table 3.1 also provides a summary of the areas of activation found in other n-back studies.

Elderly Group: Load dependent activation was observed in the inferior parietal lobule (BA 40) bilaterally and the left superior parietal lobule (BA 7). The left inferior parietal lobule and the left superior parietal lobule are thought to be used in phonological storage (Awh et al., 1996). Activation of the right inferior parietal lobe has been reported to be used in tasks of vigilance (Posner & Raichle, 1997). The progressive activation of the right inferior parietal region in the present contrast may therefore, be related to increased levels of attention that are required as working memory load is incremented. Additional areas of activation were also observed in the right postcentral gyrus (BA 7) and the right precuneus (BA 19).

Similar to the young, activation was not found in Broca's area (BA 44). In the elderly group, however, activation was observed in the left inferior frontal gyrus (BA 45). The activation of this region may suggest the increased involvement of subvocal rehearsal mechanisms in the elderly as working memory load increased through the n-back conditions. In the parametric n-back study of the prefrontal cortex, by Braver et al. (1997), activation was reported in the left inferior frontal gyrus (BA 44/45).

The elderly also activated a number of other regions in the prefrontal cortex. These were the left middle frontal gyrus (BA 6, 9 and 10), the right superior frontal gyrus (BA 8) and the right medial frontal gyrus (BA 8). Increases in activation of DLPFC regions have been reported in other parametric n-back studies e.g. Braver et al. (1997) and Veltman et al. (2003). Like in the young group, the elderly activated the right inferior frontal gyrus (BA 47). The elderly group activated the right insula (BA 13). The activation of this region was not observed in the young group. The insular cortex has been described to be used during the planning of speech sounds (Dronkers, 1996).

Activation was found in the right caudate body and the caudate head, bilaterally. The activation of the caudate may represent the searching of rules or strategies by the elderly group, to aid in task completion. Activation also occurred in the right medial dorsal nucleus and the pulvinar, bilaterally. The activation of these thalamic regions might coincide with increased levels of alertness as working memory load is increased.

In summary, the elderly participants appeared to activate a number of similar regions to the young group (See Figures 3.21 and 3.22). The elderly activated the left inferior parietal lobule (BA 40), the DLPFC bilaterally, the caudate and the thalamus. In the elderly group, additional areas of activation were observed compared to the young group, for example, in the left inferior frontal gyrus (BA 45), the right inferior parietal lobule (BA 40) and the right insula (BA 13). The activation of these additional regions may have been compensatory.

3.9.8.8 fMRI Experiment 1d: The Effect of Ageing on Increased Working Memory Load

Young Group versus Elderly Group Comparison: The young group appeared to activate the left superior parietal lobule (BA 7) and the inferior parietal lobule (BA 40) bilaterally to significantly higher levels than the elderly group. The left middle frontal gyrus (BA 6) was also activated to significantly higher levels in the young group than the elderly group. The differences between the young and the elderly groups in the parietal areas and in the left middle frontal gyrus appear to quantitative.

Increased levels of activation were observed in the left precentral gyrus (BA 6 and 44) of the young group compared to the elderly group. Broca's area (BA 44) is considered to be one of the main components of subvocal rehearsal (Paulesu et al., 1993). The left precentral gyrus (BA 6) is suggested to be used in motor planning for speech (Paulesu et al., 1993). A significant difference was also found between the groups in the left inferior frontal gyrus (BA 47). The left inferior frontal gyrus is thought to be used during the controlled retrieval of information (Gold & Buckner, 2002).

The young group activated the cingulate gyrus (BA 32) bilaterally, to significantly higher levels than the elderly group. The cingulate gyrus (BA 32) has been described to be involved with target detection and increased levels of attention (Posner & Raichle, 1997).

Differential levels of activation were also observed in the left superior temporal gyrus (BA 22 and 38) and the right superior temporal gyrus (BA 13). The left superior temporal gyrus (BA 22) may be used in phonological processing (Paulesu et al., 1993).

In summary, the young group activated a number of regions to significantly higher levels than the elderly group. The differences in activation found in the parietal regions and in the left middle frontal gyrus (BA 6) of the young group compared to the elderly group, appear to be quantitative in nature e.g. the elderly group are activating these areas, but the young group are activating them more. There are also certain qualitative differences between the young and the elderly groups. The young group also appeared to activate different areas to the elderly group, for example, the left precentral gyrus (BA 6/44), the left inferior frontal gyrus (BA 47), the cingulate gyrus (BA 32), and a number of regions in the temporal cortex. These qualitative differences may be more informative than the quantitative differences, as they appear to illustrate the areas that the young used, but the elderly did not. The quantitative differences, however, show that the elderly still tend to recruit the areas that the young use, only at lower levels of activation.

Elderly Group versus Young Group Comparison: Significant differences in activation were detected in the left inferior parietal lobule (BA 39), the left angular gyrus (BA 39) and the right middle temporal gyrus (BA 39). It appears that the elderly group were recruiting these brain areas (that are thought to be associated with language) to higher levels than the young group. The angular gyrus is thought to be involved in the visual symbolic aspects of language (Mellers et al., 1995). Collette et al. (2001) also described the temporo-parietal junction (BA 39) to be involved in lexical processing. The increased activation in these parietal areas by the elderly group may reflect a mechanism of compensation.

A number of areas associated with visual discrimination were activated to higher levels in the elderly group than the young group. These areas included the left cuneus (BA 17 and 19), the left middle occipital gyrus (BA 19), the right superior occipital gyrus (BA 19), the left lingual gyrus (BA 18) and the right fusiform gyrus (BA 37). The additional activation of these areas in the elderly may be in compensation for areas that are not functioning optimally because of the ageing process.

Significantly different levels of activation were seen also in the right precentral gyrus (BA 4 and 6). The activation of these areas may suggest greater right-hemisphere involvement on behalf of the elderly group. The random effects analysis of the young group showed activation of the left precentral gyrus (BA 6). This result may provide partial evidence of HAROLD (Cabeza, 2002), but as the elderly do not activate either of these regions in the random effects analysis, it is difficult to conclude this with certainty.

The caudate head was activated bilaterally, to significantly higher levels in the elderly group than the young group. The elderly group may have activated this area to significantly higher levels than the young group because of a greater need to find a strategy to cope with the progressively increasing working memory load that is fundamental to the parametric n-back task.

In summary, the elderly group appeared to activate a number of regions differentially compared to the young group. Differential activation was observed in areas that are thought to be associated with lexical processing e.g. the left inferior parietal lobule (BA 39), the left angular gyrus (BA 39) and the right middle temporal gyrus (BA 39). Significantly different levels of activation were also observed in areas associated with visual discrimination and in the caudate head (bilaterally). The

involvement of these areas that are considered to be associated with lexical processing, visual discrimination and procedural learning, may reflect methods of compensation that are available to the elderly group as working memory load increases. The elderly group may need to compensate for higher working memory load because of the detrimental effects of ageing.

Conclusions: The parametric design was implemented because of the criticisms of subtractive designs (Friston et al., 1996; Sidtis et al., 1999; E. E. Smith et al., 1998). The parametric design was constructed to reveal those areas in the brain that increase in activation when working memory load is progressively incremented. The young group activated areas that appear to be common to n-back working memory tasks of parametric design e.g. Braver et al. (1997) and Veltman et al. (2003). Examples of the areas of activation found in the young group in the present study are the left inferior parietal lobule (BA 40), the right precuneus (BA 7), the left cingulate gyrus (BA 32), the caudate body and the DLPFC cortex bilaterally. The areas of activation also appear to be similar to studies which use subtractive designs, for example, Awh et al. (1996) and Schumacher et al. (1996). The subtractive designs therefore, appear to be effective at isolating the areas associated with a higher working memory load.

In the elderly group load dependent activation was observed in the inferior parietal lobule (BA 40) bilaterally, the left superior parietal lobule (BA 7), the caudate (body and head) and the DLPFC bilaterally. The patterns of activation found in the young and elderly groups seem to look very similar (see Figure 3.21 for the young group and Figure 3.22 for the elderly group). Differences do appear to exist between the groups, however. The elderly group had a focus of activation in the right inferior parietal lobule (BA 40). A focus of activation was not observed in this area in the young group. The elderly may be activating this area (which is homologous to the area considered to be used in phonological storage) in order to compensate for areas of the brain that have been affected by the ageing process. The elderly also activated the right insula (BA 13). The activation of this region was not seen in the young group and again may be due to methods of compensation.

When the young group were statistically compared to the elderly group activation was observed in the left superior parietal lobule (BA 7), the inferior parietal

lobule (BA 40) bilaterally, and the left middle frontal gyrus (BA 6). The elderly seem to be displaying an effect of underactivation, which may be due to the consequences of ageing. The young group also activated the precentral gyrus (BA 6/44) to significantly higher levels than the elderly group. The random effects analysis of the elderly group showed activation of the left inferior frontal gyrus (BA 45), however. The focus of activation therefore, appears to be shifted in the elderly group.

The comparison of the elderly group to the young group revealed differential activation in areas associated with language and visual discrimination. These areas were not activated due to working memory load in the random effects analysis of the young group, which suggests that the elderly may be recruiting the areas in compensation for ageing-related deficits. The significantly higher levels of activation in the caudate head of the elderly group than the young group may suggest that the elderly are engaging a more effortful search for rules or strategies to aid in task completion.

Differential activation was observed in the right precentral gyrus (BA 6). The difference in activation of this region may be evidence for the HAROLD (Cabeza, 2002), but as the random effects analysis of the elderly does not show activation of the homologous region in the left, the evidence for the HAROLD is not conclusive. In the parametric contrast no evidence was found in support of the right hemi-ageing hypothesis (Dolcos et al., 2002) i.e. that the right hemisphere is more affected by ageing than the left.

In summary, the random effects analyses of both the young and elderly groups showed the activation of similar regions in response to an increased working memory load. The elderly appeared to have additional activations in the right inferior parietal lobule (BA 40), the left inferior frontal gyrus (BA 45) and the right insula (BA 13). The statistical comparison of the young group to the elderly group highlighted areas of underactivation in the frontal/parietal working memory network in the elderly group, in addition to a small number of shifts in the locations of activation. The statistical comparison of the elderly group to the young group revealed differences in activation in a number of areas e.g. those associated with visual discrimination, language and procedural learning. These differences may be due to compensation by the elderly group in response to age-related decline in cognitive ability.

3.10 Experiment 2: The Effect of Pathological Ageing on Vigilance and Working Memory

The working memory system generally becomes impaired very early in the course of Alzheimer's disease (AD). The impairments to working memory can usually be observed when patients with AD attempt to retain information in memory. Specific tasks can be used to highlight the problems with the working memory system that patients with AD exhibit, for example, digit, letter, word and spatial location span tasks, as well as delayed response tasks.

A number of studies have investigated the amount of information that patients with AD can hold in working memory. For example, Belleville et al. (1996), Cherry et al. (1996) and Kopelman (1985) examined digit span. Belleville et al. (1996) compared the digit span of a group of patients with DAT to the digit spans of young and elderly controls. The results showed that the mean digit span scores of the young, elderly and patients with DAT were 6.33, 6.08 and 4.85, respectively. The mean digit span score of the patients with DAT was significantly different to the mean digit span score of the elderly control group. The mean scores of the young and elderly controls did not differ significantly. This study reveals that patients with DAT appear to have reduced digit spans in comparison to normal controls. The study by Kopelman (1985) also demonstrated a significant decrease in the digit span of patients with AD compared to adult controls (the effect was still present after co-varying for age).

Belleville et al. (1996) examined the letter span of patients with DAT. The study was not based on absolute measures of span, however. The aim of the study was to examine the phonological similarity effect. This was examined by finding the letter span of each participant for a set of phonologically dissimilar letters. After the length of phonological dissimilar letter span was discovered, the participant was tested on five sequences of phonologically dissimilar sets of letters at their span length and on five sequences of phonologically similar sets of letters at their span length. The experiment was carried out both with auditory presentation of the letters and with visual presentation. Analysis of the data revealed a significant effect, in which dissimilar sets of letters were recalled more accurately than similar sets. The group by similarity

interaction also reached significance, revealing a larger decrement in recall due to phonological similarity in the young and elderly participants than in the patients with DAT. The patients with DAT did not have a significant drop in recall due to the phonological similarity effect. Although this result appears to show superior performance in patients with DAT, it should be remembered that the experiment is based relative to the mean letter span scores for each individual participant. The experiment demonstrated a decrease in the phonological similarity effect of patients with DAT. The above studies illustrate the reduced capacity for working memory that is exhibited by patients with AD.

Moss, Albert, Butters and Payne (1986) carried out a study which consisted of a delayed recognition span test (DRST). The task involved the participant watching a board. Disks were consecutively laid out on a board which was out of view of the participant. The disks conveyed various information e.g. positions, colours, words, patterns and faces. After the addition of each disk the board was revealed and the participant had to point to the disk which was the latest addition. To do well in the task the participant must remember an increasingly large number of disks. The disks are added one by one until an error is made, this reveals the participants delayed recognition span. The groups that were tested consisted of normal controls, patients with AD, amnesic patients with Korsakoff syndrome (KS) and dementing patients with Huntington disease (HD). The results revealed that all three patient groups were significantly impaired compared to the controls. The patient groups did not differ significantly except for the comparison of the disks conveying verbal information. It was found that the patients with Huntington disease performed significantly better than the patients with AD or KS when the disks containing the verbal stimuli were used. This experiment shows that the AD patients have a lower delayed recognition span than the normal controls.

Perhaps more interestingly, however, the researchers also added a recall task to the study which was to be completed at both 15 seconds and 2 minutes after the completion of the last verbal recognition trial. The results revealed that all three patient groups appeared to be equally impaired compared to the control groups at the 15 second period. The AD patients recalled significantly fewer words at the 2 minute mark, however, than either the patients with HD or KS. At the 2 minute interval, eleven out of

twelve of the patients with AD could recall fewer than 3 of the 16 available words. Of these eleven, seven were unable to recall any of the words at the 2 minute mark.

Only the patients with AD performed significantly worse at the 2 minute mark when compared to the 15 second mark. On average the patients with HD and KS appeared to lose about 10-15% of the verbal information between the 15 second and 2 minute interval. This is in contrast to the patients with AD which appeared to lose on average about 75% of the information between the two intervals.

This study demonstrates the rapid rate of loss of information from verbal working memory that can be observed in patients with AD. The study also suggests that although verbal information is lost in patients with HD, KS and AD by an early time interval (15 seconds), if the amount of verbal information retained at this point is compared with a later interval (i.e. 2 minutes), this may be of diagnostic significance. Only the patients with AD were observed to have a significant loss of verbal information between the two time periods.

A further study by Moss and Albert (1988) investigated AD and frontotemporal dementia using the same DRST. The difference in the recall of verbal information between the 15 second and 2 minute mark differentiated the two groups, with the patients with AD losing a great deal of information, whereas, the patients with frontotemporal dementia had near normal performance.

Albert (1996) suggested that problems also exist with delayed recall performance in normal ageing. Albert (1996) proposed that the reason that the problems exist is because older people take longer to learn information. Once the information has been learned it might be retained well after a delay. R. C. Petersen, Smith, Kokmen, Ivnik and Tangalos (1992) carried out a study which investigated the differences between immediate and delayed recall. The study showed that there were no age-related differences. This is contrary to what appears to happen in AD, as demonstrated in the Moss et al. (1986) study, in which substantial drops in the information that was retained were observed between the immediate recall condition (15 seconds after the completion of the DRST) and delayed recall condition (2 minutes after the completion of the DRST). It should be noted however, that although the AD patients are losing information very quickly, they are probably not learning the information as well as controls initially and this will most likely increase the rate of forgetting. The very fast rate of information decline that is observed in patients with

AD between immediate recall and the delayed recall is interesting, as the delay period of 2 minutes is still a very short period of time and this interval appears to distinguish AD patients from normal elderly, patients with Huntington disease, patients with Korsakoff syndrome and from patients with Frontotemporal dementia.

Kopelman (1985) carried out a study, employing a version of the Brown-Peterson test. Kopelman considered that patients with AD would have accelerated forgetting on the Brown-Peterson test when compared to normal elderly and patients with Korsakoff's syndrome. The task involved the presentation of three words which had to be remembered for varying amounts of time (0, 2, 5, 10 and 20 seconds). A distractor task was also used during the various delays (except for the time delay of zero), in which the participant had to count backwards from one hundred in either twos or threes (the number to subtract was determined prior to the experiment). There was a significant main effect of group for the period 0-20 seconds. There was also a significant interaction of group by interval. The experiment investigated the rate of forgetting in AD, finding that the fastest rate of forgetting appeared to be up to approximately 5 seconds (after which the AD patients appeared to be close to their "floor"). Stringent investigation of the assumption that a reduced ability to retain information contributes to the impairments of working memory in AD (in addition to encoding/retrieval deficits), presumes that the performance of the AD patients is intact at the zero delay. When only the period of 0-5 seconds was analysed, a significant interaction was observed for not only the three groups, but also for the groups of AD by control and for the groups of AD by Korsakoff's syndrome. When the zero point was excluded and the 2-5 second interval analysed, a significant effect of group was observed, but the interaction effect fell just short of statistical significance. The outcome of the experiment, although not providing concrete evidence of an increased rate of forgetting in AD, in addition to encoding/retrieval deficits, demonstrates the rapid decline of information that can be observed during brief periods of time following encoding (also demonstrated in the Albert (1996) study).

Belleville et al. (1996) also used an adapted Brown-Peterson procedure to investigate working memory in AD. The participant had to remember three consonants which were presented auditorily. The experiment consisted of a between subjects factor, which was group (DAT, elderly or young) and two within subjects factors which

were delay (0, 10, 20 and 30 seconds) and interference (no interference, tapping and addition). The analyses revealed that a three way interaction between the factors was significant. The analyses were broken down into each interference condition in order to attempt to explain the results.

The no interference condition revealed a significant interaction between group and delay. The researchers explained this interaction to relate to the significant decline in performance due to delay in the patients with DAT, which was not present in the elderly or young groups. The tapping condition also revealed a significant effect of group in which the patients with DAT had lower recall compared to the normal control groups. The effect of delay and the interaction between group and delay only approached significance in this condition, however. The addition condition had a significant effect of delay as well as a significant interaction between delay and group. Delay was found to reduce performance significantly in all groups, the patients with DAT, however, were found to be affected more severely.

This experiment demonstrates that the patients with AD had impaired recall on the Brown-Peterson task, especially when required to carry out the addition interference task. The combination of the recall and the addition interference condition was considered by Belleville et al. (1996) to be the most demanding on attentional resources.

The above experiments provide evidence that the Brown-Peterson technique may be useful in distinguishing patients with AD from controls. The experiments show that patients with AD are only capable of storing information in working memory for very short periods of time and that the addition of an attentionally demanding distractor test impairs patients with AD to a greater extent than it does controls. As one of the uses of the Brown-Peterson technique is to examine executive function, further investigation into the functioning of the central executive and the application of dual tasks can be informative in attempting to understand the WM deficits that can be observed in patients with AD.

A study by Baddeley, Logie, Bressi, Della Sala and Spinnler (1986) employed a dual task paradigm to investigate the issue of central executive dysfunction in AD. The tasks consisted of a tracking task in which the participant had to follow a moving stimulus on a computer screen with a light pen, and also a digit repetition task. The tasks were performed by normal participants (both young and elderly) and patients with

AD. Each of the tasks was individually equated for difficulty between the groups of normal participants and the patients with AD (i.e. the tasks were performed separately). The tasks were then completed simultaneously by the test groups. The results showed that the performance of the patients with AD was substantially lower than that of the control groups. Baddeley, Bressi, Della Sala, Logie and Spinnler (1991) also carried out a follow up study on the patients with AD after a period of six months. The results revealed that the performance of the patients doing each task separately remained unchanged. The scores of the patients when doing both tasks simultaneously, however, had decreased significantly. The impaired performance of the patients on this dual task demonstrates the executive dysfunction that appears to affect patients with AD. The executive impairment also seems to increase over time, as disease severity increases, even while the patient is still capable of completing the tasks adequately when performed separately.

Using dual-task paradigms, R. G. Morris (1986) found that central executive impairments in AD could be observed even when using relatively simple distractor tasks. For example, if the patient engaged in a short term memory task while also consistently tapping the palm of their hand on a desk, a deficit in memory performance could be seen, that was not present in the controls. R. G. Morris (1986) also showed that a secondary task of adding or reversing the order of two single digit numbers was adequate to cause impairment in patients with AD.

Further dysfunction of working memory and the central executive can be seen in the form of perseverations. During tasks of verbal fluency, in which a patient must name as many items as possible within a set time limit for example, 60 seconds, from a chosen category e.g. "cities", patients can sometimes be seen to repeat items which they have mentioned previously. When the experimenter changes the category, from time to time intrusions can also be observed. For example, the patient recites a city, when this response is no longer appropriate and the category has subsequently been set as "animals" (with the previous category as "cities"). The Wisconsin Card Sorting Test is also useful for assessing perseverations in patients with AD. Perseverations on this task are characteristically observed in patients with frontal lobe damage (Baddeley, 1996).

Perseverations are not only limited to speech and can also be seen, for example, in the written spelling of words. Examples of this phenomenon are "streeet", "CCCarl"

or "Reagagen" (Lezak, 1995). Perseverations can also be observed when drawing, in the form of the patient duplicating items of the picture that they have already drawn. Impaired working memory is not the only problem in perseverations, as the patient can review what they have for example, written or drawn. This shows that something else, possibly central executive dysfunction, is also contributing to the behaviour.

Vecchi, Saveriano and Paciaroni (1998) investigated the differences in working memory impairment between patients with AD and elderly controls. The researchers examined specific functions of working memory, such as passive storage and the active processing of information. The results showed that the AD group performed with less accuracy than the controls on all the tasks. The greatest impairment was found in the tasks which involved active processing, regardless of whether the task was verbal or visuo-spatial.

The reduced capacity of working memory in the elderly that was suggested by Stuart-Hamilton (2000), was described to be quantitative in nature. The reduction in working memory capacity of patients with DAT, however, was considered to be qualitative. The elderly appeared to perform the task in the same ways as the young and failed in similar ways. If the elderly were aided with additional memory cues (i.e. coloured stimuli), performance tended to increase (Stuart-Hamilton, Rabbitt, & Huddy, 1988). The reverse was true for patients with DAT. If additional information was provided the patients still tended to perform at lower levels than usual. This may have been because the patients were easily confused and the additional information hindered performance rather than increasing it (Stuart-Hamilton et al., 1988).

As observed in the above studies, one of the potential causes of the deficits in working memory appears to be associated with a problem with the central executive, whereas, when problems of new learning are observed these have been suggested to be because of poor encoding or mediational processes (Becker, 1988). It has been suggested that the reduced ability to retain information in working memory impacts on the ability of the patient to learn new information, as they are able to store less information than normal individuals (Lezak, 1995).

Many explanations for working memory deficits in AD have referred to the central executive component of the working memory model by Baddeley (1974). This is not surprising as a great deal of evidence shows that central executive dysfunction occurs in AD. The most recent addition to the model, the episodic buffer (Baddeley, 2000), may provide an additional reason for the deterioration of working memory in AD. It is no longer only the central executive component that is thought to deteriorate in AD, the dysfunction of other working memory components, functions, and related underlying brain areas may also occur.

The heterogeneity of patients with AD complicates matters. In a number of the working memory studies that have been mentioned above, it is entirely possible that some of the patients with AD were not impaired on all the tasks. The analyses are usually on groups of patients and the mean scores of these groups can sometimes conceal subgroups of AD patients with differing impairments (all the patients, however, may be deemed to be of the same disease severity). It is possible to investigate the pathologies of patients with AD at the individual level as well as at the group level. Belleville et al. (1996) used a number of various tests to examine patients with AD not only at the group level, but also individually. The various tests that were used were an adapted Brown-Peterson procedure (described above), a phonological similarity letter task, a word length span task (using two sets of words - monosyllabic words and words with four syllables), and three phonological judgement tasks (one in the auditory domain - syllable judgement, and two in the visual domain - a homophony task, and a rhyme judgement task).

Belleville et al. (1996) found that the patients appeared to be impaired on some types of tasks but not others. For example, of the ten patients, three were impaired only on the adapted Brown-Peterson procedure. This finding tends to suggest a problem with the central executive in these patients. Five other patients were also impaired on the Brown-Peterson test but also had further impairment. One of these patients was impaired on the auditory syllable discrimination task. The second of these patients was impaired on both the visual and auditory phonological tasks. The third patient revealed no phonological similarity effects for either the visual or auditory modalities, the researchers suggest that this shows that for this patient information was not stored using a phonological code. This patient was also impaired on the rhyme judgement task. The fourth patient did not exhibit the phonological similarity effect in either modality. The

fifth patient again demonstrated a different pattern of performance, in which an intact phonological similarity effect was observed in the auditory modality but not in the visual modality, and vice versa for the word length effect. The test scores of the final two of the ten patients fell within the normal range for all the tasks.

These findings appear to show that there are various sub-types of AD pathology that produced differing deficits. Although the patients in the Belleville et al. (1996) study were all classified as having approximately the same disease severity, the various tests revealed that most of the patients appeared to be impaired on the central executive component, but only some of the patients had a phonological deficiency. Of those patients that were impaired phonologically there appeared to be a range of observed deficits, which further demonstrated the variability in the progression of AD pathology.

The central executive as demonstrated by the Brown-Peterson procedure revealed that eight out of ten AD patients were impaired on this task. Executive dysfunction may, therefore, present a means of distinguishing normal ageing from AD pathology. It should be noted that the performance of the normal aged participants on the Brown Peterson procedure in the Belleville et al. (1996) study, did not present any impairment in performance, in relation to the normal young participants. An alternative study by Puckett & Lawson (1989) using the Brown-Peterson task, showed that age differences in performance were minimal to non-existent. Belleville et al. (1996) suggest that it is possible that any executive impairment that is observed in normal elderly (if at all present), may be less severe than that observed in AD, and/or that the adapted Brown-Peterson procedure may not be sensitive enough to illustrate any such impairment.

In addition to executive function, phonological impairment might be a useful means of distinguishing AD patients from those of normal ageing. In the Belleville et al. (1996) study, the phonological loop appeared to be intact in the normal elderly participants, but was impaired in various ways in five of the AD patients. In comparison to the cases in which holding information in working memory is the primary deficit, other patients with Alzheimer's disease can show a different pattern of impairment in the early stages, in which learning and/or retrieval processes are the most greatly damaged (Grafman et al., 1990).

In summary, patients with AD can be seen to have severe problems retaining information, even for very limited periods of time. Impairment caused by the effect of AD has been considered to be qualitative, whereas the impairment caused by the effect of normal ageing seems more likely to be quantitative. Patients with Alzheimer's disease appear to have different patterns of impairment in the domain of working memory. The study of individuals with AD (as opposed to group studies) has revealed that central executive processes are often impaired and that there may be additional impairments in phonological processing and storage in some instances.

3.10.1 Neuro-imaging Evidence of the Effect of AD on Working Memory

Patients with very early AD, although possibly having the capability of performing within normal limits on pencil and paper neuropsychological tests, may have different functional networks than those of normal participants. The changes in activation patterns may exist due to the neuronal and structural changes that often take place within the brains of patients with AD. Neuro-imaging may provide a useful method for the investigation of Alzheimer's disease.

Becker et al. (1996) investigated the components of auditory-verbal short term memory in AD. The authors found that the AD patients had an increased field of activation compared to controls. This wider field of activation was found in those areas normally associated with working memory. In addition, the patients with AD also activated various cortical regions that were not activated by normal controls.

Rombouts, Barkhof, Van Meel and Scheltens (2002) carried out a study that used an n-back task in AD patients that consisted of 2-back, 1-back and 0-back conditions. The focus of this study, however, was to investigate the effects of the drug therapy Rivastigmine, on the activation patterns found in AD patients. The authors reported activations in the right superior frontal gyrus, the middle frontal gyrus bilaterally and the inferior frontal gyrus bilaterally, for the 1-back versus 0-back contrast. In the 2-back versus 1-back contrast, activations were seen in the superior frontal gyrus, the middle frontal gyrus, the inferior frontal gyrus and the precuneus, bilaterally, in addition to activation of the left superior parietal lobule. The experiment

showed increased activation in areas associated with working memory after the treatment with Rivastigmine. The researchers did not include an aged control group, however, so no comparisons could be made to investigate the differences due to the effects of pathological ageing that might exist between the baseline AD group and normal elderly people.

A study carried out by Saykin et al. (2004) investigated the response individuals with MCI had to the drug therapy Donepezil. The researchers used an n-back task (2-back, 1-back, 0-back) in conjunction with fMRI. The results showed that the control group of elderly participants activated the frontal and parietal cortex bilaterally, in addition to other regions. The individuals with MCI had reduced frontoparietal activation before the treatment. After treatment with Donepezil, increased frontal activation was observed in response to the n-back task.

In summary, patients with AD have been reported to activate additional areas of the cortex and to have increased fields of activation compared to normal elderly participants (Becker et al., 1996). This additional activation was considered to be due to compensatory mechanisms. The Rombouts et al. (2002) study that was described, provides a record of the brain areas activated by AD patients during an n-back task, but unfortunately it does not deal with the differences between these individuals and normal elderly people. The Saykin et al. (2004) study reported the underactivation of frontoparietal regions during an n-back task in a group with MCI that are at risk of converting to AD, when compared to a group of normal elderly. Patients with AD, when engaging in verbal working memory tasks, therefore appear to underactivate frontoparietal regions compared to normal elderly, as well as producing activation in additional areas which may be due to compensation.

3.10.2 Why might AD related changes in working memory exist?

Atrophic changes in the AD brain may contribute to the impairments in working memory that can be observed in AD patients. Salat et al. (1999) investigated the differences in grey and white matter volumes between young elderly (mean age 70), old elderly (mean age 90) and patients with AD (mean age 70). The results showed that the

AD patients had a total prefrontal volume that was approximately 15% lower than the young elderly. The AD patients had approximately 20% less white matter volume than the young elderly. The old elderly however, had approximately 30% less white matter volume than the young elderly. AD patients therefore, had reduced white matter when compared to the age matched controls, but a similar decrease in white matter was also observed as an effect of ageing. The AD participants did not differ significantly in the grey-white matter ratio when compared to either the young elderly or old elderly groups. The young elderly and old elderly groups did differ significantly on this ratio, however. The researchers reported that this result demonstrated that the effect of age on brain volume is different to the effect of AD. White matter was found to decline disproportionately more compared to grey matter in the old elderly group, whereas this difference between the deterioration between grey and white matter density did not appear to exist in AD. This result suggested that in the AD group both grey and white matter decline contributed to the decreases in prefrontal volume, whereas in the older elderly disproportionate white matter decline was the cause of the loss in prefrontal volume.

Salat et al. (2001) performed a further volumetric analysis to investigate the differences in brain volume between a group of elderly participants (mean age 72.4) and a group of patients with AD (mean age 69.8). The results revealed that the AD group had less total PFC grey matter than the age-matched controls. The differences in volume were significantly lower in the inferior PFC region alone.

The Bartzokis et al. (2003) study also revealed structural differences between a group of patients with AD and a group of participants undergoing normal ageing. The AD group that was studied consisted of 34 participants between the ages of 59 and 85. These were compared to a group of control participants that consisted of 252 participants between the ages of 19 to 82. As described, the frontal lobe white matter (FLWM) tended to increase in the control group until the age of 38 and tended to decrease after this age. However, in the AD group the FLWM volume was significantly lower when compared to a subsection of the control participants that were age and gender matched. The researchers claim that this greater reduction in FLWM in patients with AD reflects more extensive myelin breakdown to that which is observed due to the effects of normal ageing.

Decreased perfusion and metabolism of the temporo-parietal regions appears to be common amongst patients with AD. Using a longitudinal and cross-sectional design, G. S. Smith et al. (1992) reported glucose metabolic deficits in both the temporal and parietal association areas of patients with AD. Hashikawa et al. (1995) carried out a SPECT study which investigated perfusion in AD. Perfusion abnormalities were described in the temporo-parietal regions of the patients with AD.

Deficits of the cholinergic system are evident in patients with AD. One of the main sites of cholinergic depletion is the pathway from the nucleus basalis of Meynert to the cerebral cortex (Mesulam, 2000). Cholinergic projection from the nucleus basalis is used when maintaining low voltage fast activity in the surface EEG, which is arousal-related (Vanderwolf & Stewart, 1988). Cholinergic inhibition interferes with performance on sustained attention tasks (Mesulam, 2000). The cholinergic system appears to be important therefore, for attentional processes and the functioning of working memory.

In summary, various deficits occur in AD that can contribute to working memory functioning. The working memory network is thought to consist of a fronto-parietal network. Disease related changes may occur to both the frontal and parietal regions. A loss of prefrontal grey and white matter has been identified in patients with AD. Atrophy and decreased metabolism have been reported in the parietal regions. A cholinergic deficit has also been described that can create problems with attention and memory in patients with AD. Any of these disease related changes may contribute to impaired working memory function in patients with AD.

3.10.3 Benefits of the n-back task in diagnosing early AD

The use of the n-back task appears to be beneficial as a number of previous neuro-imaging studies have used versions of the n-back task to examine the working memory networks of normal controls. What is considered to be a normal pattern of activation is therefore well documented. This is useful information to have in order to compare patterns of pathological activation.

Patients with AD can be observed to have major problems in retaining information, even if it is for very brief periods of time. The drawback to using a working memory task to attempt to differentiate pathological ageing from normal ageing is that elderly controls are also prone to have decreases in the working memory load that can be retained. The effect of AD on working memory has been proposed to be qualitative, however, whereas the effect of ageing on working memory has been suggested to be quantitative (Stuart-Hamilton, 2000). If differences in brain activations can be observed on working memory tasks between patients with AD and normal control participants, this technique might present a useful method for distinguishing normal from pathological ageing. The n-back working memory task appears to be useful for investigating the differences between normal and pathological ageing as the WM load can be manipulated and the brain activations induced by these manipulations examined. By manipulating the WM load under fMRI conditions, theoretically it is possible to observe both qualitative and quantitative differences in brain activations.

Patients with AD also tend to be impaired on tasks involving the central executive. The n-back task involves manipulation of the information i.e. updating the target letter in the 1-back task and inhibiting the responses to non-target letters. These processes are tasks associated with the central executive system. The n-back task appears to be useful for investigating the differences between normal and pathological ageing as it involves phonological storage, rehearsal and the involvement of the central executive system. Looking at the various stages involved for the completion of the 1-back task, a breakdown to any one of these stages (or at multiple stages) could provide impairment on the task. Even if the severity or locus of the impairments to the possible stages varied between different patients, the framework of the working memory task could be used to account for the observed impairments. This logic (suggested by Coltheart (1984) allows us to attempt to generalise the damage across the AD patients even though they may be a somewhat heterogeneous group. It is very likely in AD that impairments may appear at many of the stages suggested to be needed for the successful completion of the task. It is because AD may impair a number of the cognitive operations necessary for the 1-back task that it may be possible to observe distinctive patterns of activation using fMRI. These patterns of activation might aid the discrimination of AD from normal ageing, even before behavioural scores show any difference.

3.10.4 Experiment 2: Hypotheses

3.10.4.1 Experiment 2a: Vigilance Hypotheses

From the previous experiment on ageing we have observed the areas that were significantly activated by the elderly group in order to complete the task. The areas activated significantly were related to:

1) Visual discrimination: The fusiform gyrus bilaterally, the left inferior occipital gyrus, the lingual gyrus bilaterally, and the cuneus bilaterally.
2) Working memory and vigilance: The left precuneus (BA 19/7). Additional and possibly compensatory areas of activation were found in the left cingulate (BA 23) and the right cingulate (BA 24 and 30).

The effects of pathological ageing are expected to exhibit a number of differences from the effects of normal ageing. These will be detailed in the hypotheses below.

AD Group:

1) Using the results of the elderly group in order to base predictions of the areas that will be activated in the AD group, areas associated with visual discrimination are likely to be activated. In the elderly these were the fusiform gyri bilaterally, the left inferior occipital gyrus, the lingual gyrus bilaterally, and the cuneus bilaterally.
2) The patients with AD are also predicted to activate those areas thought to be associated with working memory and vigilance, which were activated by the elderly. In the elderly group activation was observed in the left precuneus, the left cingulate (BA 23) and the right cingulate (BA 24 and 30).
3) The patients with AD may have reduced levels of activation in the areas used by the elderly in order to perform the task.

4) The patients with AD may employ areas of their brains that are relatively unaffected by the disease, in order to attempt to compensate for the dysfunctional areas.
5) Widespread non-selective activation might also be found in the patients with AD. This may indicate a breakdown of the vigilance network.

Note that hypotheses numbers 1 and 2 are formed on observations from the elderly. Whereas, hypotheses numbers 3-5 are based on the theory from the literature about the effects of AD on the brain.

As mentioned previously, individuals with MCI are observed to convert to AD at a higher rate than those in the normal population. At least four out of the six individuals with MCI were in the preclinical stages of AD. The MCI group are likely therefore, to have certain similarities with the AD group, but the pathological effects are expected to be less severe. It is difficult to predict whether the MCI group will look more similar to the normal elderly group or to the AD group. It should be noted that the MCI group is a purely amnestic group i.e. the cognitive impairment found in these individuals does not as yet stretch into other domains. Behaviourally the MCI group do not have attentional deficits so the activation patterns of the group might look more like the elderly group than the AD group. To summarise, the MCI group should have similarities to both the AD group and the elderly group, the extent of these similarities can not be known until the experiment has been carried out.

MCI Group:

1) Using the results of the elderly group in order to base predictions of the areas that will be activated in the MCI group, areas associated with visual discrimination are likely to be activated. In the elderly these were the fusiform gyri bilaterally, the left inferior occipital gyrus, the lingual gyrus bilaterally, and the cuneus bilaterally.
2) The individuals with MCI are also predicted to activate the areas that were activated by the elderly thought to be associated with working memory and

vigilance. In the elderly activation was observed in the left precuneus, the left cingulate (BA 23) and the right cingulate (BA 24 and 30).

3) The individuals with MCI may have reduced levels of activation in the areas used by the elderly in order to perform the task. The levels of activation will most likely not be as reduced as the levels of activation found in the AD group.
4) The individuals with MCI may activate other areas of the brain than the elderly in order to compensate for dysfunctional areas.
5) More widespread activation might be observed than that found in the elderly (this may indicate the beginnings of a breakdown of the vigilance network).

Note that hypotheses numbers 1 and 2 are formed on observations from the elderly. Whereas, hypotheses numbers 3-5 are based on the theory that a number of the individuals with MCI are in the very early stages of AD and will be exhibiting changes in activation that are characteristic of the disease. Hypotheses numbered 3-5 are therefore based on the literature about the effects of AD on the brain.

3.10.4.2 Experiment 2b: Light Working Memory Load Hypotheses

The previous experiment examined the effect of normal ageing on the 1back versus 0-back comparison. From this earlier experiment significant areas of activation were observed for the elderly group. The areas that were activated significantly were the left inferior parietal lobule (BA 40), the left superior parietal lobule (BA 7), the left precuneus (BA 7), the left middle frontal gyrus (BA 9), the right middle frontal gyrus (BA 13), the right precentral gyrus (BA 6), the left inferior temporal gyrus (BA 37) and the right insula (BA 13). These areas have been mentioned to be involved in verbal working memory, speech planning and phoneme processing. Additional areas of activation included the left middle occipital gyrus (BA 19) and the right parahippocampal gyrus (BA 27).

In the patients with AD, the same areas that were used by the elderly may be expected to be activated if the patients are to perform the task successfully. A number of differences between the effects of normal ageing and the effects of pathological

ageing in the form of AD might be expected however, these will be outlined in the hypotheses below.

AD Group:

1) Using the activation of the elderly to predict the pattern of activation in the AD group, activation would be expected in the left inferior parietal lobule (BA 40), the left superior parietal lobule (BA 7), the left precuneus (BA 7), the left middle frontal gyrus (BA 9), the right middle frontal gyrus (BA 13), the right precentral gyrus (BA 6), the left inferior temporal gyrus (BA 37), the right insula (BA 13), the left middle occipital gyrus (BA 19) and the right parahippocampal gyrus (BA 27).
2) Underactivation to certain areas activated by the elderly may occur in brains of the patients with AD.
3) A number of areas used by the elderly may be dysfunctional in the AD group. If this is the case, compensation may be attempted by the AD group, during which alternative areas of the brain may be activated than those seen in the elderly group.
4) Widespread activation, possibly in a non-selective manner might be observed in the brains of the patients with AD.

Note that hypothesis number 1 is based on predictions from the elderly. Hypotheses 2-4 are based on the literature on AD.

The individuals with MCI would be expected to share sites of activation to some extent with the elderly group, as they themselves are elderly and the four individuals that are known to have converted to AD were only in the preclinical stages of the disease at the time of scanning. As at least four out of the six individuals with MCI were in the very early stages of AD however, some similarities to the AD group may be expected (and subsequently certain differences to the elderly group might be expected).

MCI group:

1) Again using the activation of the elderly to predict the pattern of activation. The MCI group would be expected to activate the left inferior parietal lobule (BA 40), the left superior parietal lobule (BA 7), the left precuneus (BA 7), the left middle frontal gyrus (BA 9), the right middle frontal gyrus (BA 13), the right precentral gyrus (BA 6), the left inferior temporal gyrus (BA 37), the right insula (BA 13), the left middle occipital gyrus (BA 19) and the right parahippocampal gyrus (BA 27).
2) A number of areas that were activated by the elderly may be under-activated in the MCI group.
3) The individuals with MCI that are experiencing pathological changes may attempt to compensate for these by activating alternative regions to aid successful task completion.
4) The MCI group may exhibit a more widespread pattern of activation than that seen in the elderly group. This activation might be non-selective and have no obvious explanation for its occurrence.

3.10.5 Methods

3.10.5.1 Participants

The participant groups consisted of 8 elderly participants, 6 individuals with MCI and 12 patients with AD. The elderly controls consisted of 2 males and 6 females between the ages of 72 and 77. The mean age of the elderly participants was 75 (SD 1.69). The AD group was made up of 7 males and 5 females between the ages of 69 and 88. The mean age of the patients with AD was 78 (SD 5.51). The individuals with MCI were composed of 4 males and 2 females between the ages of 66 and 87. The mean age of the MCI group was 76.33 (SD 7.61).

The participants were all British and English was their first language. All the participants recruited for the study were right handed. Ethical approval was approved by the joint Grampian Health Board and the University of Aberdeen Ethics Committee.

3.10.5.2 Patient Selection

Twelve patients diagnosed with AD in the early stages and six individuals identified with MCI were enrolled into the fMRI n-back study. The patients with AD and individuals with MCI were selected from approximately one hundred patients with memory problems that were referred to an old age psychiatry memory clinic in Aberdeen to be screened for participation in this study. Patients were excluded if they were claustrophobic, if they had vascular risk factors (a Hachinski Ischaemia score (Hachinski et al., 1975) greater than four), or a score on the Mini Mental State Exam (MMSE) of less than eighteen. The patients that were selected for the study met the NINCDS-ADRDA criteria for probable AD (McKhann et al., 1984) of minimal to mild severity. The diagnosis of MCI was made using the R. C. Petersen (1997) criteria for amnestic MCI. A summary of the neuropsychological assessment scores for the AD patients and individuals with MCI is included below (Table 3.20).

Table 3.20

The means (and standard deviations) for the neuropsychological test scores of the patients with AD and the individuals with MCI.

Neuropsychological Test	AD group		n	MCI group		n
	Mean	(SD)		Mean	(SD)	
Mini Mental State Exam (MMSE)	24.08	(2.31)	12	27.00	(3.63)	6
ADAS Cog	17.5	(4.83)	12	NA	NA	0
Confrontational Naming	16.83	(3.76)	12	17.83	(1.47)	6
Verbal Paired Associates	8.91	(2.84)	11	9.00	(2.00)	6
The Pyramids and Palm Trees Test	47.88	(4.76)	8	50.00	(3.46)	3
Rey's Complex Figure Test (Copy)	23.92	(8.13)	6	25.50	(0.00)	1
Rey's Complex Figure Test (Delay)	2.25	(2.19)	6	0.00	(0.00)	1
Semantic Fluency	29.30	(11.63)	10	40.33	(15.92)	6
Phonemic Fluency	24.40	(9.58)	10	42.00	(23.87)	6
Digit Span Forward	6.56	(0.73)	9	6.17	(1.47)	6
Digit Span Backward	4.56	(0.88)	9	4.67	(1.21)	6
Logical Memory: Immediate	6.00	(4.69)	8	5.00	(1.73)	3
Delayed (10 minutes)	3.50	(5.10)	8	6.67	(2.52)	3
Raven's Progressive Matrices	23.42	(3.37)	12	27.33	(4.84)	6
Stroop task (Error Interference)	8.79	(10.76)	12	0.90	(1.02)	5
Stroop task (Time Interference)	39.67	(22.30)	12	27.70	(8.89)	5
Digit Cancellation	44.70	(6.20)	10	48.67	(14.74)	3
Visuoconstructive Apraxia Test	12.00	(2.12)	5	12.33	(1.15)	3
Token Task	31.00	(1.83)	8	28.50	(0.00)	1

Note: NA - Not Available
ADAS - cog: Alzheimer's Disease Assessment Scale - cognitive subscale
Not all the AD patients or individuals with MCI did all the tests. The numbers that comprise each mean and standard deviation have been included.

3.10.5.3 Materials

fMRI was performed on a 1.5 Tesla MRI system equipped with echo-planar imaging capabilities using a standard head coil. The stimuli where presented onto a screen viewable with a mirror attached to the head coil with the use of a PC via LCD projector. The participants were equipped with a response device in the left and right hand.

3.10.5.4 fMRI Paradigm

The same fMRI n-back paradigm that was employed in the previous working memory experiment to investigate the ageing effect was used (with the exception of the 2-back condition). The AD patients performed the conditions of baseline, 0-back and 1-back. The elderly data from the previous working memory ageing experiment were used in order to make comparisons with the patients with AD. The elderly had performed the conditions of baseline, 0-back, 1-back and 2-back. The AD patients were tested on a reduced set of conditions (excluding the 2-back task), to keep the tasks as short as possible, in order to maintain attention and furthermore, to reduce the difficulty of the task. The 2-back condition is quite demanding on working memory, and the patients would most likely have had problems in completing the task. The addition of the 2-back task could also have lead to confusion in the other conditions. Even with the reduced set of conditions, however, vigilance could be inspected using the comparison of the 0-back condition versus Baseline condition, and working memory could be examined using the 1-back condition versus the 0-back condition. For each of the tasks the presentation screen was white and the letters or symbols were presented in a black "Times New Roman" font.

Note that the n-back task could have been constructed in such a way as to reveal perseverations by the patients (or the controls). The n-back task in the present study was not set up in such a manner. In the current experiment the possibility of perseveration was not created in the paradigm, the reason being that the task was

thought to be difficult enough for the patients with AD, without trying to provoke perseverative behaviour (which might have caused confusion in the patients). Therefore, in the present experiment, during the 1-back condition, no presentations of the letter "X" were made (which was the target in the 0-back) and any letter that was repeated (i.e. a target) in the 1-back condition was not re-presented as a single letter in the same condition.

The first condition in the experiment was the baseline. This consisted of the baseline instructions which lasted for five seconds, after which came the test stimuli. Eighteen hash symbols were presented serially (in the centre of the screen), for 2000ms each, with a blank screen interstimulus interval of 500ms. The participant had to observe the hash symbols and push a response button every time the hash symbol was presented.

The second condition was the 0-back. The 0-back instructions lasted for five seconds after which the 0-back test sequence was presented. Each letter was presented for 2000ms with a blank screen interstimulus interval of 500ms. In total eighteen letters were projected before the beginning of the next condition. The participant's task in this condition was to watch the letters and push a response button, whenever the letter X was presented. It should be noted that this is the only condition in which the letter X was displayed. This condition was used to test the vigilance of the participant.

The third condition was the 1-back condition. The 1-back instructions lasted for five seconds before the 1-back test sequence was presented. Each letter was presented for 2000ms with a blank screen interstimulus interval of 500ms. Eighteen letters were projected before the next set of instructions appeared. The participant had to observe the letters and had to push a response button every time the same letter appeared consecutively. This condition was used to produce a low working memory load.

In all the letter conditions only consonants were used. There were no vowels and the letter Y was absent from the presentations. The exception of the vowels and the letter Y was to prevent the participants using syllables to remember the letters. The participants had a button positioned for response with the left hand and one for the right

hand. The participants responded to the task demands using the button with which they felt most comfortable.

3.10.5.5 Procedure

The training procedure for the individuals with MCI and the patients with AD was the same as for the elderly in the previous experiment. During the scanning sessions each participant was instructed to lie on their back in the scanner. By looking upwards at an angled mirror, the participants could see a projector screen on which the stimuli were presented. The participants had to respond to the stimuli by pushing either the left or right button on their left or right hand. All participants requiring corrected vision were provided with plastic framed glasses which fitted their prescription.

The first part of the scanning procedure consisted of four dummy scans, the duration of which allowed the scanner to reach equilibrium. The order in which the conditions were presented was baseline, 0-back and 1-back. This completed the first complete run of all the conditions. All the conditions were repeated two more times, meaning that the participant performed three baseline test phases, three 0-back test phases and three 1-back test phases. This completed the first test session. In total, the first test session consisted of 135 seconds of baseline scanning, 135 seconds of 0-back scanning and 135 seconds of 1-back scanning. In addition, the entire test session was repeated, in order to strengthen the statistical power of the data analysis.

The number of targets in each condition for session 1 consisted of 18, 18 and 18 for the baseline runs 1, 2, and 3 respectively. There were 5, 5 and 6 targets for the 0-back runs 1, 2 and 3, respectively. There were 3, 4 and 4 targets for the 1-back runs 1, 2 and 3, respectively. The number of targets was the same for session two. Different stimuli and target positions were used in session 2.

3.10.5.6 fMRI Methods

The fMRI acquisition was carried out on a 1.5 Tesla GE MRI system that was equipped with echo-planar imaging capabilities using a standard head coil. The following parameters were used: TE = 35ms, TR = 2.5s, in plane resolution 2x2mm^2, 5mm slice thickness.

3.10.5.7 fMRI Data Analyses

The statistical design consisted of three different participant groups undergoing the n-back task (an AD patient group, an MCI group and an elderly group). Both the AD and MCI groups performed the conditions of baseline, 0-back, 1-back. This enabled the effect of Alzheimer's disease to be examined for both the vigilance and the working memory conditions.

The fMRI data were analysed using Statistical Parametric Mapping (SPM99) (Wellcome Department of Imaging Neuroscience, London). Images were re-aligned using a double pass procedure (first creating a mean of the images and then realigning to this mean. The following steps involved normalisation into standard stereotactic space and smoothing using a Gaussian filter set at 8 mm.

3.10.6 Results

3.10.6.1 Analysis of behavioural performance

The ages, years of education and scores on the Mini Mental State Examination (MMSE) were examined in the elderly, AD and MCI groups (Table 3.21). ANOVA was used to compare the groups on these variables. No main effect of age was observed, $F(2,23) = .790$; p = ns. Main effects of years of education, $F(2,23) = 3.674$; $p < 0.05$ and of MMSE, $F(2,23) = 10.019$; $p < 0.001$, were found however. Planned between-subjects contrasts showed that the MMSE scores of the AD group were significantly lower the elderly group ($p < 0.001$) and the MCI group ($p < 0.05$). Scheffe

post-hoc testing revealed, the number of years of education were significantly higher for the MCI group compared to the AD group ($p < 0.05$). The number of years of education did not differ significantly for any other combinations of the groups.

Table 3.21

Displays the means (and standard deviations) for the ages, educations and MMSE scores of the elderly, MCI and AD groups.

Group	N	Age	Education (yrs)	MMSE
Elderly	8	75.00 (1.69)	11.88 (2.36)	28.88 (0.99)
MCI	6	76.33 (7.61)	13.83 (3.60)	27.00 (3.63)
AD	12	78.00 (5.51)	10.25 (2.34)	24.08 (2.31)

Note: The maximum attainable score on the MMSE is thirty.

The behavioural scores on the fMRI paradigm for the elderly, the individuals with MCI and the AD patients were compared (Table 3.22). ANOVA was used to investigate the mean proportion of correct scores on the 0-back and 1-back tasks for the three groups. The within-subjects factor was condition (0-back and 1-back) and the between-subjects factor was group (elderly, MCI and AD). A main effect of condition was observed, $F(1,23) = 4.995$; $p < 0.05$. The groups had a significantly lower proportion of correct scores on the 1-back than the 0-back. No main effect of group was seen, $F(1,23) = .610$; p = ns, neither was any interaction between condition and group, $F(2,23) = 1.377$; p = ns. When the ANOVA was broken down into group, no main effect of condition was seen for the elderly group, $F(1,7) = .354$; p = ns, or the MCI group, $F(1,5) = 2.797$; p = ns, or the AD group, $F(1,11) = 3.667$; p = ns. This analysis shows that the difference in the proportion of scores correct for each condition (0-back and 1-back) is not attributed to one group in particular, but is due to a combination of the groups.

Table 3.22

The mean scores for the elderly, MCI and AD groups on the 0-back and 1-back conditions

Condition	Group	N	Mean (SD)
0-back scores	Elderly	8	31.88 (0.35)
	MCI	6	31.83 (0.41)
	AD	12	31.75 (0.45)
1-back scores	Elderly	8	21.75 (0.71)
	MCI	6	21.33 (0.82)
	AD	12	21.75 (0.45)

Note: The maximum score of the 0-back is 32.
The maximum score of the 1-back is 22.

Figure 3.25 shows the mean reaction times of the elderly, MCI and AD groups on the 0-back and 1-back conditions. The reaction times were investigated using ANOVA. There was no main effect of condition, F (1,23) = 2.128; p = ns, or group, F (2,23) = 3.000; p = ns, and no interaction between condition and group, F (2,23) = .630; p = ns.

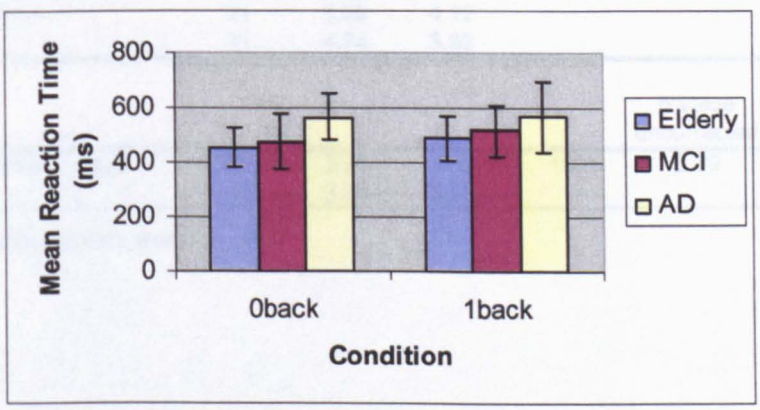

Fig 3.25: The mean reaction times for the elderly, MCI and AD groups on each experimental condition (error bars of the standard deviations are provided).

3.10.6.2 fMRI Experiment 2a: Detection of the Areas used in Sustained Attention, Target Detection and Visual Discrimination

AD Group: A random effects analysis (0-back versus baseline contrast) was performed on the twenty-four available sessions of the AD group. Activation was detected in the left superior temporal gyrus (BA 39), the right cingulate gyrus (BA 31) and the right precuneus (BA 31) at the $p < 0.01$ level of significance (corrected). Additional activation was also observed in the right superior parietal lobule (BA 7) when viewed with an uncorrected threshold. The particulars of the activations can be found in Table 3.23, and a visual depiction of the locations of the activations can be seen in Fig 3.26.

Table 3.23

The areas of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the 0-back versus Baseline contrast in the AD group.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Superior Temporal Gyrus	39	5.66	4.43	5364	0.000	-32	-53	32
Right Cingulate Gyrus	31	5.08	4.12			18	-45	24
Left Precuneus	31	4.74	3.92			-14	-49	28
b)					p-value uncorrected			
Right Superior Parietal Lobule	7	3.92	3.4	190	0.79	28	-67	51
	7	3.54	3.13			12	-67	57

Note: * BA refers to Brodmann's Areas.

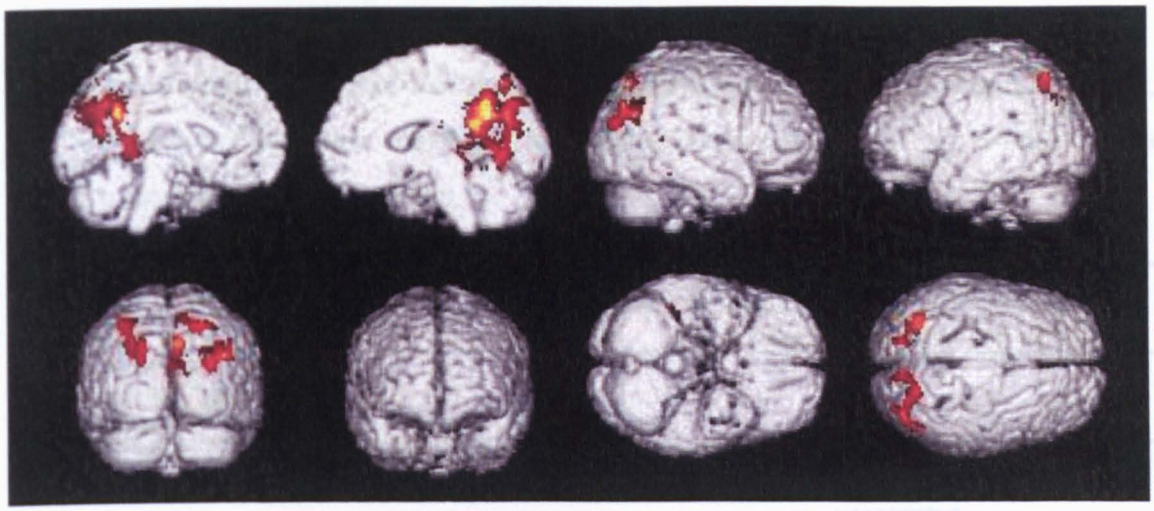

Fig 3.26: The sites of activation in the AD group for the 0-back versus Baseline contrast (corrected and uncorrected activations are displayed).

The activation in the AD group did not look very similar to the activation observed in the elderly group. For this reason, the 0-back versus Baseline comparison in the AD group was also repeated at the $p < 0.05$ level of significance (see Table 3.24 and Figure 3.27). This more liberal threshold of significance was used in order to investigate whether the AD group are activating the same structures as the elderly, except at a lower level. The results revealed activation (corrected) in the left superior temporal gyrus (BA 39), the right cingulate gyrus (BA 31), and the left precuneus (BA 31). Activation was also observed (uncorrected) in the left anterior cingulate (BA 32) and in the left lentiform nucleus (putamen).

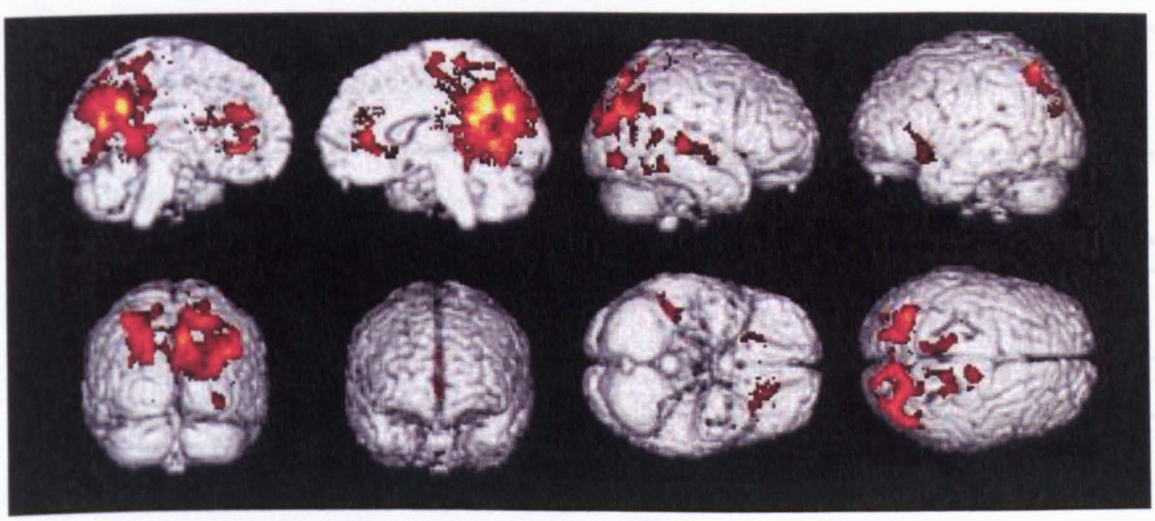

Fig 3.27: The areas of activation in the AD group found for the 0-back versus Baseline contrast (both corrected and uncorrected activations are shown).

Table 3.24

The areas of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the 0-back versus Baseline contrast in the AD group.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Superior Temporal Gyrus	39	5.66	4.43	17427	0.000	-32	-53	32
Right Cingulate Gyrus	31	5.08	4.12			18	-45	24
Left Precuneus	31	4.74	3.92			-14	-49	28
b)					p-value uncorrected			
Left Anterior Cingulate	32	4.39	3.7	2269	0.055	-10	31	-5
	32	3.99	3.44			-2	38	17
Left Lentiform Nucleus		3.64	3.2			-24	3	13

Note: * BA refers to Brodmann's Areas.

AD Group versus Elderly Group Comparison: A significant difference in activation was seen in the right precuneus (BA 31), at the $p < 0.01$ level of significance (corrected). Differences in activation were also observed, in the left anterior cingulate (BA 32) and the left caudate head (uncorrected). See Table 3.25 and Figure 3.28 for further details.

Table 3.25

Sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for AD group versus the elderly group comparison on the 0-back versus Baseline contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Right Precuneus	31	4.47	3.98	1971	0.000	10	-67	27
b)					p-value uncorrected			
Left Caudate Head		4.54	4.03	195	0.046	-16	25	1
Left Anterior Cingulate	32	2.67	2.54			-6	39	-2

Note: * BA refers to Brodmann's Areas.

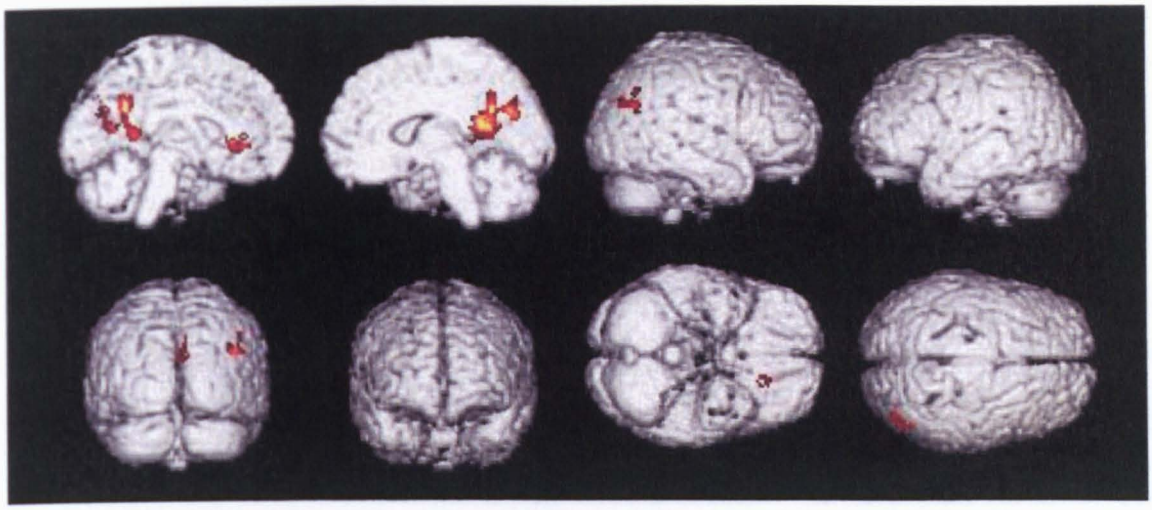

Fig 3.28: Differences in activation for the comparison of the Patients with AD versus Elderly found for the 0-back versus Baseline contrast (corrected and uncorrected thresholds).

At the 0.05 level of significance, additional activation was also observed in the right anterior cingulate (BA 24).

Elderly Group versus AD Group Comparison: At the $p < 0.01$ level of significance, no significant differences were observed for this comparison. At the $p < 0.05$ level of significance (uncorrected), differences were found in the right inferior frontal gyrus (BA 9), the right precentral gyrus (BA 44) and the right middle frontal gyrus (BA 6). The areas that had significant differences in activation can be seen in Table 3.26 and in Figure 3.29.

Table 3.26

The areas of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the 0-back versus Baseline contrast in the elderly group versus AD group comparison.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Right Inferior Frontal Gyrus	9	3.23	3.02	1245	0.01	48	10	22
Right Precentral Gyrus	44	2.84	2.68			52	8	12
Right Middle Frontal Gyrus	6	2.72	2.58			34	14	42

Note: * BA refers to Brodmann's Areas.

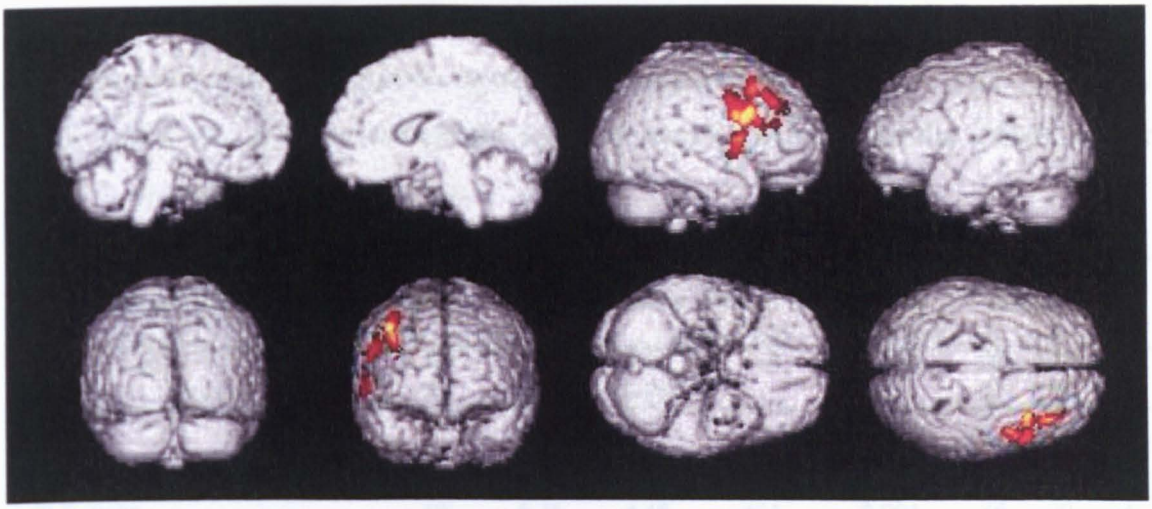

Fig 3.29: The differences in the Elderly versus Patients with AD comparison found for the 0-back versus Baseline comparison.

MCI Group: The right precuneus (BA 19) and the right middle temporal gyrus (BA 39) were activated at the $p < 0.01$ level of significance (corrected). When an uncorrected threshold was used, activation was observed in the left cuneus (BA 19), the left precuneus (BA 19), the right superior temporal gyrus (BA 21 and 38), the right middle temporal gyrus (BA 21 and 38) and the right insula (BA 13). Further descriptions of these activations can be seen in Table 3.27, in addition to a visual representation, which can be viewed in Figure 3.30.

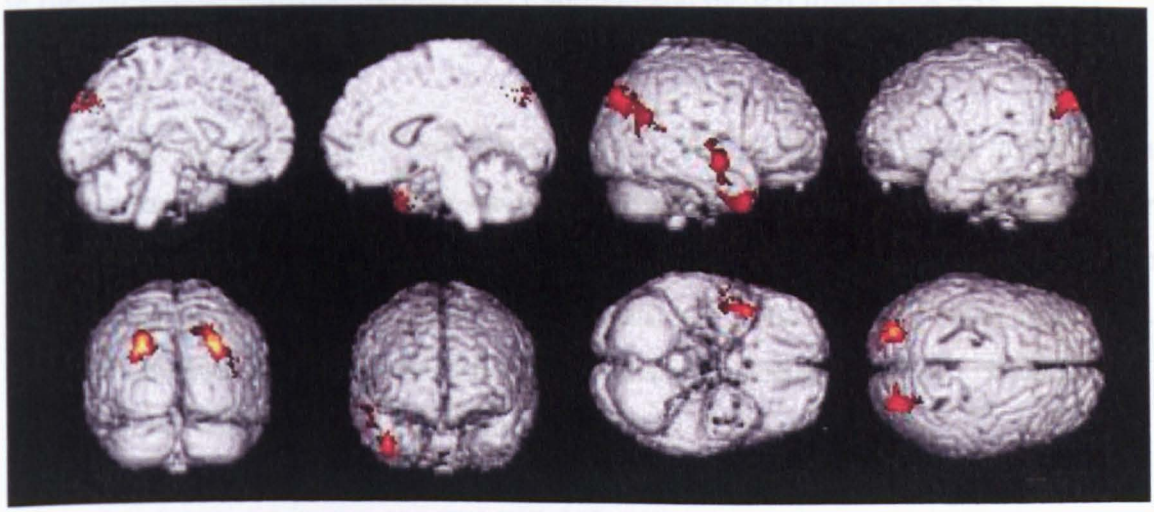

Fig 3.30: The areas of activation in the MCI group found for the 0-back versus Baseline contrast (corrected and uncorrected levels of significance are shown).

Table 3.27

The sites of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the 0-back versus Baseline contrast in the MCI group.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Right Precuneus	19	9.48	4.85	768	0.016	28	-72	35
Right Middle Temporal Gyrus	39	5.98	3.91			38	-59	25
b)					p-value uncorrected			
Left Cuneus	19	6.71	4.15	454	0.004	-18	-92	34
Left Precuneus	19	6.11	3.96			-28	-72	28
Left Precuneus	19	5.17	3.61			-26	-80	36
Right Superior Temporal Gyrus	21	5.27	3.65	276	0.018	50	-8	-12
Right Insula	13	4.24	3.2			44	-2	-6
Right Middle Temporal Gyrus	21	3.52	2.82			54	-2	-22
Right Middle Temporal Gyrus	21	4.52	3.33	212	0.034	42	10	-36
	38	3.85	3			38	14	-46
Right Superior Temporal Gyrus	38	3.56	2.84			44	20	-34

Note: * BA refers to Brodmann's Areas.

The 0-back versus Baseline contrast was also investigated at the $p < 0.05$ threshold of significance in the MCI group in order to see if lower levels of activation were present in the areas associated with the visual discrimination of letters, or in the well-documented areas associated with vigilance. Additional activation was observed in the left middle temporal gyrus (BA 21 and 22) and the left insula (BA 13).

MCI Group versus Elderly Group Comparison: Significant differences in activation were detected in the left middle temporal gyrus (BA 21 and 22), the left superior temporal gyrus (BA 41), the right middle temporal gyrus (BA 39), the right superior temporal gyrus (BA 22), the right supramarginal gyrus (BA 40), the right insula (BA 13), the right substantia nigra and the right subthalamic nucleus ($p < 0.01$, uncorrected). These can be seen in Table 3.28 and in Figure 3.31.

Table 3.28

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the 0-back versus Baseline contrast in the MCI group versus elderly group comparison.

Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Middle Temporal Gyrus	22	4.05	3.53	395	0.01	-59	-39	6
Left Superior Temporal Gyrus	41	3.3	2.99			-46	-34	11
Left Middle Temporal Gyrus	21	3.25	2.95			-51	-31	-3
Right Middle Temporal Gyrus	39	5.31	4.33	399	0.010	42	-57	23
Right Supramarginal Gyrus	40	2.81	2.6			48	-47	30
Right Superior Temporal Gyrus	22	5.22	4.28	423	0.008	48	-4	-8
Right Superior Temporal Gyrus	22	4.29	3.7			48	-16	-4
Right Insula	13	3.89	3.42			40	-4	-3
Right Substantia Nigra		3.78	3.34	385	0.011	6	-14	-13
Right Subthalamic Nucleus		3.77	3.34			8	-12	-3

Note: * BA refers to Brodmann's Areas.

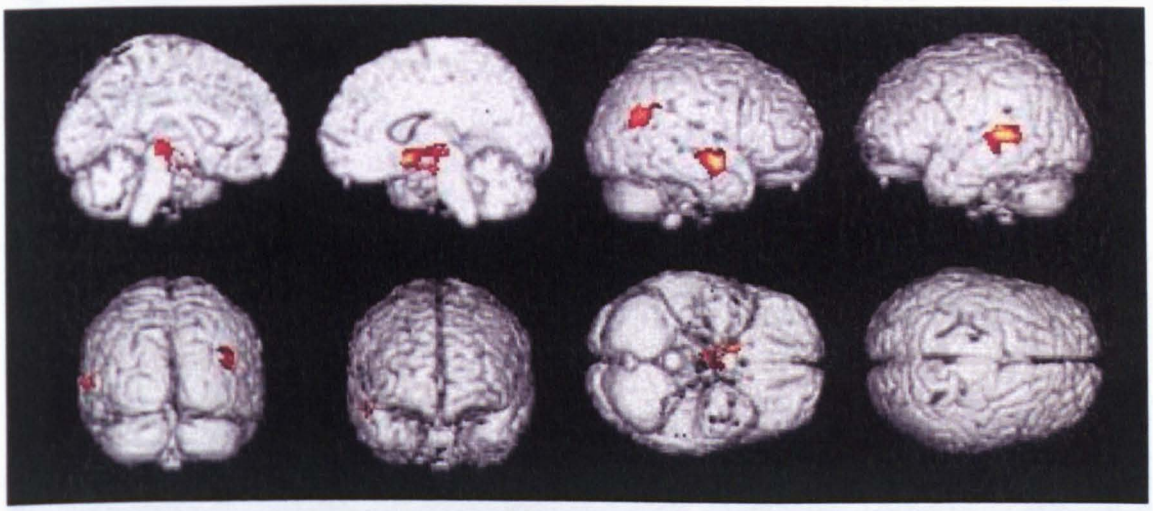

Fig 3.31: Significant differences in the MCI group versus elderly group comparison found for the 0-back versus Baseline contrast.

At the more liberal significance threshold of $p < 0.05$ (uncorrected), additional differences in activation were observed in the left inferior frontal gyrus (BA 47), the left middle occipital gyrus (BA 19), the left precuneus (BA 19), the left hippocampus, the left cingulate gyrus (BA 31) and the right thalamus.

Elderly group versus MCI group Comparison: This comparison yielded activations in the left superior frontal gyrus (BA 6), the right cingulate gyrus (BA 23), the left cingulate gyrus (BA 24), the right precuneus (BA 7) and the right postcentral gyrus (BA 5) when the $p < 0.01$ (uncorrected) level of significance was used (see Table 3.29 and Figure 3.32).

Table 3.29

The areas of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the 0-back versus Baseline contrast in the elderly group versus MCI group comparison.

Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Superior Frontal Gyrus	6	4.24	3.67	358	0.014	0	5	53
Right Cingulate Gyrus	23	3.93	3.45			6	-20	32
Left Cingulate Gyrus	24	3.61	3.22			-4	-8	39
Right Precuneus	7	3.55	3.18	347	0.015	2	-52	47
Right Postcentral Gyrus	5	3.49	3.09			6	-45	67
Right Precuneus	7	3.35	3.02			2	-44	52

Note: * BA refers to Brodmann's Areas.

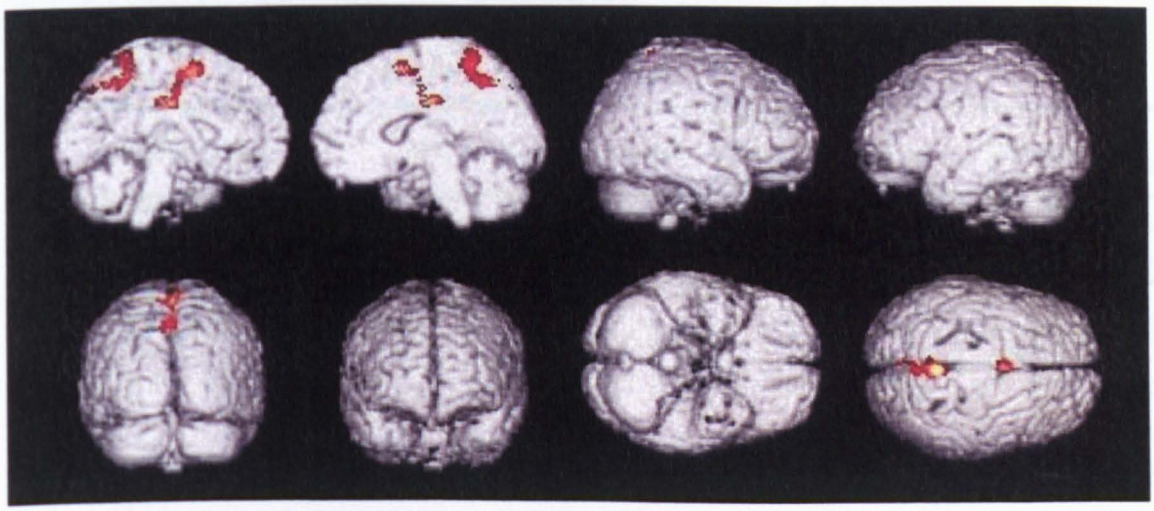

Fig 3.32: Significant differences in activation in the elderly group versus MCI group comparison found for the 0-back versus Baseline contrast.

When a less conservative threshold of significance ($p < 0.05$, corrected) was investigated, an additional significant difference was seen in the left cingulate gyrus (BA 23). Differences in activation also occurred in the right cingulate cortex (BA 42) and the right medial frontal gyrus (BA 9) when an uncorrected level of significance was used.

MCI group versus AD group Comparison: There were no significant differences for this comparison even at a liberal threshold ($p < 0.05$).

AD group versus MCI group Comparison: Differences in activation were present in the right precuneus (BA 7), the right cuneus (BA 7) and the right cingulate gyrus (BA 31), at the $p < 0.01$ level of significance (corrected). The areas that showed these differences are detailed in Table 3.30 and illustrated in Figure 3.33.

Table 3.30

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the 0-back versus Baseline contrast in the AD group versus MCI group comparison.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Right Precuenus	7	4.64	4.05	742	0.029	4	-55	46
Right Cuneus	7	4.17	3.72			10	-68	31
Right Cingulate Gyrus	31	3.67	3.35			7	-42	33

Note: * BA refers to Brodmann's Areas.

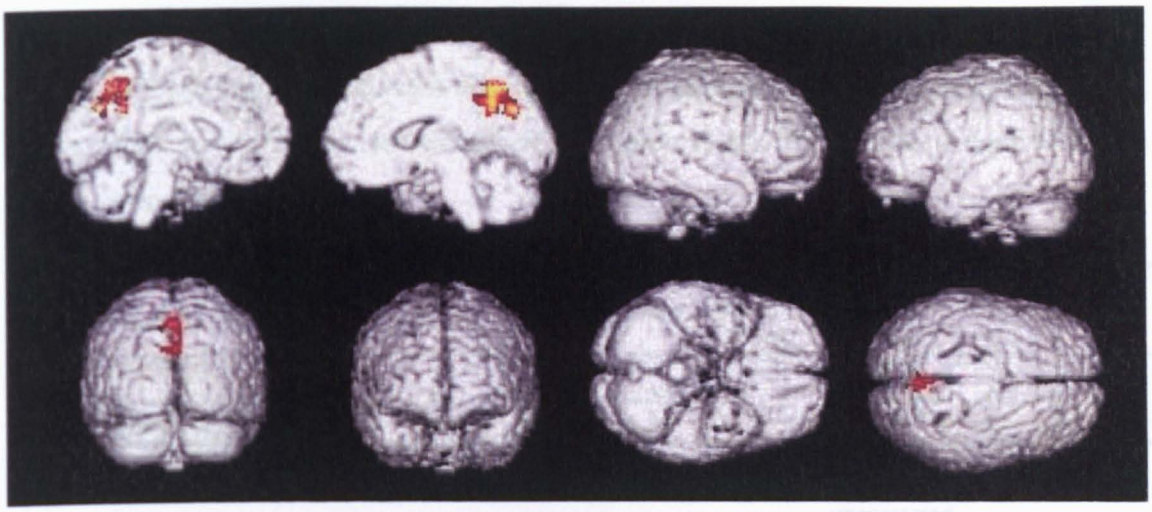

Fig 3.33: Significant differences in the AD group versus MCI group comparison found for the 0-back versus Baseline contrast.

When the results were examined with a less conservative threshold, additional differences in activation were observed in the left anterior cingulate (BA 32), the left inferior parietal lobule (BA 40), the left postcentral gyrus (BA 40), the left supramarginal gyrus (BA 40) and the right thalamus ($p < 0.05$).

3.10.6.3 fMRI Experiment 2b: Detection of Regions Involved with a Low Working Memory Load

AD Group: The left precentral gyrus (BA 6/4) and the left middle frontal gyrus (BA 9) were activated significantly ($p < 0.01$, corrected). The left cingulate gyrus (BA 24), the left anterior cingulate (BA 33/24), the right cingulate gyrus (BA 32), the right medial frontal gyrus (BA 6/32), the right inferior frontal gyrus (BA 47), and the right insula (BA 47) were activated at the uncorrected level of significance. Table 3.31 gives more information on the clusters of significant activation, whereas Figure 3.34 provides a visualisation of the activations.

Table 3.31

The sites of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the 1-back versus 0-back contrast in the AD group.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Precentral Gyrus	6	5.4	4.3	927	0.002	-50	-2	35
Left Middle Frontal Gyrus	9	4.96	4.05			-44	9	33
Left Precentral Gyrus	4	3.87	3.36			-50	-8	41
b)					p-value uncorrected			
Left Cingulate Gyrus	24	4.25	3.61	157	0.048	-6	-2	28
Left Anterior Cingulate	33	3.98	3.49			-4	11	20
	24	2.65	2.45			-8	19	23
Right Inferior Frontal Gyrus	47	7.11	5.12	196	0.030	34	25	-3
Right Insula	47	4.4	3.71			42	17	-1
Right Cingulate Gyrus	32	4.55	3.81	277	0.012	8	17	32
Right Medial Frontal Gyrus	6	3.08	2.79			6	33	35
	32	3	2.79			10	14	45

Note: * BA refers to Brodmann's Areas.

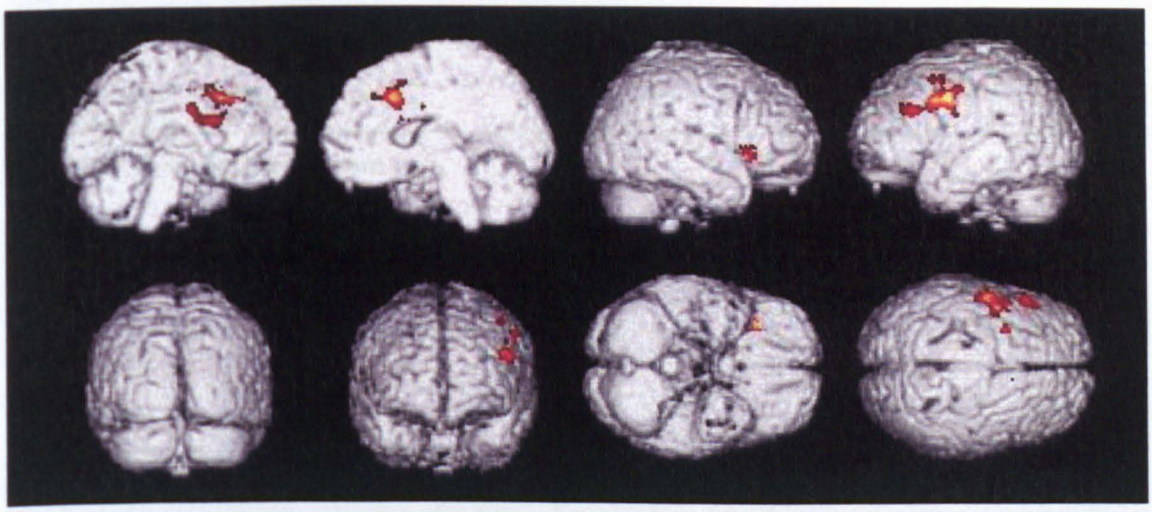

Fig 3.34: Areas of activation found in the AD group for the 1-back versus 0-back contrast (both for corrected and uncorrected thresholds).

The AD group were also investigated at the $p < 0.05$ level of significance (corrected) in order to examine if further activation was occurring at a lower intensity (see Table 3.32 and Figure 3.35). Additional activations were observed in the right middle frontal gyrus (BA 6) and the right caudate body. Further activations were seen

in the right inferior parietal lobule (BA 40), the right superior parietal lobule (BA 7), the left thalamus (ventral lateral nucleus), the right thalamus (medial dorsal nucleus) and the right lentiform nucleus (lateral globus pallidus), when uncorrected threshold was used.

Table 3.32

Areas of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a), and uncorrected (b), for the 1-back versus 0-back contrast in the AD group ($p < 0.05$).

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Right Inferior Frontal Gyrus	47	7.11	5.12	2278	0.038	34	25	-3
Right Insula	47	4.4	3.71			42	17	-1
Right Middle Frontal Gyrus	6	4.28	3.63			40	37	35
Left Precentral Gyrus	6	5.4	4.3	4975	0.000	-50	-2	35
Left Middle Frontal Gyrus	9	4.96	4.05			-44	9	33
Right Caudate Body		4.9	4.01			6	14	18
b)					p-value uncorrected			
Right Inferior Parietal Lobule	40	3.52	3.11	733	0.028	50	-46	48
Right Superior Parietal Lobule	7	3.45	3.06			34	-61	56
Right Inferior Parietal Lobule	40	3.2	2.88			38	-50	41
Left Thalamus		3.45	3.06	637	0.039	-12	-11	4
Right Lentiform Nucleus		3.17	2.85			14	-4	4
Right Thalamus		2.69	2.49			4	-15	10

Note: * BA refers to Brodmann's Areas.

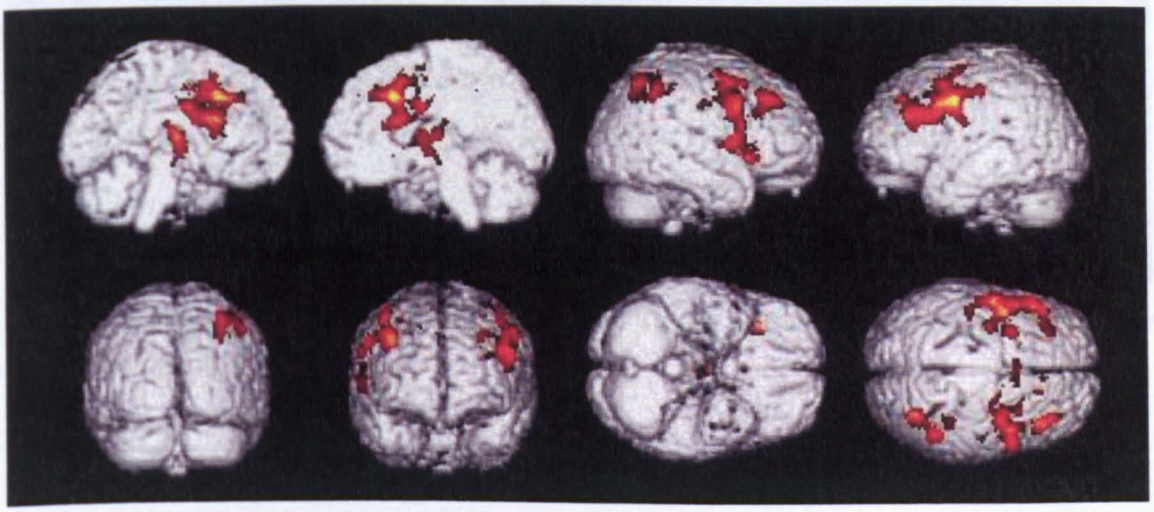

Fig 3.35: Significant activations found in the AD group for the 1-back versus 0-back contrast at the $p < 0.05$ threshold (both for corrected and uncorrected thresholds).

AD Group versus Elderly Group Comparison: At the $p < 0.01$ level of significance, no significant differences arose from this comparison. Using a more liberal threshold of significance ($p < 0.05$, uncorrected), differences occurred in the right cingulate gyrus (BA 32), the left middle frontal gyrus (BA 6) and the left caudate body (see Table 3.33 and Figure 3.36).

Table 3.33

Sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the 1-back versus 0-back contrast in the AD group versus Elderly group comparison.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Right Cingulate Gyrus	32	3.71	3.41	1786	0.002	8	14	38
Left Middle Frontal Gyrus	6	3.29	3.07			-22	-4	42
Left Caudate Body		3.16	2.96			-6	0	20

Note: * BA refers to Brodmann's Areas.

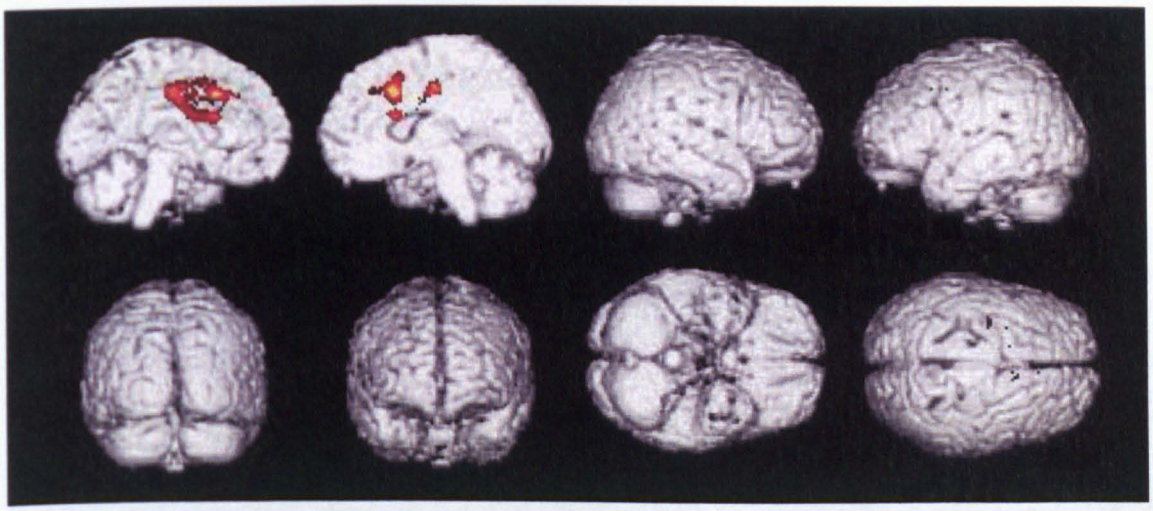

Fig 3.36: Differences in the AD group versus Elderly group comparison found for the 1-back versus 0-back contrast.

Elderly Group versus AD Group Comparison: Significant differences in activation were detected in the left parahippocampal gyrus (BA 19/27), the right parahippocampal gyrus (BA 19), the left posterior cingulate (BA 23), the right posterior cingulate (BA 29), the left precuneus (BA 31), the right fusiform gyrus (BA 19) and the left lentiform nucleus (lateral globus pallidus) at the $p < 0.01$ level of significance (uncorrected). Extra information on the differences can be found in Table 3.34 and an illustration of these can be seen in Figure 3.37.

Table 3.34

Sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the 1-back versus 0-back contrast in the Elderly group versus AD group comparison.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Parahippocampal Gyrus	19	4.44	3.96	465	0.003	-18	-47	-9
Left Lentiform Nucleus		3.99	3.62			-24	-18	-6
Left Parahippocampal Gyrus	27	3.86	3.52			-22	-33	-5
Right Posterior Cingulate	29	4.27	3.83	500	0.002	2	-38	13
Left Precuneus	31	3.14	2.94			-2	-51	30
Left Posterior Cingulate	23	3.09	2.9			-4	-55	18
Right Sub-Gyral	19	4.27	3.83	402	0.005	12	-49	-11
Right Fusiform Gyrus	19	3.41	3.16			24	-62	-5
Right Parahippocampal Gyrus	19	2.98	2.81			30	-45	-6

Note: * BA refers to Brodmann's Areas.

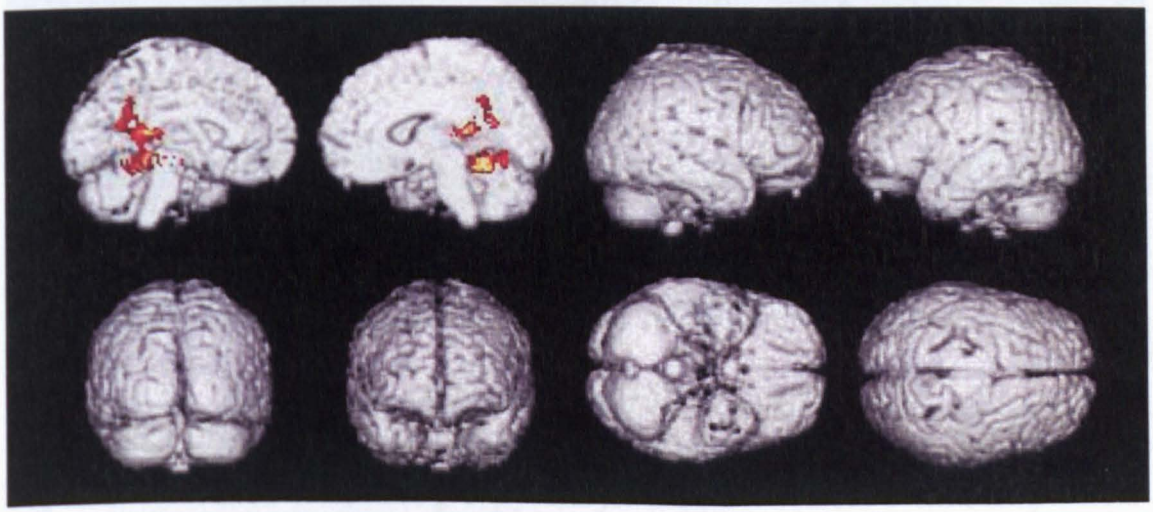

Fig 3.37: Differences in the Elderly group versus AD group comparison found for the 1-back versus 0-back contrast.

Additional differences in activation occurred in the cerebellum (culmen) bilaterally ($p < 0.05$).

MCI Group: The right inferior frontal gyrus (BA 9), the right precentral gyrus (BA 6) and the right inferior parietal lobule (BA 40) were activated significantly ($p < 0.01$, corrected). Table 3.35 and Figure 3.38 provide more information on these activations.

Table 3.35

Areas of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the 1-back versus 0-back contrast in the MCI group.

Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Right Inferior Frontal Gyrus	9	13.19	5.47	1814	0.000	36	7	25
Right Precentral Gyrus	6	9.52	4.86			42	-1	24
Right Inferior Frontal Gyrus	9	8.97	4.6			46	13	21
Right Inferior Parietal Lobule	40	5.58	3.77	444	0.035	40	-35	42
	40	5.42	3.71			50	-39	35
	40	4.94	3.52			42	-44	43

Note: * BA refers to Brodmann's Areas.

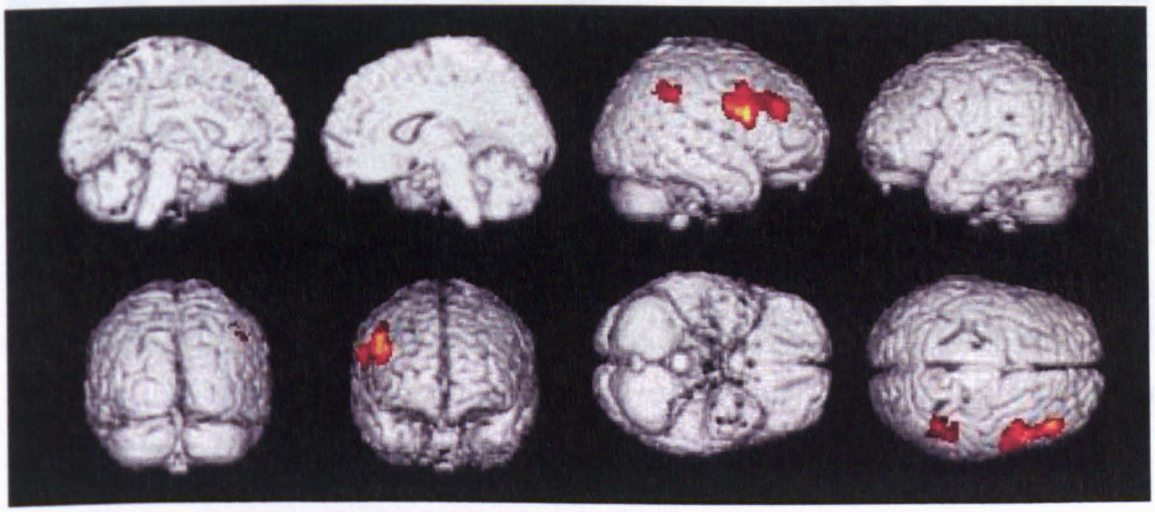

Fig 3.38: Activation in the MCI group found for the 1-back versus 0-back comparison.

At a more liberal threshold ($p < 0.05$), no additional areas were activated.

MCI Group versus Elderly Group Comparison: Significantly different levels of activation were seen in the right inferior parietal lobule (BA 40), the right postcentral gyrus (BA 2), the right precuneus (BA 7) and the right inferior frontal gyrus (BA 9) at the $p < 0.01$ level of significance (uncorrected). Table 3.36 provides additional details about the differences and Figure 3.39 shows the locations of these differences.

Table 3.36

Sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the 1-back versus 0-back contrast in the MCI group versus elderly group comparison.

Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Right Inferior Parietal Lobule	40	4.47	3.81	416	0.003	42	-37	41
	40	4.26	3.68			50	-39	35
Right Postcentral Gyrus	2	3.04	2.79			50	-25	45
Right Precuneus	7	3.99	3.49	212	0.026	14	-51	38
	7	3.2	2.91			4	-66	44
	7	2.99	2.75			6	-58	43
Right Inferior Frontal Gyrus	9	3.83	3.38	189	0.034	46	11	22
	9	2.86	2.65			44	-3	24

Note: * BA refers to Brodmann's Areas.

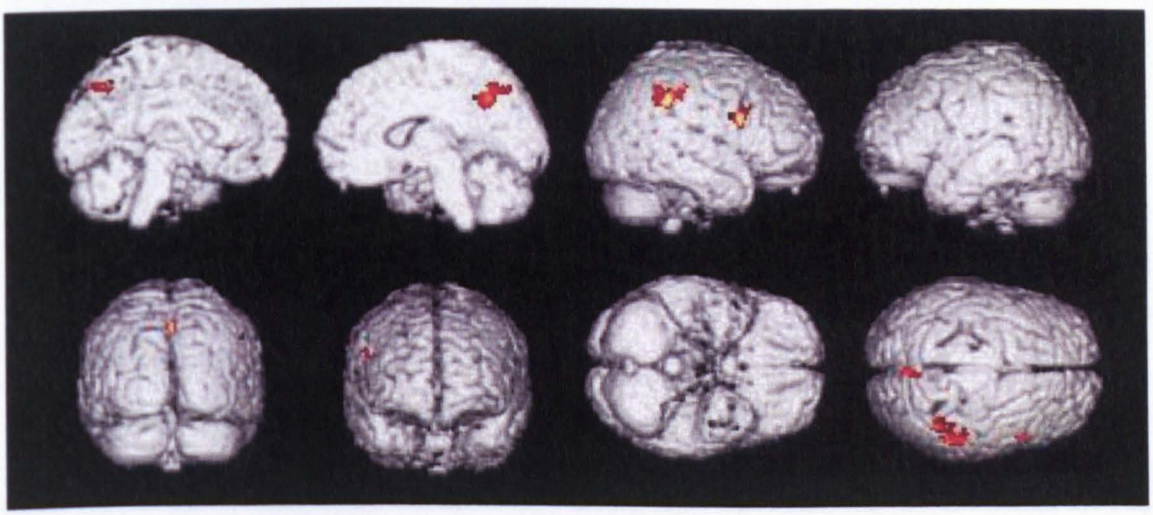

Fig 3.39: Differences in activation in the MCI group versus elderly group comparison found for the 1-back versus 0-back contrast.

At a less conservative threshold ($p < 0.05$), further differential activation was observed in the right precentral gyrus (BA 43).

Elderly Group versus MCI Group Comparison: Significant differences in activation were observed in the left fusiform gyrus (BA 37), the right fusiform gyrus (BA 19), the left middle temporal gyrus (BA 21 and 39), the left parahippocampal gyrus (BA 19) and the right cerebellum (culmen) at the $p < 0.01$ level of significance, uncorrected (see Table 3.37 and Figure 3.40).

Table 3.37

Areas of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the 1-back versus 0-back contrast in the Elderly group versus MCI group comparison.

Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Middle Temporal Gyrus	39	4.43	3.79	263	0.015	-51	-67	11
	39	3.73	3.31			-57	-58	8
Right Cerebellum		4.02	3.51	314	0.009	16	-46	-18
Right Fusiform Gyrus	19	3.66	3.26			22	-61	-9
	19	3.6	3.21			24	-53	-12
Left Fusiform Gyrus	37	3.95	3.47	367	0.005	-44	-53	-9
Left Middle Temporal Gyrus	21	3.3	2.99			-51	-35	-5
Left Parahippocampal Gyrus	19	3.22	2.99			-34	-47	1

Note: * BA refers to Brodmann's Areas.

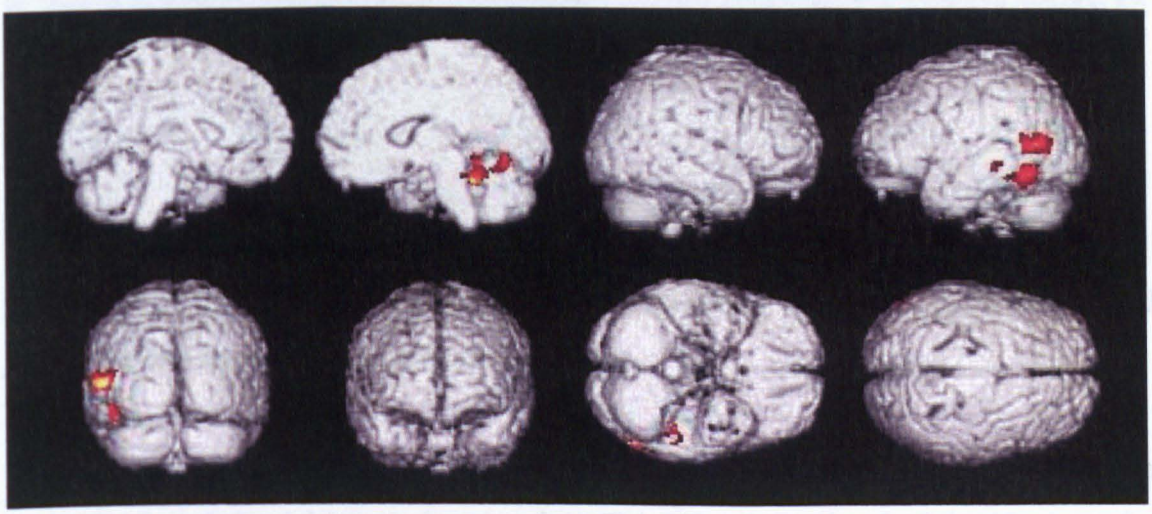

Fig 3.40: Significant differences in the Elderly group versus MCI group comparison found for the 1-back versus 0-back contrast.

Using a more liberal threshold of significance ($p < 0.05$), differential activation was also revealed in the left middle occipital gyrus (BA 19).

MCI Group versus AD Group Comparison: The levels of activation in the right precuneus (BA 7) were significantly different at the $p < 0.01$ level of significance, uncorrected (see Table 3.38 and Figure 3.41).

Table 3.38

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the 1-back versus 0-back contrast in the MCI group versus AD group comparison.

Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Right Precuneus	7	4.14	3.7	190	0.039	12	-49	36

Note: * BA refers to Brodmann's Areas.

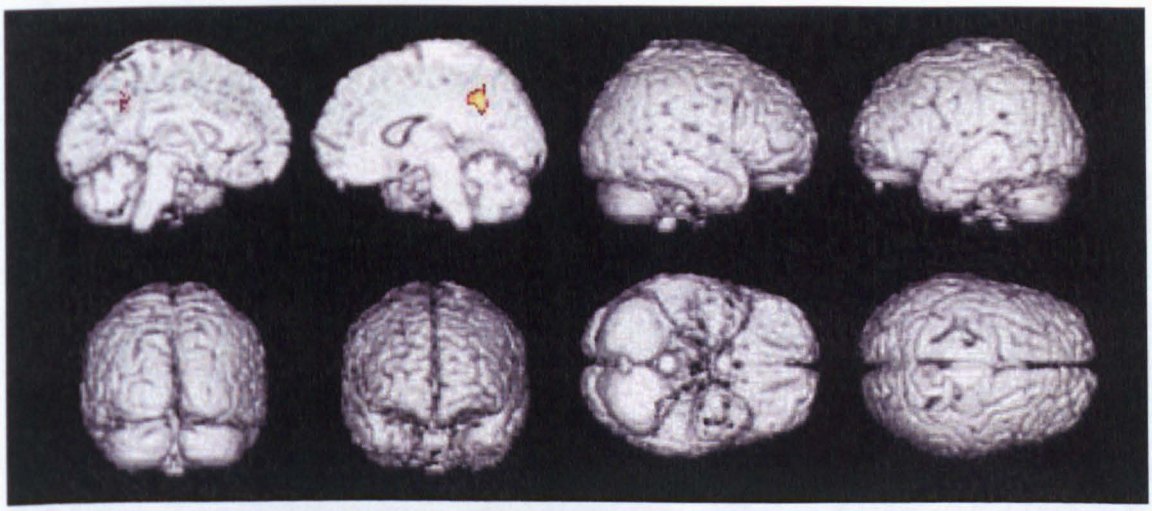

Fig 3.41: Significant differences in the MCI group versus AD group comparison found for the 1-back versus 0-back contrast.

Further differences in activation occurred in the right inferior parietal lobule (BA 39/40) and the right posterior cingulate (BA 29), when a level of significance of $p < 0.05$ (uncorrected) was used to examine the results.

AD Group versus MCI Group Comparison: Significant differences were detected in the left cingulate gyrus (BA 32) and the right cingulate gyrus (BA 24) at the $p < 0.01$ level of significance (uncorrected). More information on these differences can be found in Table 3.39. Figure 3.42 provides illustration of the differences.

Table 3.39

Areas of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the 1-back versus 0-back contrast in the AD group versus MCI group comparison.

Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Cingulate Gyrus	32	4.08	3.66	350	0.008	-2	18	40
	32	4.04	3.63			-7	24	38
Right Cingulate Gyrus	24	3.43	3.16			8	14	31

Note: * BA refers to Brodmann's Areas.

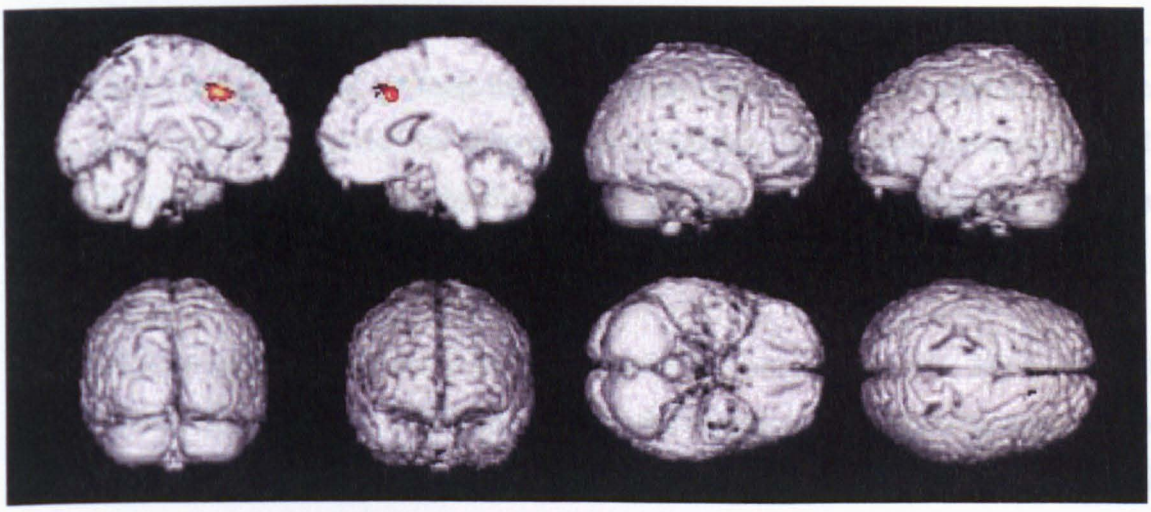

Fig 3.42: Significant differences in the AD group versus MCI group comparison found for the 1-back versus 0-back contrast.

At a less conservative threshold ($p < 0.05$), no additional areas of activation were observed.

3.10.7 Discussion

3.10.7.1 fMRI Experiment 2a: The Regions Associated with Sustained Attention, Target Detection and Visual Discrimination in Alzheimer's Disease

During the completion of the vigilance task, even at a liberal threshold of significance, the patients with AD did not activate the areas used for visual discrimination that were used by the elderly, for example, the left fusiform gyrus. This finding suggests that the AD patients lacked significant activation in the important areas used for the visual discrimination of letters.

The AD group activated the right cingulate gyrus (BA 31) and the left precuneus (BA 31) at the $p < 0.01$ level of significance and at a more liberal threshold ($p < 0.05$) were observed to activate the left anterior cingulate (BA 32). The AD patients may have recruited these midline cortical regions in order to compensate for dysfunctional areas related to the disease. Higher levels of activation have been reported in regions of the cingulate cortex as attentional demands are increased. For example, Pardo et al. (1990) showed that during a stroop task, activation increased in the anterior cingulate while participants performed the incongruent condition. The right superior parietal lobule (BA 7) was also activated by the AD group. The activation of this area has been described during tests of attention e.g. Pardo et al. (1991).

Activation was observed in the left superior temporal gyrus (BA 39) in the AD group. This region was not activated in either the young or the elderly groups, which suggests that it might aid the diagnosis of pathological ageing. At a more liberal threshold ($p < 0.05$) additional activation was seen in the left lentiform nucleus (putamen).

3.10.7.2 fMRI Experiment 2a: The Effect of Alzheimer's Disease on Sustained Attention, Target Detection and Visual Discrimination

AD Group versus Elderly Group Comparison: The left anterior cingulate (BA 32), the right anterior cingulate (BA 24) and the right precuneus (BA 31) were activated to a

significantly higher level in the AD group than the elderly. These areas may have been differentially activated by the patients with AD in order to compensate for the regions of the brain associated with sustained attention that are not functioning as efficiently as those found in the normal elderly group. Differential activation was also observed in the left caudate head. The differential activation of this region suggests that the AD group may be finding the task more demanding than the elderly group.

Elderly Group versus AD Group Comparison: It should be noted that the elderly did not activate the areas used for visual discrimination to a significantly higher level than the patients with AD. This finding suggests that as a group the patients with AD were activating the areas used in visual discrimination, but that the activation failed to reach the chosen threshold of significance.

The elderly did appear however, to activate areas of the right prefrontal cortex to a higher level than the patients with AD, i.e. the right inferior frontal gyrus (BA 9), the right precentral gyrus (BA 44), and the right middle frontal gyrus (BA 6). Right frontal areas, especially the right middle frontal gyrus, have been mentioned previously to be associated with the maintenance of alertness. The significantly greater activation observed in the elderly participants than in the AD patients may demonstrate the breakdown of the vigilance network in patients with AD even when in the early stages of the disease.

It is possible that the significantly different pattern of activation in the right frontal areas could also be created (or amplified) because of deactivation on behalf of the AD group. Either way, if created by greater activation in the elderly group and/or by deactivation in the AD group, a deviation can be observed from the pattern of activation that is considered normal for this age-group (as illustrated by the brain activations in the group of normal elderly). This deviation from the normal pattern of activation appears to demonstrate a breakdown in the vigilance networks of the patients with AD.

In summary, the elderly were observed to activate right frontal areas associated with vigilance to significantly higher levels than the patients with AD. This result may portray the breakdown of the vigilance network in patients with AD.

Conclusions: In the group of AD patients no significant activation was observed in the areas associated with the visual discrimination of letters, for example the left fusiform gyrus or the left middle occipital gyrus, even when a liberal threshold was used. The under-activation of the fusiform region may be due to the pathological formations found in AD. When the elderly and the AD groups were compared, no significant differences are observed in the areas used for visual discrimination, which suggests that activation may be occurring in the AD group at a sub-threshold level.

A lack of significant activation was detected in the right frontal areas (i.e. the right middle frontal gyrus) of the patients with AD. The right middle frontal gyrus is thought to be a crucial component of the vigilance network (Posner & Raichle, 1997). A significant difference in activation of the right frontal areas was also observed between the elderly group and the AD group. This deviation from normal (as represented by the elderly group) by the AD group, is thought to demonstrate the beginning of a breakdown of the vigilance network in these patients. The patients with AD did manage to complete the vigilance task successfully however (there were no significant differences in the behavioural scores of the AD group and the elderly group). This suggests that the brains of the AD patients, despite the presumed deficits in certain areas of the vigilance network, are finding a way of sustaining performance.

Significantly greater activation was observed in the left superior temporal gyrus (BA 39) of the AD group compared to the elderly group. This area was not activated significantly in either the young group or the elderly group and may signify compensation by the AD group.

Like the elderly, the AD patients managed to perform at a behavioural level close to ceiling (the scores of the groups did not differ significantly). The AD patients may have been able to sustain successful performance on the task because of additional compensatory activation. Significantly greater activation occurred in the patients with AD in the left anterior cingulate (BA 32) and the right anterior cingulate (BA 24). It may have been the activation of these regions that compensated for the dysfunction in the other areas associated with vigilance and enabled the patients with AD to perform the task. The patients with AD appear to be recruiting these midline cortical areas, even

when the task that they are required to perform is relatively simple (vigilance as opposed to the working memory task that is to follow).

In summary, when the elderly brains were compared to young, the activation of midline regions was observed. Earlier the assumption was made that these activations could reflect mechanisms of compensation that were employed by the brains of the elderly participants. As the AD group activated similar areas of the cingulate cortex, to a significantly higher level than the elderly group, we may also draw the conclusion that the patients with AD are compensating more than the elderly group, in order to maintain high scores on the test.

Activation of left temporal regions, e.g. the superior temporal gyrus, may also represent a method of compensation that was adopted by the AD group. Dysfunction to the areas used to maintain alertness appears to be present in the AD group, for example, in regions of the right prefrontal cortex. Grey matter atrophy of the prefrontal cortex has been reported to occur in AD (Salat et al., 2001). This atrophy may be one of the causes for the differential pattern of activation that was seen in the prefrontal cortex of the AD group.

3.10.7.3 fMRI Experiment 2a: The Regions Involved with Sustained Attention, Target Detection and Visual Discrimination in MCI

The MCI group did not appear to have any significant activation in the visual discrimination areas of the left middle occipital gyrus or the left fusiform gyrus even when examined at a liberal threshold. Significant activation was however, observed in the left cuneus (BA 19) and the precuneus (BA 19) bilaterally. The areas that were activated in the elderly participants were the fusiform gyri bilaterally, the lingual gyri bilaterally, the cuneus bilaterally, the left inferior occipital gyrus and the left precuneus. The MCI group do not appear therefore, to significantly activate the same areas used for the visual discrimination of letters as the elderly at the chosen threshold.

Turning now to the vigilance network, no significant activation was observed for the MCI group in the right middle frontal gyrus. In the elderly group however, significant activation was also absent in this region at the chosen threshold.

Bilateral activation of the insula (BA 13) occurred in the MCI group. The insula has been reported to be activated in verbal working memory tasks, e.g. Braver et al. (1997), Awh et al. (1996) and Paulesu et al. (1993). Paulesu et al. (1993) suggested that the insular cortex may be involved in phonological processing. The MCI may be recruiting the insular pathways even for the relatively simple 0-back (vigilance) task.

A number of temporal regions were also activated significantly by the MCI group i.e. the right superior temporal gyrus (BA 21 and 38), the right middle temporal gyrus (BA 21, 38 and 39), and the left middle temporal gyrus (BA 21 and 22). These regions of the temporal cortex did not appear to be activated significantly by the elderly group. It should be noted that of the areas of the temporal cortex that the MCI group activated, the young group also activated the right middle temporal gyrus (BA 39) and the right superior temporal gyrus (BA 22). Neither the young nor the elderly groups activated any of the regions of the left temporal cortex observed in the MCI group, however. This finding may imply that the MCI group still fall within the limits of normal ageing in the activation of some of the regions of the right temporal cortex, but that the areas of activation in the left temporal cortex (BA 21 and 22) may be signs of pathological ageing.

The bilateral activation of the temporal cortex regions may illustrate an attempt at compensation by the MCI group. Previous studies (on normal participants) have produced evidence of bilateral activation which occurs in certain tasks (which usually involve lateralised patterns of activation), as difficulty is increased, for example, Anderson et al. (2002) and Klingberg et al. (1997). Another explanation for the activation of the left temporal regions by the MCI group could be non-selective activation i.e. the activation of these areas might not be of any real advantage to the MCI group. Whatever the explanation for the activation may be, this more widespread pattern of activation might signify the presence of very early disease effects.

3.10.7.4 fMRI Experiment 2a: The Effect of MCI on Sustained Attention, Target Detection and Visual Discrimination

MCI Group versus Elderly Group Comparison: In this comparison, significant differences in activation were observed in the left superior temporal gyrus (BA 41), the

right superior temporal gyrus (BA 22), the left middle temporal gyrus (BA 21 and 22) and the right middle temporal gyrus (BA 39). Regions of the superior temporal gyri (BA 22) as suggested by Paulesu et al. (1993) may be involved in phoneme processing. The activation of the temporal cortex regions by the MCI group do not appear to coincide with the activations of the elderly participants in the current study. The increased activation of the left superior and middle temporal cortex regions by the MCI group in the current experiment may be indicative of changes that are occurring due to processes associated with pathological ageing. The left temporal cortex regions are highlighted as possible signs of pathological ageing because in the young versus elderly group comparison, higher levels of activation were observed in the right superior temporal gyrus (BA 21) and the right middle temporal gyrus (BA 39) in the young than the elderly. The activation of these right temporal regions by the young was considered normal. It is possible that the greater activation of the right temporal cortex regions by the MCI group than the elderly group might therefore place them within the continuum of normal ageing (in this case between the young and elderly groups). Neither the young nor the elderly groups activated any left temporal cortex regions, however. The left superior temporal gyrus (BA 41) and the left middle temporal gyrus (BA 21 and 22) were differentially activated to higher levels in the MCI group than the elderly which suggests that these left temporal regions might bear greater importance than the right temporal regions in distinguishing normal from pathological ageing.

Significantly different levels of activation were also observed in the right insula (BA 13), when the MCI group were compared to the elderly group. Significant activation of the insula was not observed in the random effects analyses of the elderly group (but was observed in the elderly group versus the young group comparison). The significantly greater right-sided insular activation witnessed in the MCI group may illustrate additional demands on this area incurred by the MCI group (compared to the normal elderly group).

The right supramarginal gyrus (BA 40) was activated to a significantly higher level by the MCI group than the elderly group. This difference in activation might exist because of a mechanism of compensation of the MCI group. It could be possible that the MCI group were recruiting this area in order to aid performance on the vigilance task. Significantly different activation was seen in the right substantia nigra and the

right subthalamic nucleus. The substantia nigra and the subthalamic nuclei project to the frontal areas and are thought to be involved with attentional processes, as well as movement.

At the more liberal threshold, differential activation was observed in the left inferior frontal gyrus (BA 47). Differences in activation in this area do not appear to be useful in the diagnosis of pathological ageing as the young group activated this area to a significantly higher level than the elderly group. A higher level of left hippocampal activation also occurred in the MCI group compared to the elderly group. Similarly, this area showed differential activation in the young group versus the elderly group comparison. Activation in the left hippocampus does not appear to be a useful diagnostic marker of very early AD. A significant difference was also seen in the right thalamus (pulvinar).

Differential activation occurred in the left precuneus (BA 19). The random effects analysis of the elderly group revealed significant activation of this region. The MCI group appeared to activate the left precuneus (BA 19) to a significantly higher level than the elderly, however.

The MCI group activated the left middle occipital gyrus (BA 19) to a higher level than the elderly. The left middle occipital gyrus has been implicated in the visual discrimination of letters. It is possible that the activation of this region by the MCI group is within the limits of normal ageing. Another interpretation of the activation may be that this area is activated to a higher level because of compensation by the MCI group to account for dysfunction in the fusiform gyri. In the random effects analysis of the MCI group no activation in the fusiform gyri was observed (whereas in the young, the left fusiform gyrus was activated, and in the elderly, bilateral activation of the fusiform gyri was observed). It should be noted however, that the elderly did not have any significantly greater activation in the fusiform gyri than the MCI group.

The MCI group activated the left cingulate cortex (BA 31) to a higher level than the elderly. The activation of this region may be due to compensation on behalf of the MCI group. Another explanation for the activation of this region may be that the greater activation found in the MCI group than the elderly group (and the higher level of activation in the AD group compared to the MCI group) might be due to increased levels of emotional distress while performing the vigilance task. For example, the task

might be more demanding on the MCI group than the elderly group (and on the AD group than the MCI group) because of the increased presence of AD pathology. Whichever the correct reason for the increased activation of the cingulate gyrus, if this deviation from the normal pattern of ageing is found to be consistent, then the level of activation in this area (or in any of the other areas that deviate from the normal in the MCI group) will be useful for the early diagnosis of pathological ageing.

Elderly Group versus MCI Group Comparison: No significant differences were found in the right middle frontal gyrus (one of the main regions associated with vigilance) when the elderly group was compared to the MCI group. In the elderly group versus the AD group comparison, however, significantly different activation was present in this region. The right middle frontal gyrus might therefore, be useful in discriminating patients with early AD from normal elderly but it does not appear to be useful in distinguishing the individuals with MCI in the present study from the normal elderly group.

Significant differences occurred in the left superior frontal gyrus (BA 6), the right postcentral gyrus (BA 5) and the right precuneus (BA 7). For no obvious reason the elderly group activated the left cingulate gyrus (BA 24) and the right cingulate gyrus (BA 23) to a significantly greater level than the MCI group. The activation of similar areas in the elderly group versus young group comparison was earlier attributed to compensation (e.g. significantly different levels of activation were observed in the cingulate gyrus (BA 24) bilaterally). Similarly, the activation that was seen when the AD group was compared to the elderly group (differential activation of the left anterior cingulate (BA 32) and the right anterior cingulate (BA 24)) was attributed to compensatory mechanisms. The significantly higher levels of activation revealed in the MCI group compared to the elderly does not appear to fit with the described pattern, that activation in these regions increases as increments in compensation are considered to be needed. The pattern that would be expected of this hypothesis is that the MCI group (if they did require more compensation) would activate these cingulate regions to higher levels than the elderly (like the AD group), but this is not what was observed. The MCI group therefore appear to fall within the levels of activation observed along the continuum of normal ageing i.e. the elderly activate the cingulate gyrus (BA 24)

bilaterally more than the young, and the left cingulate gyrus (BA 24) and right cingulate gyrus (BA 23) more than the MCI group.

Additional differential activation also occurred in the cingulate cortex when a less conservative threshold was used. The areas activated to a significantly higher level in the elderly group than the MCI group were the left cingulate gyrus (BA 23) and the right cingulate cortex (BA 42). The MCI group may be lacking activation in the right cingulate cortex (BA 42) compared to the elderly group. The elderly also activated the right medial frontal gyrus (BA 9) to a significantly higher level than the MCI group.

MCI Group versus AD Group Comparison: No significant differences in activation were observed when the MCI group were compared to the AD group even at the most liberal threshold. This analysis shows that the MCI group do not appear to be activating any brain regions to higher levels than the AD group. The finding suggests that the levels of activation found in the brains of the MCI group appear to be somewhat comparable to the activations in the brains of AD patients (whereas a number of areas have increased activation in the MCI group compared to the normal elderly group).

AD Group versus MCI Group Comparison: The AD group activated the right precuneus (BA 7) and the right cuneus (BA 7) to a significantly higher level than the MCI group. Note that the elderly also activated the right precuneus (BA 7) to a significantly higher level than the MCI group. Activation of the right precuneus, therefore does not appear to have any diagnostic benefits for preclinical AD.

In the AD group, significantly higher levels of activation were observed in the right cingulate gyrus (BA 31), than in the MCI group. Note that activation of the left cingulate gyrus (BA 31) was significantly higher in the MCI group than the elderly group. The cingulate gyri (BA 31) may therefore, be important in discriminating pathological ageing (MCI and AD) from normal ageing.

Additional differences in activation were observed in the left inferior parietal lobule (BA 40), the left postcentral gyrus (BA 40), the left supramarginal gyrus (BA 40)

and the right thalamus when a more liberal threshold was used. The differential levels of activation in the left inferior parietal lobule (BA 40) and the left supramarginal gyrus (BA 40) suggest that the AD group are attempting to use phonological storage to higher levels than the MCI group. This finding may show that the AD are having to employ more effort in order to remember to push only on the letter "X", compared to the MCI group. A significant difference also occurred in the left anterior cingulate (BA 32). The differential activation in this area may relate to increased compensation that is required in the AD group compared to the MCI group.

Conclusions: The activation pattern of the MCI group in the current study appears to fall along the continuum of normal ageing with a number of possibly important differences. In the MCI group, regions of the cingulate cortex (BA 23 and 24), the right temporal cortex (BA 22 and 39), the left middle occipital gyrus (BA 19) and the right precuneus (BA 7) appear to function somewhere along the continuum of activation found in normal ageing (i.e. between young and elderly groups). The levels of activation in these areas in the MCI group may fall between that of the young and elderly groups because the mean number of years of education in the MCI group was higher than the mean number of years of education in the elderly group. The difference between the mean years of education was not significant however (the only significant difference was between the MCI group and the AD group).

The elderly participants activated the left cingulate gyrus (BA 24) and the cingulate gyrus (BA 23) bilaterally to significantly higher levels than the MCI group. The MCI group may be activating these cingulate regions within the limits of normal ageing (as differential activation of the cingulate gyrus (BA 24) bilaterally, is also observed when the elderly group are compared to the young). It may therefore, be beneficial to disregard the cingulate gyri regions (BA 23 and 24) as effective diagnostic markers of preclinical AD during vigilance and instead turn to other areas that are involved in the completion of the task.

Differences in activation were expected in some areas in the brains of the MCI group when compared to the normal elderly group, as in the duration of the experiment and write up of this thesis (over a period of four years) four out of the six individuals

with MCI converted to AD. On tasks such as the vigilance task (0-back) a specific impairment might not be expected in the individuals with MCI as the diagnosis of these individuals was amnestic MCI only (the cognitive impairment was not known to stretch into other domains). As four out of the six individuals converted to AD however, the disease most likely was affecting the individuals to a certain extent. Therefore, in the MCI group, subtle changes in their patterns of activation while performing the vigilance task might be expected.

One of the main differences that appeared to exist in the MCI group was a more widespread pattern of activation compared to the normal elderly. This widespread pattern of activation included regions of the left middle and superior temporal gyri. The activation of these left hemispheric temporal cortex regions might indicate signs of pathological ageing. Additional areas of activation in the MCI group included the right insula and the right supramarginal gyrus. These areas that were differentially activated to higher levels in the MCI group than the elderly group might be useful in distinguishing normal from pathological ageing as both areas have been observed to be activated in verbal working memory tasks, such as that of Paulesu et al. (1993). It may be that the MCI group needed to recruit these areas to perform this relatively simple vigilance task, as opposed to a working memory task.

The elderly group had significantly different activation in the right cingulate cortex (BA 42) and the right medial frontal gyrus (BA 9) compared to the MCI group. The lack of activation in these areas by the MCI group illustrates yet more areas in which the pattern of activation deviates from the pattern of normal ageing. The converse comparison showed that the MCI group had significantly greater activation in the left cingulate gyrus (BA 31) than the elderly group. This activation might reflect compensatory mechanisms which are at work in the MCI group that are making up for areas that are beginning to be affected by the Alzheimer's disease process (in those MCI's that have preclinical AD).

In summary, a number of the activations found in the MCI group appeared to fall within the continuum of normal ageing. There were interesting differences compared to the normal elderly group however. The pattern of activation in the MCI group was more widespread than that of the elderly group. The more extensive pattern of activation included regions in the left temporal cortex. The activation of these regions may suggest pathological ageing, as neither the young or elderly groups

activated these areas significantly. The MCI group also showed a significantly different level of activation in the left cingulate gyrus (BA 31) compared to the elderly group. This difference in activation may be illustrative of the presence of pathological ageing in the MCI group.

3.10.7.5 The Effect of Pathological Ageing on Sustained Attention, Target Detection and Visual Discrimination

Behavioural performance on the 0-back task does not vary significantly between the elderly, MCI or AD groups. The scores of all the groups were very high (close to ceiling level). All the groups were therefore, managing to succeed in performing the task. There are some interesting differences in the underlying patterns of activation, however.

The effect of under-activation was observed in various areas associated with visual discrimination in the AD group. There were no significant differences between the AD group and the elderly group in these areas, however, which suggested that activation was occurring in the AD group but it was at a sub-threshold level. A finding which may be more important was the lack of significant activation in the right middle frontal gyrus (which is strongly associated with vigilance) in the AD group when compared to the elderly group. This difference may illustrate the beginnings of vigilance impairments in the AD group. Significant activation of the right middle frontal gyrus was also absent in the MCI group, but no significantly greater activation was observed in the elderly group when compared to the MCI group. Activation in the right middle frontal gyrus, therefore, appears to be useful in discriminating AD from normal ageing, but does not seem to be effective in distinguishing this MCI group from the normal elderly group.

In the MCI group a lack of activation was observed in the fusiform gyrus (which was used by both the young and elderly to complete the task). There were no significant differences in the fusiform gyri between the MCI group and the elderly, however. Sub-threshold activation is therefore, presumed to be occurring in the MCI group (as in the AD group). The lower levels of activation in the fusiform gyri in AD

and MCI groups may be due to AD pathology reaching these areas. The fusiform gyri are adjacent to the hippocampal complex (one of the first areas to be affected by AD) and neurofibrillary tangles can be found in these areas very early in the disease process (Mesulam, 2000). Figure 1.3 shows the progression of neurofibrillary tangles in MCI and AD.

A substantial amount of overlap in the activation of various areas in the MCI group was found in the young and/or the elderly, for example, areas of the cingulate cortex (BA 24 and BA 23), the left inferior frontal gyrus (BA 47), the left middle occipital gyrus (BA 19) and the left hippocampus. For diagnostic purposes, rather than focus on the levels of activation in these areas, it may be more beneficial to highlight the abnormal activation was found, for example, in the areas not usually activated during the completion of the task. Areas of the left temporal cortex were activated in both the AD group and the MCI group. Neither the young nor the elderly activated these regions. The activation of these areas contributes to a more widespread pattern of activation in the MCI and AD groups (compared to the elderly), which may reflect methods of compensation, or may be associated with non-selective activation and a breakdown of the vigilance network. The level of activation in areas of the left temporal cortex may be useful in distinguishing preclinical AD from normal ageing.

The cingulate gyrus (BA 31) was found to be activated to significantly higher levels in the MCI group than the elderly group. The cingulate gyrus (BA 31) was also found to be activated to a significantly higher level in the AD group than the MCI group. Significant activation of these areas of the cingulate gyrus was not observed in either the young or the elderly groups. The increments of activation found in the cingulate gyrus (BA 31) between the elderly, MCI and AD groups, respectively, might be associated with greater levels of compensation that is required as the effects of AD become more established.

Significantly different levels of activation occurred in the left inferior parietal lobule (BA 40), the left supramarginal gyrus (BA 40) and the left anterior cingulate gyrus (BA 32) when the AD group was compared to the MCI group. These additional areas of activation may suggest that the AD group need to greater amounts of

compensation on the vigilance task possibly because of more established disease pathology.

In summary, areas of under-activation were observed in both the MCI and AD groups, for example, in the fusiform gyri. The AD group appeared to have a lack of activation in the right middle frontal gyrus (associated with vigilance). The MCI group did not differ significantly from the elderly in this area, but other possibly important differences were seen. The MCI group and the AD group exhibited more widespread activation than the elderly group and activated areas, for example regions of the left temporal cortex that were not activated in either the young or the elderly groups. The cingulate gyrus (BA 31) was also activated incrementally between the elderly, MCI and AD groups respectively. The reason for the activation of these additional areas is expected to be due to compensation. These differences in levels of activation seem to enable pathological effects (such as preclinical AD and early AD) to be distinguished from normal ageing using the 0-back vigilance task in association with fMRI, before a difference in behavioural performance can be observed.

3.10.7.6 fMRI Experiment 2b: The Regions Associated with a Light Working Memory Load in Alzheimer's Disease

The patients with AD did not appear to activate a number of the areas that are closely associated with verbal working memory, even when examined at a liberal threshold. The AD group seemed to lack activation in the areas related to the phonological store and loop, for example, the left inferior and superior parietal cortices and the left inferior frontal gyrus. Note that both the young and the elderly groups activated the left inferior parietal and superior parietal cortices (the young also activated the LIFG). In the case of the patients with AD, the lack of significant activation in these areas, might reflect the presence of an impairment to the working memory network. One interpretation of the lack of activation in the areas used for phonological storage and rehearsal may be that the patients with AD may not be using exactly the same behavioural strategy as the young and elderly (i.e. to subvocally rehearse each letter that was observed until the next letter was presented) and may rely on a different mechanism to judge which letters are targets. This interpretation might reflect an impairment of the

AD group to engage the same (and possibly most effective) strategy as employed by the young and elderly groups.

In the AD group, activation was observed in the left cingulate gyrus (BA 33 and 24), the right cingulate gyrus (BA 32) and the right medial frontal gyrus (BA 6/32). Activation of these areas was not observed in the random effects analyses of the elderly and it appears that the patients with AD are performing the task differently to the controls. The activation of these midline cingulate areas (which are generally associated with attention) might reflect the employment of a compensatory mechanism in the AD patients. The activation observed in the cingulate areas may help the AD patients to sustain performance.

The observed activation of areas associated with vigilance i.e. the right middle frontal gyrus (BA 6), the right inferior parietal lobule (BA 40) and the superior parietal lobule (BA 7) might aid the AD group to complete the task (possible compensatory activation). Note that the elderly appeared to activate the left inferior parietal lobule (associated with phonological storage) and lacked activation in the right inferior parietal lobule (associated with vigilance), whereas, the AD group seemed to exhibit the opposite pattern.

The AD group activated the right inferior frontal gyrus (BA 47) and the right insula (BA 47). Activation of the right inferior frontal gyrus (BA 47) was seen in the young group. The activation of this region has been suggested to occur when the inhibition of a response to an erroneous stimulus is required (Arrington et al., 2000; Garrett et al., 2000). During the 1-back task, button pushes must be inhibited on every letter that is not a target.

Additional activation was observed in the left precentral gyrus (BA 6/4), mentioned previously to be related to speech programming (Paulesu et al., 1993). The elderly activated the precentral gyrus (BA 6), although the activation was found in the opposite hemisphere to that of the AD group.

The AD group activated the left middle frontal gyrus (BA 9). The elderly were also observed to have activation in the left middle frontal gyrus (BA 9). This area appeared to be activated significantly by both the AD and elderly groups. At a more liberal threshold of significance, additional activations were seen in the right caudate body, the left thalamus (ventral lateral nucleus), the right thalamus (medial dorsal

nucleus) and the right lentiform nucleus (lateral globus pallidus). The activation of the right caudate body may suggest that the AD patients are recruiting this area to aid in task completion.

In summary, the patients with AD appeared to activate some areas activated by the elderly group, for example, areas in the right middle frontal gyrus, which are associated with vigilance and alertness. At the chosen threshold, the AD group lacked activation to the areas associated with phonological storage and rehearsal. The lack of activation in these left hemisphere areas might reflect dysfunction that is taking place in the brains of the patients with AD. The AD group also appeared to activate the right inferior parietal lobule (BA 40), which was not observed in the random effects analyses of the elderly. Additional areas of activation, not seen in the young or elderly groups, were observed in the AD group, for example, the left cingulate cortex (BA 24 and 33), the right cingulate cortex (BA 32) and the right medial frontal gyrus (BA 6/32). The activation of these additional regions might explain how the AD group are still managing to perform the 1-back task.

3.10.7.7 fMRI Experiment 2b: The Effect of Alzheimer's Disease on a Light Working Memory Load

AD Group versus Elderly Group Comparison: The AD group appeared to activate the right cingulate gyrus (BA 32) to a significantly higher level than the elderly group. This area might help the patients with AD to compensate for areas that are dysfunctional due to the disease, but which are operational and available to the elderly group.

The left middle frontal gyrus (BA 6) and the left caudate body were also activated differentially when the AD group was compared to the elderly group. The greater activation of these areas may reflect compensation on behalf of the AD group. Bilateral activation in the DLPFC has been shown to occur when working memory tasks increase in the level of difficulty (Klingberg et al., 1997). The AD group may be recruiting this left hemisphere region of the DLPFC to a higher level than the elderly group in order to maintain performance.

It should be noted that the AD group do not activate the right inferior parietal lobule to a significantly higher level than the elderly. The elderly group are therefore, most likely activating this region, but the activation is at the sub-threshold level.

In summary, the differential activation that is observed in the right cingulate gyrus (BA 32) and the left middle frontal gyrus (BA 6) of the AD group, when compared to the elderly group, might be related to compensation on behalf of the patients with AD.

Elderly Group versus AD Group Comparison: Significant differences were observed between the elderly group and the AD group in a number of areas. Differential activation occurred in the left (BA 19/27) and right (BA 19) parahippocampal gyri. The parahippocampal gyrus is thought to receive visual information from the neocortex, which it processes and sends to the hippocampus (Joseph, 1996). The differential activation in the parahippocampal gyri therefore, may be due to the elderly engaging LTM processes to aid in task completion and the AD group might not be able to employ this system to the same extent.

The level of activation in the right fusiform gyrus (BA 19) was also significantly different between the elderly and the AD groups. Increased activation in this area in the elderly group compared to the AD group might reflect the foundation of underlying disease pathology in the AD group.

Differential activation was also observed in regions of the posterior cingulate cortex i.e. left Brodmann's area 23 and right Brodmann's area 29. This differential activation may have occurred due to dysfunction in the AD group. An additional difference in activation was seen in the left lentiform nucleus (lateral globus pallidus) and when using a less conservative threshold, differences occurred in the cerebellum (culmen) bilaterally.

It should be noted that the elderly group did not activate the left inferior or superior parietal cortices (BA 40 or 7) to significantly higher levels than the AD group. Activation might therefore be occurring in these areas in the AD group, but may be below the chosen threshold of significance. A significantly higher level of activation in

the left precuneus (BA 31) was however, observed when the elderly were compared to the AD group.

Conclusions: The random effects analyses revealed that the AD group appeared to lack activation in the left hemispheric regions associated with verbal WM, for example the LIFG, the left inferior parietal lobule (BA 40) and the left superior parietal lobule (BA 7). Note that the elderly group did not activate the LIFG significantly, but did activate the other two regions of the left hemisphere. The AD group activated the right inferior parietal lobule (BA 40), which is associated with vigilance. The elderly did not activate this region. It appears therefore, that the elderly tended to activate the regions of the left parietal cortices, whereas the AD group exhibited the opposite pattern and activated regions of the right parietal cortex. This result may be attributed to greater impairment to the left parietal areas than the right, which is characteristic of AD. This pattern has been described in the literature, for example, using SPECT, Blanco et al. (1998), reported predominantly left parietal dysfunction in patients with AD. The activation of the right inferior parietal lobule in the AD group may be compensatory, to enable the AD group to sustain performance. The AD group also activated a number of regions in the cingulate cortex, for example, the left cingulate gyrus (BA 33 and 24), the right cingulate gyrus (BA 32) and the right medial frontal gyrus (BA 6/32). These areas of activation were not observed in the elderly group and may reflect the use of a compensatory mechanism that is being employed by the AD group.

When the AD group were statistically compared to the elderly, activation was observed in the right cingulate gyrus (BA 32). The activation of this area might be associated with the maintaining performance in the AD group. It is possible that the level of activation in this area might help discriminate AD from normal ageing. Higher levels of activation were also observed in the left middle frontal gyrus (BA 6) in the AD group compared to the elderly group. The increased level of DLPFC activity may also be aiding the AD group to sustain performance.

The comparison of the elderly group to the AD group yielded activation in the parahippocampal gyri. The elderly group may be employing LTM processes to aid performance that are not available to the AD group. Greater activation was also observed in the right fusiform gyrus of the elderly group, the lack of activation in this area by the AD group may relate to the pattern of underlying disease pathology.

Differential activation occurred in the posterior cingulate regions (BA 24 and 29). This result may reflect dysfunction in the AD group.

To summarise, compared to the elderly group, the AD group appeared to underactivate regions associated with working memory. The AD group may have compensated for their shortcomings by activating homologous regions (e.g. the right inferior parietal lobule) to those activated by the elderly, midline cortical regions and the left DLPFC.

3.10.7.8 fMRI Experiment 2b: The Regions Associated with a Light Working Memory Load in MCI

The MCI group, like the AD group, do not appear to activate the regions that are closely related to verbal working memory i.e. the LIFG, the left inferior parietal lobule and the left superior parietal lobule. The MCI group (again similar to the AD group) instead appeared to activate regions in the right hemisphere, for example, the right inferior parietal lobule (BA 40). As mentioned previously the right inferior parietal lobule has been suggested to be involved with vigilance (Posner & Raichle, 1997). Activation of this area did not reach significance in the elderly group. The activation of the right inferior parietal lobule (BA 40) may have enabled the MCI group to maintain performance at a high level on the task.

Significant activation of the right precentral gyrus (BA 6) was observed. The right precentral gyrus (BA 6) was also activated in the elderly group. The activation of this area appears to be normal. Further activation was present in the right inferior frontal gyrus (BA 9). All the areas that were activated by the MCI group were right hemispheric regions. Left hemispheric activation (not exclusively) would be expected in a verbal working memory task such as the 1-back condition. The MCI group appeared to have a lack of activation in left hemispheric areas. The entirely right hemispheric pattern of activation does not appear to be observed for normal ageing, as both the young and the elderly groups exhibited the activation of left hemisphere regions, for example, the left inferior and superior parietal cortices (which would be expected from a verbal working memory task such as the 1-back condition).

In summary, the pattern of activation in the MCI group seemed to be similar to the AD group e.g. certain left hemispheric regions associated with working memory lacked significant activation. The MCI appeared to compensate for these deficits by activating right hemispheric regions such as the right inferior parietal lobule (BA40).

3.10.7.9 fMRI Experiment 2b: The Effect of MCI on a Light Working Memory Load

MCI Group versus Elderly Group Comparison: The MCI group activated the right inferior parietal lobule (BA 40) to a significantly higher level than the elderly group. The greater level of activation in this area may be occurring due to a method of compensation that is being employed by the MCI group to maintain a high level of performance.

Activation in other areas of the right hemisphere also differed significantly between the MCI group and the elderly group. These areas were the right precuneus (BA 7), the right inferior frontal gyrus (BA 9) and the right postcentral gyrus (BA 2). At a more liberal threshold of significance, differential activation was also observed in the right precentral gyrus (BA 43). The MCI group may be activating these right hemisphere areas to significantly higher levels than the elderly, in order to compensate for dysfunction that may be occurring in the left hemisphere areas generally associated with verbal working memory function.

Elderly Group versus MCI Group Comparison: The visual activation areas of the left fusiform gyrus (BA 37) and the right fusiform gyrus (BA 19) were activated to significantly higher levels in the elderly group than the MCI group. At a more liberal threshold further differential activation was observed in the left middle occipital gyrus (BA 19). The elderly may be able to activate these areas to a significantly higher level than the MCI group because the fusiform areas may be affected by AD pathology in a number of the individuals with MCI.

Significantly higher levels of activation were observed in the left parahippocampal gyrus (BA 19) when the elderly group were compared to the MCI group. The greater levels of activation found in the elderly group might reflect additional processing that is occurring in the brains of the elderly. The elderly may be

attempting to use LTM strategies, for example, trying to detect a pattern in the order the stimuli are occurring. The MCI group seem to resemble the AD group, as both groups when compared to the elderly appear to lack significant activation in the left parahippocampal gyrus (the AD group also lack activation of the right parahippocampus). The lack of activation in the left parahippocampal gyrus in the MCI group might reflect underlying pathological changes that are already occurring in this area.

Differential activation was observed in the left middle temporal gyrus (BA 21 and 39). The elderly group activated these areas which are proposed to be associated with lexical-semantic processes (Collette et al., 2001), to a significantly higher level than the MCI group. Although the elderly group activated a number of left hemisphere areas to a significantly higher level than the MCI group, the left inferior frontal gyrus, the left superior parietal lobule and the left inferior parietal lobule did not appear to show differential activation. This result suggests that the MCI group may be activating some or all of these areas at a sub-threshold level in order to do the task. Differential activation was present in the right cerebellum (culmen).

MCI Group versus AD Group Comparison: Higher levels of activation were detected in the areas of the right inferior parietal lobule (BA 39/40) and the right precuneus (BA 7) of the MCI group compared to the AD group. The random effects analyses revealed that both the AD group and the MCI group activated the right inferior parietal lobule (BA 40), possibly in order to compensate for dysfunctional areas (i.e. the corresponding region in the left hemisphere), but it seems that the MCI group are managing to activate this region to a significantly higher level than the AD group.

Differential levels of activation were observed in the right posterior cingulate (BA 29) in the MCI group compared to the AD group. The right posterior cingulate (BA 29) was also differentially activated when the elderly were compared to the AD group. This region may be undergoing pathological effects in the AD group, which might explain why the differences in activation between the MCI and elderly groups when compared to the AD group exist.

In summary, the MCI group appeared to activate a number of right hemisphere regions to higher a level than the AD group, for example, the right inferior parietal lobule (BA 39/40) and right precuneus (BA 7). Differential levels of activation were also observed in the right posterior cingulate (BA 29).

AD Group versus MCI Group Comparison: The AD group versus MCI group comparison revealed significant activation of the left cingulate gyrus (BA 32) and the right cingulate gyrus (BA 24). The AD group may be activating these regions of the cingulate gyrus in order to compensate for regions that are not activated as highly as, for example, the right inferior parietal lobule (BA 40) when compared to the MCI group, or the left inferior (BA 40) and superior (BA 7) parietal lobules when compared to the elderly group.

Conclusions: Reminiscent of the AD group, the random effects analysis of the MCI group revealed a lack of activation in the LIFG, the left inferior parietal lobule (BA 40) and the left superior parietal lobule (BA 7). Instead of activating these areas which are associated with verbal working memory, the MCI group (like the AD group) appeared to activate the right inferior parietal lobule (BA 40). The activation of this area, especially when significant activation is absent in the left inferior parietal lobule (BA 40) might help discriminate normal ageing from preclinical AD. All the areas activated by the MCI group were right hemispheric areas. The 1-back working memory task used letters as stimuli and possibly invoked subvocal rehearsal. This type of task would be expected to activate areas in the left hemisphere (as was observed in the young and elderly groups). Note that all patients and participants were right-handed. The pattern of activation observed in the MCI group, therefore does not appear to lie along the continuum of normal ageing.

The comparison of the MCI group to the elderly group revealed the activation of a number of right hemisphere areas. The recruitment of these regions might reflect methods of compensation used by the MCI group. As revealed by the comparison of the elderly to the MCI group, the individuals with MCI appeared to lack activation in the left fusiform gyrus, the left parahippocampal gyrus and the left middle temporal

gyrus (BA 21 and 39). The lack of activation in these areas might be due to underlying disease pathology (as at least four of the six individuals with MCI are in the very early stages of AD).

In comparison to the AD group, the MCI group activated the right inferior parietal lobule (BA 39/40) and the right precuneus (BA 7) to a higher level of activation. The decreased levels of activation found in the AD group may be due to the increased amounts of disease pathology that may be present. The MCI group exhibited differential activation in the posterior cingulate (BA 29) compared to the AD group. The elderly group also showed differential activation in this area in comparison to the AD group. The MCI group therefore, give the impression that they are closer to the elderly group, than the AD group, concerning the activation of this area of the cingulate cortex. When the AD group were compared to the MCI group, differential activation was observed in the left cingulate gyrus (BA 32) and the right cingulate gyrus (BA 24). The significant difference in activation in these areas might reflect compensation on behalf of the AD group.

In summary, the MCI group appear to have some similarities with the elderly group, for example, the level of activation in the regions of the cingulate cortex. Importantly for diagnosis, the MCI group also exhibit similarities with the AD group, for example, activation was present in both groups in the right inferior parietal lobule, whereas activation in this region is absent in the elderly. Finally and possibly most importantly the MCI group have differences in activation from the elderly group, for example, the MCI group appear to under-activate left hemisphere regions associated with working memory (in addition to other left hemisphere sites of activation found in the elderly group).

3.10.7.10 The Effect of Pathological Ageing on a Light Working Memory Load

There were no significant differences between the elderly, MCI or AD groups in the behavioural scores or the reaction times. Despite the lack of differences that could be observed using these measurements, a number of effects of pathological ageing were evident when examining the fMRI results. As the individuals with MCI might not all be in the preclinical stages of AD (at the time of writing only four out of six are known to

have converted), the effects of pathological ageing may not be as severe as the effects seen in the AD group. The two individuals that have not as yet converted to AD may be confounding the pathological effects that can be observed in the group. Importantly however, the pathology suspected in the individuals with MCI that have very early AD, appears to be influencing the results of the group and a number of important differences seem to exist between them and the normal elderly group. Both the AD group and the MCI group seemed to under-activate the left-hemisphere areas that are usually associated with verbal working memory tasks i.e. the LIFG, the left superior parietal lobule and the left inferior parietal lobule.

Both the MCI group and the AD group activated the right inferior parietal lobule (the activation found in the MCI group was at a significantly higher level than the AD group and the elderly group). The elderly did not significantly activate this area. The activation of this area in the AD and MCI groups may be related to mechanisms of compensation that are occurring in these groups (possibly to make up for dysfunction in the left hemisphere).

The AD group activated a number of midline cortical regions that were not activated by the elderly group. Furthermore, activation of the left cingulate (BA 32) and the right cingulate gyrus (BA 24) were found to be of a higher level in the AD group than the MCI group. During the 1-back working memory task, the activation of the cingulate regions in the AD group, especially the right cingulate gyrus (BA 32) might be important in distinguishing patients with early AD from normal elderly. The greater activation of the cingulate regions in the AD group than the MCI group and the elderly group might be related to task compensation. The levels of activation in the anterior cingulate regions did not appear to be effective at distinguishing MCI from normal ageing.

Differential activation was observed in the posterior cingulate (BA 24 and 29) when the elderly group were compared to the AD group. The MCI group also revealed differential activation in the posterior cingulate (BA 29) when compared to the AD group. The differences in the levels of activation between the elderly and MCI groups when compared to the AD group might reflect dysfunction in the AD group. During the 1-back task the posterior cingulate areas did not appear to be effective at discriminating the MCI group from the elderly, however, the findings suggested that it may be possible to discriminate early AD by the level of activation that occurs in these areas.

Signal changes in the frontal cortex might be of benefit in identifying pathological ageing. For example, the AD group activated the left middle frontal gyrus to a significantly higher level than the elderly group. In addition, the MCI group activated the right inferior frontal gyrus to a significantly higher level than the elderly. The greater activation of frontal areas might reflect compensation on behalf of the AD and MCI groups.

The elderly group activated the parahippocampal gyrus bilaterally to a significantly higher level than the AD group. The elderly also activated the left parahippocampal gyrus to a significantly higher level than the MCI group. The greater activation of the parahippocampal areas in the elderly might reflect LTM processes that are used during the 1-back working memory task which are not available (at least to the same extent) to the AD or MCI groups because of pathological changes. The levels of activation in the parahippocampal gyri might therefore, be of use in distinguishing normal from pathological ageing.

The random effects analyses of the AD and MCI groups did not reveal any activation of the fusiform gyri. On the other hand, the random effects analyses of the elderly showed activation of the left fusiform gyrus (BA 19). The elderly group activated the right fusiform gyrus (BA 19) to a significantly higher level than the AD group, and the left fusiform gyrus (BA 37) to a significantly higher level than the MCI group. The AD and the MCI groups appear to lack activation in regions of the fusiform gyri. The lack of activation in these areas might be due to the pathological effects that are occurring in the groups. The levels of activation in the fusiform gyri might be good discriminators of pathological ageing.

In summary, a number of differences could be seen between the AD and MCI groups compared to the normal elderly. In the future, examining the levels of activation found in the areas that have been described above, during a 1-back working memory task, might provide a useful method of discriminating pathological from normal ageing (even when behavioural performance is still within the normal range).

CHAPTER 4: AGE AND DISEASE EFFECTS ON THE SEMANTIC MEMORY SYSTEM

4.1 Semantic Memory

Semantic memory is generally composed from ones basic knowledge about the world. The semantic memory network incorporates the associations between stored words, as well as their meanings. Recent research has revealed that semantic memory, although once thought to be impaired only in the later stages of Alzheimer's disease (AD), can be affected very early in the AD process (Forbes et al., 2002; Hodges & Patterson, 1995). Semantic memory also appears to be relatively resistant to the consequences of ageing in comparison to other types of memory i.e. episodic memory (Nilsson, 2003). The study of semantic memory and processing ability therefore, may be beneficial for the early detection of AD. Although impairments of the semantic system may be subtle and go unnoticed in the very early stages of AD, if the appropriate tests are used, it may be possible to detect changes of diagnostic significance.

4.2 Neuro-imaging of Semantic Memory and Processing

In a review of two hundred and seventy-five various fMRI and PET studies by Cabeza and Nyberg (2000), forty-six studies on the retrieval of semantic memory, revealed that this type of memory appears to be associated with the activation of the prefrontal, temporal, anterior cingulate and cerebellar regions (Cabeza & Nyberg, 2000).

It has been suggested that a common semantic system exists which activates the same neuro-anatomical structures, regardless of the mode of presentation, i.e. either visual or auditory. Vandenberghe, Price, Wise, Josephs and Frackowiak (1996) demonstrated that the left inferior frontal gyrus (LIFG), the left temporo-parietal junction, the left inferior temporal gyrus, the left fusiform gyrus and the left superior

occipital gyrus were activated during the semantic retrieval for both pictures and words. Vandenberghe et al. also reported, that in addition to these areas, specific regions were identified which had differential activations for words or pictures. The semantic retrieval of the word stimuli activated the left anterior middle temporal gyrus, the left superior temporal sulcus and the left inferior frontal sulcus, to significantly higher levels than the semantic retrieval of the picture stimuli. The retrieval of semantic knowledge involving the picture stimuli activated the left posterior inferior temporal sulcus to significantly higher levels than the semantic retrieval concerning the word stimuli. This study and others like it (e.g. S. E. Petersen, Fox, Posner, Mintun and Raichle (1988)) appear to demonstrate that the semantic memory system consists of certain areas of the brain, for example, the LIFG, that are commonly activated independent of the mode of presentation. The study also showed that there seem to be specific brain regions that respond differentially to word and picture stimuli.

Other studies have provided evidence that different areas are activated during the retrieval of semantic knowledge, which are dependent on the type of knowledge that is being accessed. Different areas appear to be activated during the recall of, for example, visual elements, tactile elements, action elements, etc. Investigations have revealed that in addition to divisions in our perceptual systems i.e. colour perception, form perception, movement, etc, divisions also appear to exist in the semantic memory system (Thompson-Schill, 2003). Distinct areas appear to be activated in response to the recollection of e.g. size, colour, form, and motion.

The recollection of size knowledge has been reported to activate medial parietal structures (Kellenbach, Brett, & Patterson, 2001). These activations were observed when judgements of size were compared to colour and sound judgements.

Recalling colour knowledge has been described to activate the left ventral temporal region when words are used and the ventral temporal areas bilaterally when pictures are used (A. Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995). The areas that are activated with the recollection of colour appear to be 2-3 centimetres anterior to the areas activated during colour perception (Chao & Martin, 1999). Regions of the ventral temporal cortex also seem to be specific to the retrieval of colour knowledge, relative to size and sound knowledge (Kellenbach et al., 2001).

The retrieval of knowledge of form about the visual attributes of objects has been observed to activate the left fusiform gyrus (Thompson-Schill, Aguirre, D'Esposito, & Farah, 1999), however, it should be noted that although the majority of questions in the experiment were about form, there was no direct comparison between the retrieval of knowledge of form and the retrieval of knowledge concerning any other visual attributes.

The retrieval of knowledge concerning motion appears to activate regions of the lateral temporal cortex. The left middle temporal gyrus especially, appears to be activated during the retrieval of object motion (A. Martin, Ungerleider, & Haxby, 2000). In other studies that also invoked the retrieval of the knowledge of motion e.g. Warburton et al. (1996); Wise et al. (1991), activation could be seen in the left middle temporal gyrus anterior to the area activated in the perception of motion (Thompson-Schill, 2003).

Divisions in the semantic system therefore, appear to exist when recalling, for example, size, colour, form and motion. When recalling conceptual information, mental imagery appears to be recruited when required. The use of mental representation was observed during a property verification task, in which the participant had to make a number of judgements, for example, "Does a camel have a hump?" (Kan, Barsalou, Solomon, Minor, & Thompson-Schill, 2003). When no explicit instructions to use mental imagery were given, activation was observed in the visual association cortex (i.e. the left fusiform gyrus). This activation was observed only when conceptual knowledge was required, not when the stimuli allowed for word association strength to be sufficient to answer the question correctly. This shows that when conceptual knowledge is required the semantic memory system appears to incorporate perceptual representations in order to successfully retrieve the appropriate semantic knowledge.

To summarise, activation of the LIFG is thought to occur during the retrieval of semantic knowledge. The activation of this region will be discussed in greater detail later in the thesis. Demonstrations have revealed that the semantic memory system appears to have distinct areas that are activated by the different attributes of the information to be recollected. Colour appears to activate the left or bilateral ventral temporal cortex, motion appears to activate the left lateral temporal cortex, size appears to activate medial parietal structures and form appears to activate the ventral temporal

cortex including the left fusiform gyrus. The areas of activation observed due to the retrieval of certain attributes of semantic knowledge e.g. colour and motion, appear to be anterior in location to the areas of activation found in the same structures during the perception of the attribute. It has also been demonstrated that mental representations are often utilized when recalling conceptual information (resulting in the activation of the left fusiform gyrus).

The semantic memory system therefore, appears to incorporate distinct areas that are activated due to the various attributes of the knowledge to be remembered. Furthermore, the areas that are activated during the recall of a specific attribute also appear to be related to the regions that were active during the acquisition of the semantic information.

4.3 Neuro-imaging Evidence of Taxonomic Divisions in Semantic Memory

Evidence also points to the division of the semantic memory network into taxonomic categories e.g. tools, animals, living, non-living. A number of studies that claim to have demonstrated these divisions have been carried out, for example, Grossman, Smith, et al. (2002); A. Martin, Wiggs, Ungerleider and Haxby (1996); Mummery, Patterson, Hodges and Wise (1996). Note that the theories described in the previous section attempted to explain the divisions in semantic memory in terms of the perceptual features of the stored knowledge, as opposed to categorical differences.

The study by A. Martin et al. (1996) used PET to investigate picture naming of animals and tools. Animal naming was reported to activate the left medial occipital cortex (an area associated with early visual processing), whereas tool naming was reported to activate the left premotor cortex (which is also activated with imagined hand movements) and the left middle temporal cortex (which is activated during the generation of action words) (A. Martin et al., 1996). Activation of the left prefrontal cortex and the ventral temporal cortex (i.e. the fusiform gyrus) bilaterally, was observed for both the naming of animals and tools.

Caramazza & Shelton (1998) reported a patient with greater difficulty naming animals than fruits, as did Hart & Gordon (1992). The reverse has also been observed

i.e. a greater impairment in naming fruits (and also vegetables) than animals (Farah & Wallace, 1992). These studies suggest that taxonomical divisions exist in the semantic memory system, even within the categories of e.g. living things.

An fMRI study by Chao, Haxby and Martin (1999) revealed a number of differential sites of activation in the ventral and lateral temporal cortex, for the categories of animals, faces, houses and tools. The semantic memory system might therefore, have neuroanatomical divisions due to both the specific attributes of the knowledge to be remembered and also to the taxonomic category of the information to be remembered.

These studies and others like them appear to demonstrate that the semantic memory system is divided neuro-anatomically with regard to the category of the knowledge that is to be remembered. The weighting of the attributes present in the different taxonomic categories might be the underlying cause of the differential activations, however.

An experiment that lends evidence to this proposal is that of Mummery et al. (1998). The authors proposed that attribute-specific distinctions may be more important neurally than category-specific distinctions. This conclusion was reached after the implementation of an experiment with a fully crossed design, which required similarity judgements to be made about the colour or typical environmental location (attributes) of words for different categories i.e. living or artefact. The authors reported small differences between the living versus the artefact judgements. Whereas, larger differences existed within the attribute judgements e.g. colour judgements activated the left anteromedial temporal cortex and caudate nucleus, and location judgements activated the left temporo-occipito-parietal junction, the posterior cingulate and the medial parietal lobe. Mummery et al. suggested that it is likely that the most important anatomical distinctions are found due to attribute type (i.e. what the object looks like or where it is found) and that category distinctions (i.e. living things versus artefacts) come secondary to these.

Thompson-Schill et al. (1999) carried out an experiment to examine the category-specificity distinction that can be observed between living and non-living things. The impetus of the experiment was to examine if category-specific activations can be produced due to attribute-specific stimuli. For the retrieval of information about

living things it was hypothesised that the retrieval of both visual and non-visual information would result in the activation of visual representations because of the disproportionate amount of visual information that is present in living things. Whereas, during the retrieval of information about non-living things the visual representations will only be activated when specifically required (i.e. with questions concerning visual information) and will not be activated with questions concerning non-visual information, the reason being that non-living things are proposed to not depend on visual representations to the same levels as living things. The authors found that the activation in the left fusiform gyrus followed this pattern. Thompson-Schill et al. (1999) proposed that the experiment provided evidence that category-specific activations (living things versus non-living things) are caused by the underlying attribute-specific representations (i.e. the high level of visual components found in living things versus non-living things).

In summary, the category-specific activations that have been mentioned have been suggested to be caused by underlying attribute-specific information (Thompson-Schill et al., 1999). It is not completely clear however, if category specific neuro-anatomical divisions do exist in the brain or if the different areas of activation are completely due to the underlying attributes that are present for each category. Mummery et al. (1998) stated that the results of their experiment suggest that object attributes appear to be more important neurally than object categories.

It should be noted that evidence for attribute-specific representations does not rule out the presence of category-specific representations and vice-versa, it may be possible that the semantic system incorporates both components in the underlying neuroanatomy (Thompson-Schill, 2003). Models have been proposed such as that of Coltheart et al. (1998) which suggest that the semantic system involves both attribute and categorical divisions. The categorical divisions were suggested to occur for non-perceptual knowledge.

It is difficult to know if the activations due to taxonomical divisions reflect actual semantic representations or the lexical organisation in the brain. The reason for this being, that the majority of studies to date have been verbal.

4.4 Word imageability in the semantic system

Sabsevitz, Medler, Seidenberg and Binder (2005) carried out an event related fMRI experiment that investigated the differences in the brain activation patterns produced by processing either concrete nouns or abstract nouns. The task that was used required the participants to look at a triad of words and decide which of the bottom words had the strongest semantic relation to the top word. The word triads consisted of either concrete or abstract nouns. The concrete nouns were composed from a variety of semantic categories, for example, animals, fruits and vegetables, musical instruments, vehicles, items of clothing, furniture and carpentry tools. When the fMRI data from the concrete semantic judgements were compared to the data from the abstract semantic judgements, significant differences in activation were observed in the orbital frontal cortex (BA 11/47), the posterior middle frontal gyrus (BA 6/8) and the medial superior frontal gyrus, bilaterally. Significant differences also occurred in the right inferior frontal gyrus (BA 45/46), the ventral inferior temporal cortex (including the anterior hippocampus, the parahippocampal gyrus and the medial fusiform gyrus), the angular gyrus (BA 39) bilaterally and the left superior occipital gyrus (BA 19). Further significant differences were also present in the ventral precuneus, the posterior cingulate gyrus and the cingulate isthmus. These widespread cortical areas, which showed differential activation for the semantic processing of concrete noun triads compared to abstract noun triads, were considered by the authors to be involved in the recall of perceptually based representations.

The converse comparison, abstract semantic similarity judgements compared to concrete similarity judgements, showed differential activation in the left inferior frontal gyrus (BA 44, 45, 47), the anterior left superior temporal gyrus, the left superior temporal sulcus, the posterior dorsal middle temporal gyrus and the left medial frontal gyrus (BA 9). A small area of activation was also observed in the right superior temporal sulcus.

The results appear to be consistent with the dual coding theory, which was proposed by Paivio (1971). Dual coding theory predicts that concrete concepts are encoded both with a "verbal" code and an "image" code (which is provided by perceptual experience). Abstract concepts on the other hand are encoded and stored only in the form of "verbal" representations. If a concrete concept was dual encoded

e.g. a verbal and an image code was used, one might suspect that activation would occur over a more distributed network in the brain (possibly extending to both hemispheres), compared to the left sided pattern that would be expected for abstract concepts (which only have verbal encoding). The areas of greater activation observed in the experiment by Sabsevitz et al. (2005), for the comparison of the semantic similarity judgements of concrete nouns to the judgements of abstract nouns, followed this pattern. The reverse comparison of the abstract similarity judgements to the concrete judgements seemed to have a predominantly left sided pattern of activation, as would be expected with verbal coding (in the absence of imagery).

In summary, Sabsevitz et al. (2005) considered the concrete nouns to have perceptually based representations. When the concrete judgements were compared to the abstract judgements, significant differences in activation were present over both hemispheres. The areas of activation included ventral and medial temporal regions, frontal regions, the parietal cortices and the posterior cingulate. The differences in activation were attributed to the greater perceptual involvement of concrete similarity judgements compared to abstract judgements. The abstract judgements compared to the concrete judgements produced differential activation in the left inferior frontal gyrus and a number of temporal cortex regions (including the left superior temporal gyrus). These differences in activation were suggested by Sabsevitz et al. to reflect the greater involvement of the verbal semantic system in processing abstract concepts.

4.5 The Involvement of the Frontal Lobes in Semantic Memory Retrieval

The activation of the anterior frontal cortex appears to occur when complete retrieval cues are not provided and instead memory retrieval must be directed (Buckner, 2003). It is often the case in the environment when the memory to be remembered is guided, but not uniquely specified by the cue. The anterior prefrontal cortex has been activated in a number of different situations. For example, greater activation occurs in the left anterior prefrontal cortex when the level of perceptual detail required at the time of retrieval is increased (Ranganath, Johnson, & D'Esposito, 2000).

The results of an experiment by Wheeler and Buckner (2003) demonstrated that if information to be retrieved is studied minimally this results in greater activation of the

left anterior prefrontal cortex during retrieval, than if the information is studied repeatedly. This greater activation might be due to the greater level of control processing that must be employed by the participant when the information is studied minimally (Wheeler & Buckner, 2003).

These studies show that the anterior prefrontal cortex appears to be activated to greater levels when more effort is required to retrieve the information correctly. For example, more activation is observed when the choice between conflicting nodes of information is increased and the correct node must be discriminated.

The Left Inferior Frontal Gyrus (LIFG) appears to be commonly activated in many tasks that require semantic memory retrieval, for example the studies of A. Martin et al. (1996); Mummery et al. (1998); Vandenberghe et al. (1996). A possible reason for these activations could be that if the external cues provided are not great enough to provoke a direct retrieval then the LIFG is used to select among the competing alternatives to specify the retrieval path. Price, Mummery, Moore, Frackowiak and Friston (1999) demonstrated that a patient with LIFG damage (and no activation to this area as revealed by fMRI) could make semantic similarity judgements. It appears, therefore, that the LIFG is not absolutely necessary for the retrieval of semantic information, but seems to be used in selection. Further evidence for a role of the LIFG in selection is provided by the activation of this region in tasks that do not involve semantic memory retrieval e.g. the selection of target sets in a working memory test involving letter stimuli (Zhang et al., 2004).

The above evidence provides support that the LIFG is used to select between competing alternatives during a semantic memory search, rather than as a specific or essential semantic memory component.

Researchers have attempted to tease apart the function of the LIFG from the semantic memory system by using functional neuro-imaging, for example, Thompson-Schill et al. (1997) attempted to demonstrate the function of the LIFG in selection with fMRI, by varying both selection and retrieval properties. The results revealed that the LIFG activity varied for selection properties but not for retrieval properties and the conclusion drawn from this was that the LIFG is used in selection rather than as a specialised component of semantic memory retrieval. There is difficulty in measuring the effects of retrieval without selection and vice-versa as both alternatives are usually employed in the semantic tasks and although authors may suggest that they have

demonstrated the distinction (i.e. Thompson-Schill et al. (1997), critics argue that this may not be the case and that often there is the possible interference from an aspect of the other variable (as Thompson-Schill (1997) herself suggests).

In summary, the evidence from the functional imaging studies that have been described appears to converge on a possible role of the LIFG in semantic memory, in selecting the correct information from a number of competing alternatives. Furthermore, the activation of the LIFG appears to be non-specific to the type of visual stimuli i.e. it is activated during semantic tasks for both pictures and words as demonstrated for example by Vandenberghe et al. (1996).

4.6 Neuroimaging of Semantic Association

The paradigm used in the study by Sabsevitz et al. (2005) was described above. The researchers compared judgements of semantic association for concrete words compared to abstract words. The resulting areas of activation were the parahippocampal gyri, the left inferior temporal gyrus, the left fusiform gyrus, the right hippocampus/amygdala, the angular gyri, the left superior occipital gyrus and the right supramarginal gyrus. Additional activation occurred in the inferior/orbital frontal gyri, the middle frontal gyri, the left superior frontal gyrus, the left subcallosal gyri and the posterior cingulate/isthmus bilaterally. These areas are considered by the authors to be the neuroanatomical correlates of semantic knowledge for imageable word stimuli. The converse comparison of abstract judgements compared to concrete judgements may also be relevant to the current investigation. The comparison showed activation of the superior temporal gyri and sulci, the left middle temporal gyrus, the left inferior frontal gyrus and the left superior frontal gyrus. This comparison is thought to reveal the areas used for semantic association when visual representations are not employed.

The PET study by Vandenberghe et al. (1996) also investigated semantic association. The paradigm used by Vandenberghe and colleagues to test semantic association, similar to that used by Sabsevitz et al. (2005), consisted of a triad of stimuli. The triad was formed with one of the stimuli at the top centre location and two below at the left and right sides. Vandenberghe et al. used three conditions, 1) stimuli

matching on associative semantics, 2) stimuli matching for visual semantics, and 3) stimuli matching for physical size. The stimuli for the semantic association task were taken from the Pyramids and Palm Trees test. The Pyramids and Palm Trees test was created by Howard and Patterson (1992) to assess semantic access. The semantic association task required the participants to decide which of the bottom stimuli had the strongest semantic association with the top word. In the visual semantics task the participants had to match the stimuli on the real life size of the referents. In the baseline task the participants had to match the stimuli on their physical size (i.e. what was seen on the computer screen). Vandenberghe et al. used both picture stimuli and word stimuli. An overlap of semantic judgements (semantic association and visual semantics versus baseline) between pictures and words appeared to exist in the left inferior frontal gyrus (BA 11/45/47), the left middle temporal gyrus (BA 21), the left inferior temporal gyrus (BA 20), the left fusiform gyrus (BA 21/37), the left parieto-temporal junction (BA 19/39), the left superior occipital gyrus (BA 19), the left hippocampus (BA 34), the vermis and the right cerebellum. The left hippocampal and right lateral cerebellar activations were stronger in the semantic association task than in the visual semantic task. The common areas of activation found in the semantic association tasks (words and pictures) versus the baseline tasks can be seen in Figure 4.1.

Comparing only the semantic association task to the baseline task revealed greater activation in the left inferior frontal sulcus, the left anterior middle temporal gyrus and the left superior temporal sulcus, for the word stimuli compared to the picture stimuli. Activation specific to the picture stimuli was found in the left posterior inferior temporal sulcus.

In summary, the semantic memory system appears to be widely distributed, covering areas including the left inferior frontal gyrus, the left ventral temporal cortex, the left middle temporal gyrus, the left temporo-parietal junction and the left superior occipital gyrus. A substantial overlap seems to exist in the areas used for semantic processing of words and pictures. There are certain areas which are differentially activated for each of the input types, however.

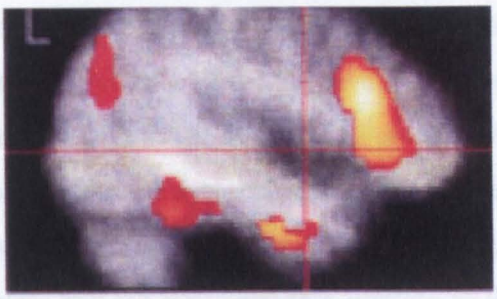

Fig 4.1: Illustrates the areas of the left hemisphere used for semantic association that are common to both word and picture stimuli. Reproduced from the Vandenberghe et al (1996) study, with kind permission from the Nature Publishing Group.

Price et al. (1999) administered a semantic association task (the word version of the Pyramids and Palm Trees test) to a set of controls (mean age 57) under PET conditions. The baseline task that was used involved judgements pertaining to the physical size of the stimuli. The stimuli were again organised in a triad. When the semantic association task was compared to the baseline task activation was seen in the left inferior frontal cortex (BA 45/47), the left anterior superior temporal cortex (BA 22), the left anterior middle temporal cortex (BA 21), the left posterior middle temporal cortex (BA 39), the left anterior medial temporal cortex (BA 28), the left inferior temporal cortex (BA 37), the left angular gyrus (BA 19/39), the left precuneus/cuneus (BA 19) and the cerebellum bilaterally. The use of this verbal paradigm under PET conditions illustrates the brain areas that are used when retrieving semantic associations.

Ricci et al. (1999) also carried out a PET study to examine the brain areas that are used during the retrieval of semantic associations. The experiment was made up of five conditions. These were 1) a baseline task, 2) a non-object matching task, 3) a size discrimination task, 4) a group matching task, and 5) a semantic association task. All the conditions were composed of picture stimuli that were arranged in a triad. Each triad like the other experiments of semantic association that have been described, consisted of one picture on top and two below. The participants were provided with a response device on which there were two buttons, one which corresponded to the bottom left stimulus and one which corresponded to the bottom right stimulus. The stimuli in the baseline task were pictures made from composites of the stimuli from the other conditions. The participant had to respond as quickly as possible when the stimuli

were presented. The non-object matching task required the participant to decide which of the bottom figures looked identical to the top picture. The requirement of the size discrimination task was to respond to the bottom picture that matched the top picture in physical size. The group match task involved deciding which item from the bottom was from the same category as the top. The semantic association task required a response to which of the bottom pictures had the best semantic relation to the top picture.

The comparison of the semantic match condition to the baseline revealed activation of the inferior temporal/occipital gyrus bilaterally. Comparing the semantic match to the figure match showed activation in the left frontal cortex (BA 44), the left inferior temporal cortex, the left parahippocampal gyrus and the occipital gyrus bilaterally. When the semantic matching task was compared to the size matching task, activation was observed in the left inferior frontal cortex (BA 47), the left parahippocampal gyrus, the left medial temporal lobe and the left superior occipital cortex. Ricci et al. (1999) commented that the focus of activation in the temporal lobe for this comparison was more anterior to the areas that have previously been found in their studies of visual naming or word reading. This finding suggests that this more anterior temporal region may be a more concise location for the semantic processing of associations. Finally, comparing the semantic matching task to the group matching task revealed activation of the left inferior temporal cortex (BA 37) and the left middle occipital gyrus. Although the experiment of Ricci et al. (1999) used picture stimuli, the study by Vandenberghe et al. (1996) suggests that there is considerable overlap in the semantic system of pictures and words. The areas defined by the comparisons in the Ricci et al. (1999) study provide useful insight into which areas are used during the retrieval of semantic associations. The experiment was especially informative considering the range of conditions that were compared to the semantic association task.

In summary, the studies that have been described above showed that the semantic memory system is composed from a distributed network of brain regions. When the results of the studies were combined, examples of the areas used in semantic memory retrieval and processing were the inferior frontal gyri, the middle frontal gyri, the superior frontal gyri, the left inferior temporal gyrus, the left middle temporal gyrus, the left superior temporal cortex, the left medial temporal cortex, the parahippocampal gyri, the hippocampus bilaterally, the left parieto-temporal junction, the angular gyri,

the left precuneus/cuneus, the left middle occipital gyrus, the left superior occipital gyrus and the posterior cingulate bilaterally.

4.7 Neuroimaging of lexical stimuli

In the present experiment which is to follow, the activation condition was composed of real words, whereas the baseline condition used non-words. It is important therefore, to identify which areas may be activated due to the presentation of words as opposed to non-words.

Using fMRI, Vigneau, Jobard, Mazoyer and Tzourio-Mazoyer (2005) investigated the differences between the reading of words versus non-words. The researchers found that during the reading of both words and non-words activation occurred in the VWFA. The activation of this area was also found by other researchers e.g. Dehaene, Le Clec, Poline, Le Bihan and Cohen (2002), in this case for words and pseudo-words. The study by Vigneau et al. (2005) did reveal a difference between the reading of words and non-words however, with the reading of words having a left hemisphere asymmetry in the visual word form area (VWFA), compared to the reading of non-words, which had a more bilateral pattern of activation e.g. in the VWFA and in its right homologue. The left lateralised pattern of activation in the VWFA which occurred during the reading of words was suggested by the authors to be involved with routing the stimuli towards the semantic areas for further processing.

Real words would be expected to activate the lexical semantic store, whereas non-words would not. When words were compared to non-words in the Vigneau et al. (2005) study, activations were also seen in the left middle temporal gyrus, the angular gyrus and the pars orbitalis of the inferior frontal gyrus. These areas are thought to be involved with semantic processing. The Vigneau et al. (2005) experiment also involved the listening of words. When a conjunction analysis was carried out on the word listening and reading conditions, a cluster of activation was observed which included the posterior and middle regions of the superior temporal sulcus and the middle temporal gyrus. Activation was also observed in the same areas in the right hemisphere (although to a smaller extent). The activation of these areas may be related to the retrieval of word meaning.

Cappa, Perani, Schnur, Tettamanti and Fazio (1998) used PET to investigate access to the visual and functional associative information of animals and tools. The conditions were 1) a rest period, 2) a baseline task requiring letter identification in pseudo-words, 3) a judgement involving the visual attributes of animals, 4) a judgement involving associative knowledge of animals, 5) a judgement requiring a visual knowledge of tools, and 6) a judgement which needed functional knowledge of tools. Pooling of the lexical conditions revealed activation of the left prefrontal cortex. Activation was also present in the left parietal-occipital junction (BA 39/19) and the posterior cingulate (BA 23/31) bilaterally. These areas were proposed to be activated when lexical semantic access was required.

In summary, Vigneau et al. (2005) showed that the processing of both words and non-words appeared to result in activation of the VWFA. Comparing the processing of words to non-words however, revealed a left lateralised pattern of activation in the left VWFA (i.e. inhibition of the corresponding right hemisphere region). Further activations were observed in the left middle temporal gyrus, the angular gyrus and the pars orbitalis of the inferior frontal gyrus. The activation of these areas was thought to be due to semantic processing. A conjunction analysis revealed that areas common to word listening and reading were the posterior and middle regions of the superior temporal sulcus and the middle temporal gyrus, bilaterally. Cappa et al. (1998) suggested that areas associated with lexical semantic access are the left prefrontal cortex, the left parietal-occipital junction and the posterior cingulate bilaterally. The semantic processing of words therefore, seems to be prompted by the left VWFA (Vigneau et al., 2005), and involves the left middle temporal gyrus and the left parietal-occipital junction, in addition to other areas.

4.8 Experiment 3: The Effect of Ageing on Semantic Memory and Processing

4.8.1 The Effect of Normal Ageing on Semantic Memory

Semantic memory appears to remain relatively stable throughout the lifespan compared to other types of memory. Nilsson (2003) described the effects of age on semantic memory, episodic memory, short-term memory, procedural memory and the perceptual representation system. Semantic memory was reported as one of the memory types that remained relatively intact.

Semantic memory appears to survive ageing in a fairly robust state (Stuart-Hamilton, 2000). Older adults appear to be able to remember facts and information relatively well.

Any impairment that may be observed on a semantic memory task may be related to factors that are not specifically semantically related. For example, slower processing ability in older adults or time restrictions on the semantic tasks may contribute to decreased performance. For reasons such as these, semantic memory and processing ability may be poorer in older adults.

The effects of normal ageing on semantic memory functioning appear to be much less severe than the effects of AD. The current experiment will examine semantic memory retrieval and processing in normal ageing, whereas the following experiment will investigate the contribution of pathological ageing.

The word version of the Pyramids and Palm Trees Test was used in the present experiment. The reason this paradigm was chosen was that a number of experiments, which have been described above, have used this task (or adaptations of it) to examine semantic memory retrieval. The Pyramids and Palm Trees Test also appears to be sensitive to the effects of AD. The sensitivity of the test to AD will be described in the next experiment. The Pyramids and Palm Trees test examines the individual's ability to recall and select the correct semantic association. A further advantage of the Pyramids and Palm Trees Test is that it can be converted easily into an fMRI paradigm.

4.8.2 Pyramids and Palm Trees Test

The Pyramids and Palm Trees Test is a type of semantic memory association task, in which conceptually related pictures must be matched. Three pictures are presented and the participant must decide between two of the pictures, which has the strongest semantic association with the third. An example could be a picture of a pair of hands and a picture of a pair of feet, the participant must choose which of the pictures is best associated with the third picture, which in this instance portrays a pair of gloves. The Pyramid and Palm Trees Test is thought to tap the individual's ability to retrieve semantic associations and categorise various stimuli according to these. In the current experiment, the verbal version of the Pyramids and Palm Trees test (i.e. the visual presentation of word stimuli as opposed to picture stimuli) was used to create the fMRI paradigm. The word version of the task eliminated any issues with the visual complexity of the pictures.

4.8.3 Experiment 3: Hypotheses

For the young adults:

1) According to the previous literature on the organisation of the distributed semantic memory system, the Pyramids and Palm Trees test may activate areas in the right inferior frontal gyrus, the middle frontal gyri, the superior frontal gyri, the left inferior temporal gyrus, the left middle temporal gyrus, the left superior temporal cortex, the left medial temporal cortex, the parahippocampal gyri, the hippocampus bilaterally, the left parieto-temporal junction, the angular gyri, the left precuneus/cuneus, the left middle occipital gyrus, the left superior occipital gyrus and the posterior cingulate bilaterally. These regions are thought to be involved in semantic memory processing and storage (including lexical identification and the retrieval of word meaning).
2) Activation may also be expected in the left inferior frontal gyrus (LIFG). The activation of this structure may be due to the process of selecting between competing alternatives during retrieval.

3) It is possible that activation may also occur in the left fusiform gyrus. The individual may activate mental representations in order to perform the categorisation correctly. The left fusiform gyrus has also been observed to be activated during the retrieval of form (most probably because of the reconstruction of mental images).

For the elderly:

1) Activation of the right inferior frontal gyrus, the middle frontal gyri, the superior frontal gyri, the left inferior temporal gyrus, the left middle temporal gyrus, the left superior temporal gyrus, the left medial temporal cortex, the parahippocampal gyri, the hippocampus bilaterally, the left parieto-temporal junction, the angular gyri, the left precuneus/cuneus, the left middle occipital gyrus, the left superior occipital gyrus and the posterior cingulate bilaterally (semantic processing and storage, which includes lexical identification and the retrieval of word meaning).
2) The left inferior frontal gyrus (retrieval selection).
3) The left fusiform gyrus (mental imagery and semantic representation of form).
4) As semantic memory is thought to be unaffected by age the patterns of activation may not differ between the young and elderly groups.
5) General effects of ageing on cognition may contribute the fMRI results, however. For example, underactivations may be observed specific regions.
6) A more bilateral pattern of activation may be expected in the elderly group than the young group if compensation is required (hypothesized in concordance with the HAROLD).

Note for the elderly hypotheses 1, 2, and 3 concern the same areas of activation found in the young group. Hypotheses 5 and 6 involve possible effects of ageing that may not be specific to semantic memory and processing.

4.8.4 Methods

4.8.4.1 Participants

The participant groups consisted of 10 young participants and 9 elderly participants. The young controls were 3 males and 7 females between the ages of 21 and 28. The mean age of the young controls was 23.1 (SD 2.18). The elderly control group included 3 males and 6 females between the ages of 72 and 77. The mean age of the elderly controls was 75.11 (SD 1.62).

The participants were all British and English was their first language. All the participants recruited for the study were right handed. Ethical approval for this study was granted by the Grampian Health Board and the University of Aberdeen Joint Ethics Committee.

4.8.4.2 Materials

The software "Presentation" for Windows was used to create the paradigm for the experiment and control the stimuli timings. fMRI was performed on a 1.5 Tesla GE MRI system. The stimuli where presented onto a screen viewable with a mirror attached to the head coil with the use of a PC via LCD projector. The participants were equipped with a fibre optic response device both in the left and right hand.

4.8.4.3 fMRI paradigm

An fMRI adapted version of the Pyramids and Palm Trees Test was created. The word version of the test was used instead of the picture version in order to reduce the perceptual component of the task. The task consisted of two conditions. In each of the conditions the presentation screen was white and the stimuli were displayed in a "Times New Roman" font.

The activation stage of the paradigm consisted of the word version of the Pyramids and Palm Trees Test. The stimuli were presented with one word on top and two below (see Fig 4.2). The participant had to decide which of the words from below

had the strongest semantic association with the top word. The participant responded by pressing the button in the left or right hand, which corresponded to the left or right word. In the activation condition, instructions for the task were presented for five seconds, followed by the test stimuli. Each screen of stimuli was present for 4500ms, with an inter-stimulus interval of 500ms.

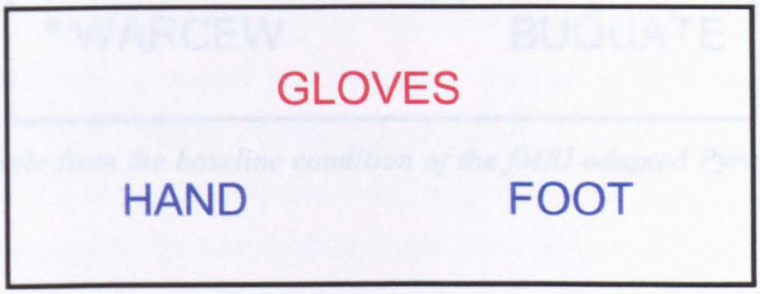

Fig 4.2: Example from the activation condition of the fMRI adapted Pyramids and Palm Trees Test.

Following the basic principles of fMRI, the baseline task for this particular experiment should have similar perceptual and motor output as the activation task, without the semantic memory association component. The baseline task that was chosen for this experiment was a simple visual discrimination which resulted in a button press. Three non-words were presented (one above and two below), in a similar arrangement to the activation task (i.e. similar perceptual input). One of the bottom non-words was accompanied by a star (see Fig 4.3). The participant had to decide which of the bottom non-words was accompanied by the star i.e. the left or right non-word. The participant answered the baseline task in the same way as during the activation task i.e. by pressing either the button in the left hand or in the right hand (i.e. similar motor output). The baseline task therefore consisted of approximately the same visual input and motor output as the activation task. The main differences between the tasks were that lexical processing (word identification and the retrieval of word meaning) and the processing of semantic memory associations were required only in the activation task. The baseline task, used non-words in order to reduce semantic processing and the decision to which side the star resided incorporated a simple perceptual judgement. In the baseline condition, instructions for the task were presented

for five seconds, followed by the test stimuli. Each screen of stimuli was present for 4500ms, with an inter-stimulus interval of 500ms.

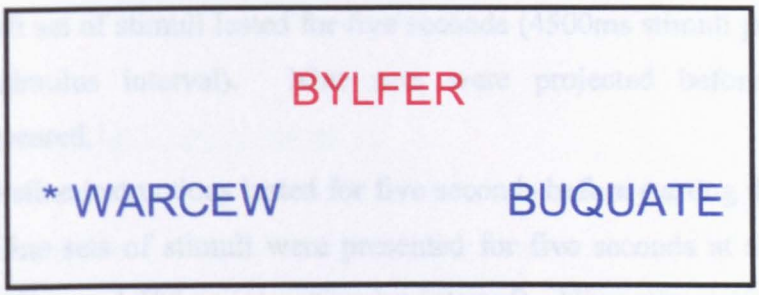

Fig 4.3: Example from the baseline condition of the fMRI adapted Pyramids and Palm Trees Test.

4.8.4.4 Procedure

During the selection process the elderly participants were required to visit a mock fMRI scanner. This was in order to familiarise the participants with the experimental procedure and also to screen if any of the participants were too claustrophobic for the scanner. Those participants that were not comfortable in the mock scanner were excluded from the study (i.e. these participants did not go on to have actual fMRI scanning).

All of the control participants (young and elderly) underwent training on the paradigm immediately before the actual fMRI scanning. The training involved the presentation of examples of the paradigm (both activation and baseline conditions) on sheets of card and the experimenter stating the instructions clearly.

In the actual fMRI session the participant was instructed to lie on their back in the scanner. By looking upwards at the mirror, the participant could see a screen on which the stimuli were presented. The participant had to respond to either the left or right word stimuli depending on which of the words had the strongest semantic association to the top word, by pressing the corresponding button on their left or right hand respectively. The same method applied to the baseline condition, this time concerning which side the star was on i.e. the left or right.

The first part of the fMRI procedure consisted of ten seconds of dummy scans, which enabled the scanner to reach equilibrium. Next came the first part of the test phase which was the activation condition of the Pyramids and Palm Trees paradigm. The activation instructions lasted for five seconds. The activation stimuli were then presented. Each set of stimuli lasted for five seconds (4500ms stimuli presentation and 500ms inter-stimulus interval). Nine sets were projected before the baseline instructions appeared.

The baseline instructions lasted for five seconds before starting the baseline test set. The baseline sets of stimuli were presented for five seconds at a time (4500ms stimuli presentation and 500ms inter-stimulus interval). Nine sets were presented until the instructions to the activation condition were projected again. This loop was repeated two more times, for a total of three activation phases and three baseline phases in each run. The scanning time for an entire run was 135 seconds for the activation phase and 135 seconds for the baseline phase.

Each patient and participant was also required to complete an additional run, in order to strengthen the statistical power of the SPM analysis.

4.8.4.5 fMRI methods

The fMRI acquisition was carried out on a 1.5 Tesla GE MRI system that was equipped with echo-planar imaging capabilities using a standard head coil. The following parameters were used: TE = 35ms, TR = 2.5s, in plane resolution $2x2mm^2$, 5mm slice thickness.

4.8.4.6 fMRI data analysis

A between subjects design was used in order to examine the effects of ageing (young versus elderly). The fMRI data were analysed using SPM99 (Wellcome Department of Imaging Neuroscience, London). Images were first re-aligned to create a mean image and then were subsequently realigned to this mean image. After the realignment procedure, the images were normalised into standard stereotactic space, then smoothed using a Gaussian filter set at 8 mm. After the modeling of the data the

significant clusters of activation were superimposed upon an anatomical template of the brain.

4.8.5 Results

4.8.5.1 Analysis of behavioural performance

An independent samples t-test was used to compare the behavioural performance of the young and elderly groups on the fMRI adapted Pyramids and Palm Trees paradigm. The mean behavioural scores of the young group were significantly higher than those of the elderly group, $t(17) = 2.532$; $p < 0.05$. The mean scores of the groups can be compared in Table 4.1.

Table 4.1

Shows the mean behavioural scores (and standard deviations) for the young and elderly groups on the Pyramids and Palm Trees Test Activation Condition

Pyramids and Palm Trees Test Activation Condition		
Group	N	Mean (SD)
Young	10	48.90 (1.73)
Elderly	9	45.78 (3.46)

Note: The maximum score achievable on the paradigm was 54

The reaction times of the groups were also compared using an independent samples t-test. The mean reaction times did not differ significantly between the groups ($t(17) = .763$; $p = ns$). The reaction times of the groups are illustrated in Fig 4.4.

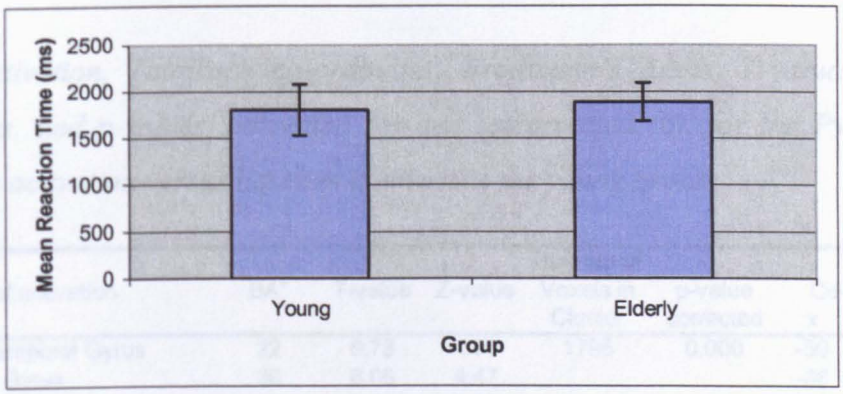

Fig 4.4: The mean reaction times for the young and elderly groups on the Pyramids and Palm Trees Activation Condition (error bars of the standard deviations are provided).

4.8.5.2 fMRI Experiment 3: Detection of the Areas Associated with Semantic Memory and Processing

Young Group: Significant activation was detected in the left inferior frontal gyrus (BA 45), the right inferior frontal gyrus (BA 47), the left middle frontal gyrus (BA 6), the right middle frontal gyrus (BA 46), the right superior frontal gyrus (BA 6), the left medial frontal gyrus (BA 8), the right medial frontal gyrus (BA 6), the left middle temporal gyrus (BA 22), the left fusiform gyrus (BA 36/20), the left precuneus (BA 19) and the left superior parietal lobule (BA 7), ($p < 0.01$, corrected). Activation was also present in the left middle occipital gyrus (BA 18), the left cuneus (BA 18), the right parahippocampal gyrus (BA 35), the left thalamus (partly in the left medial dorsal nuclei) and the right red nucleus when an uncorrected level of significance was used. More information on the activations can be seen in Table 4.2. Figure 4.5 illustrates the locations of activations in the brain.

Table 4.2

Sites of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a) and uncorrected (b), for the Pyramids and Palm Trees activation versus baseline contrast in the young group.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Middle Temporal Gyrus	22	6.73	4.76	1796	0.000	-59	-44	4
Left Fusiform Gyrus	36	6.06	4.47			-36	-40	-25
	20	5.04	3.97			-38	-26	-21
Left Inferior Frontal Gyrus	45	6.02	4.45	2874	0.000	-48	26	19
Left Middle Frontal Gyrus	6	5.62	4.26			-40	10	53
Left Inferior Frontal Gyrus	45	5.44	4.17			-53	22	14
Left Precuneus	19	5.42	4.16	1364	0.000	-32	-72	37
Left Superior Parietal Lobule	7	5.34	4.12			-24	-62	42
	7	5.09	4.00			-32	-62	47
Right Superior Frontal Gyrus	6	5.32	4.11	1344	0.000	2	22	56
Right Medial Frontal Gyrus	6	4.84	3.86			2	48	33
Left Medial Frontal Gyrus	8	4.61	3.73			-44	43	38
Right Middle Frontal Gyrus	46	5.60	4.25	838	0.007	48	42	24
	46	4.62	3.74			50	28	21
Right Inferior Frontal Gyrus	47	4.17	3.47			34	21	-11
b)					p-value uncorrected			
Left Middle Occipital Gyrus	18	4.14	3.45	172	0.044	-24	-97	12
Left Cuneus	18	3.53	3.06			-14	-98	18
	18	2.74	2.48			-14	-103	5
Left Thalamus		4.24	3.52	162	0.049	-6	-19	14
		3.96	3.34			-6	-11	10
Right Red Nucleus		4.77	3.82	296	0.011	2	-20	-9
Right Parahippocampal Gyrus	35	4.07	3.41			14	-28	-12
	35	3.39	2.96			20	-20	-9

Note: * BA refers to Brodmann's Areas.

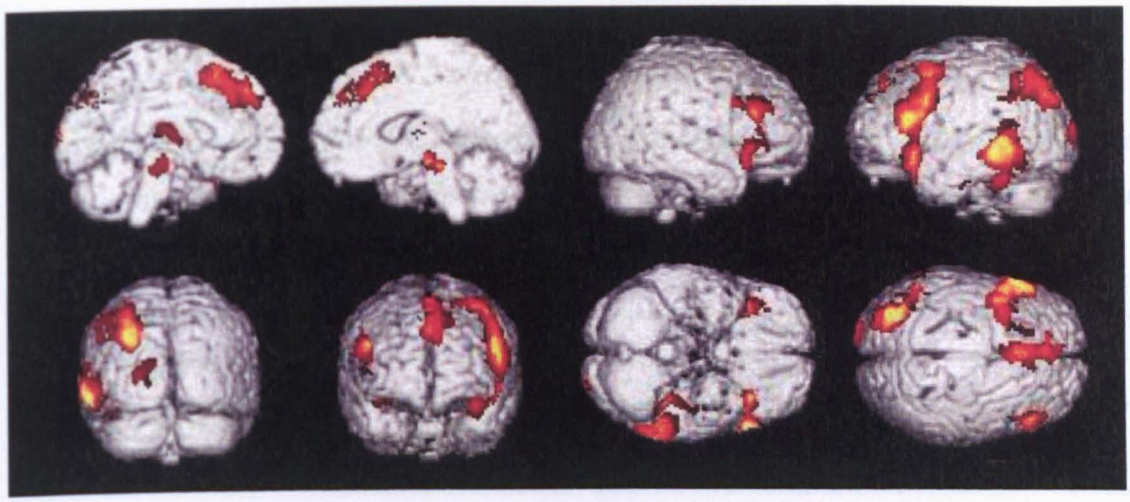

Fig 4.5: Activation detected in the young group for the Pyramids and Palm Trees activation versus baseline contrast (areas activated at the corrected and uncorrected level of significance are shown).

Elderly Group: Clusters of significant activation were observed in the left middle frontal gyrus (BA 46) and the left inferior frontal gyrus (BA 47), ($p < 0.01$, corrected). Using an uncorrected level of significance, additional activations were seen in the left middle frontal gyrus (BA 6/9), the left superior frontal gyrus (BA 8), the left superior parietal lobule (BA 7), the left precuneus (BA 7) and the cingulate gyrus (BA 32) bilaterally. The areas of activation are listed in Table 4.3 and Figure 4.6 presents the activations graphically.

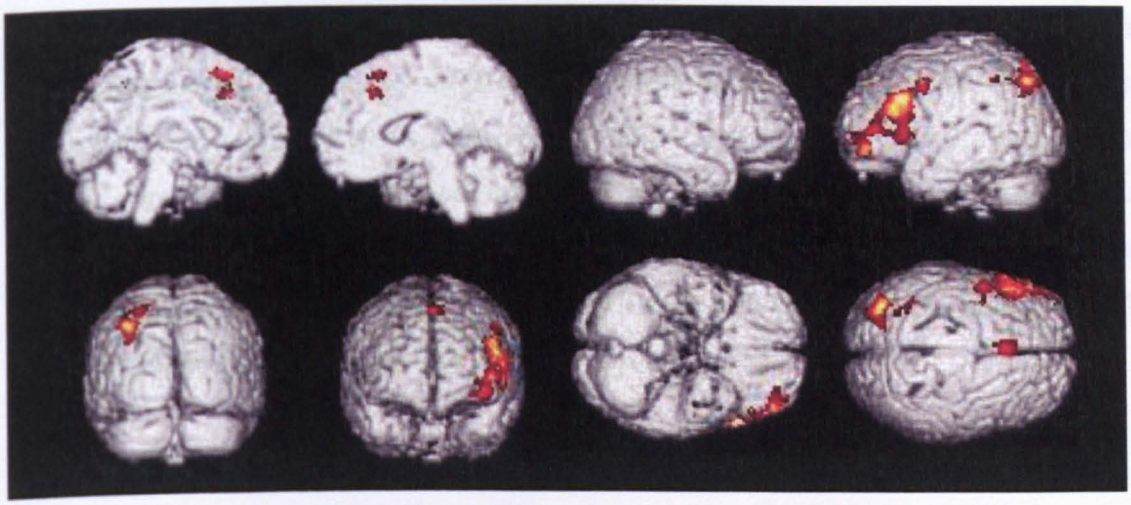

Fig 4.6: Activation found in the elderly group for the activation versus baseline contrast (corrected and uncorrected levels of significance are displayed).

Table 4.3

Areas of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a) and uncorrected (b), for the Pyramids and Palm Trees activation versus baseline contrast in the elderly group.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Middle Frontal Gyrus	46	7.75	4.93	1261	0.000	-44	21	25
	46	4.75	3.70			-51	28	19
Left Inferior Frontal Gyrus	47	4.35	3.48			-53	21	-3
b)					p-value uncorrected			
Left Superior Parietal Lobule	7	5.98	4.27	326	0.003	-34	-70	46
Left Precuneus	7	3.99	3.27			-24	-71	53
Left Superior Parietal Lobule	7	3.00	2.63			-36	-63	53
Left Superior Parietal Lobule	7	4.55	3.59	127	0.043	-30	-50	43
Left Middle Frontal Gyrus	6	3.71	3.11	138	0.036	-34	6	40
	9	3.60	3.04			-46	9	35
Left Superior Frontal Gyrus	8	4.77	3.71	213	0.012	-2	22	50
Right Cingulate Gyrus	32	3.99	2.86			6	23	38
Left Cingulate Gyrus	32	3.17	2.75			-2	25	34

Note: * BA refers to Brodmann's Areas.

At a more liberal threshold of significance ($p < 0.05$), further activation was observed in the left thalamus (incorporating the medial dorsal nucleus and the pulvinar).

Young Group versus Elderly Group Comparison: Differential activation was observed in the left superior temporal gyrus (BA 39), the left middle temporal gyrus (BA 22) and the left inferior temporal gyrus (BA 37), ($p < 0.01$, corrected). When the uncorrected level of significance was examined, additional areas that differed in activation included the right inferior frontal gyrus (BA 46/47), the left precuneus (BA 7) and the left cuneus (BA 19). Additional information on the differences is provided in Table 4.4. The locations of the differences are also displayed in Figure 4.7.

Table 4.4

Sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a) and uncorrected (b), for the young group versus the elderly group comparison on the Pyramids and Palm Trees activation versus baseline contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Superior Temporal Gyrus	39	4.04	3.64	810	0.007	-50	-52	12
Left Middle Temporal Gyrus	22	3.88	3.52			-46	-39	0
Left Inferior Temporal Gyrus	37	3.57	3.27			-50	-52	-1
b)					p-value uncorrected			
Left Precuneus	7	3.72	3.39	202	0.031	-24	-62	38
Left Cuneus	19	3.29	3.05			-20	-82	34
Left Precuneus	7	3.06	2.86			-18	-74	42
Right Inferior Frontal Gyrus	46	4.22	3.77	294	0.011	42	37	2
	47	3.48	3.20			46	21	-6
	47	3.44	3.17			44	31	-3

Note: * BA refers to Brodmann's Areas.

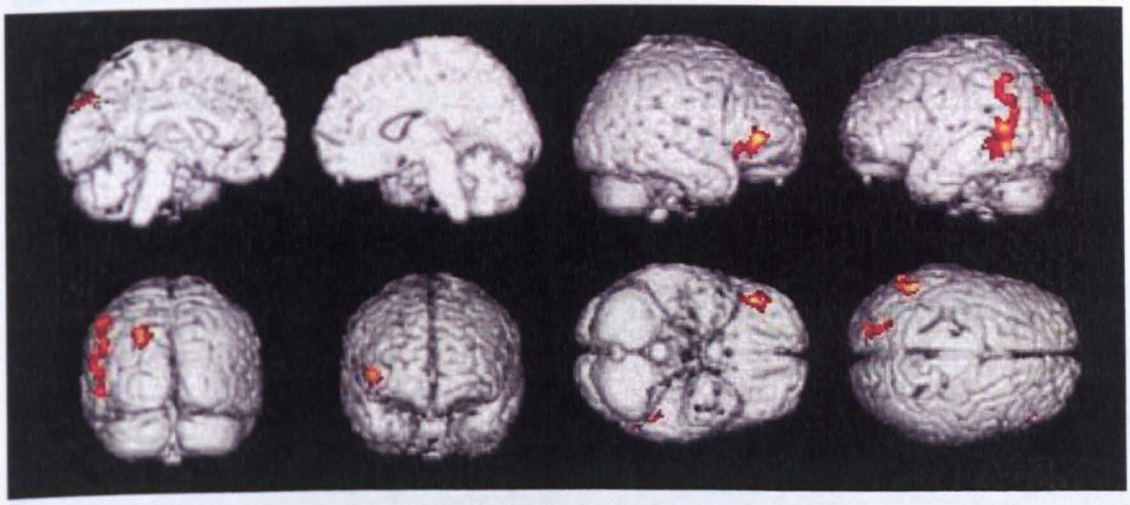

Fig 4.7: Areas that have significant differences in the comparison of the young group to the elderly group on the Pyramids and Palm Trees activation versus baseline contrast (showing corrected and uncorrected activations).

Elderly Group versus Young Group Comparison: Significant differences in activation were present in the right medial frontal gyrus (BA 6), the left precentral gyrus (BA 4) and the right precuneus (BA 7), ($p < 0.01$, corrected). Additional differences in

activation occurred in the left postcentral gyrus (BA 43), the left precentral gyrus (BA 43), the left medial frontal gyrus (BA 10) and the left superior temporal gyrus (BA 38) when examined at the uncorrected level of significance. Table 4.5 lists the areas that had significant differences, these are visualised in Figure 4.8.

Table 4.5

Areas showing differences in activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a) and uncorrected (b), for the elderly group versus the young group comparison on the Pyramids and Palm Trees activation versus baseline contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Right Medial Frontal Gyrus	6	5.16	4.42	1533	0.000	2	-18	67
Right Precuneus	7	4.83	4.20			2	-50	52
Left Precentral Gyrus	4	4.50	3.97			-26	-24	66
b)					p-value uncorrected			
Left Postcentral Gyrus	43	4.01	3.62	476	0.002	-57	-13	19
Left Superior Temporal Gyrus	38	3.71	3.39			-55	5	-7
Left Precentral Gyrus	43	3.69	3.37			-61	-5	11
Left Medial Frontal Gyrus	10	3.77	3.43	293	0.011	-2	52	-8

Note: * BA refers to Brodmann's Areas.

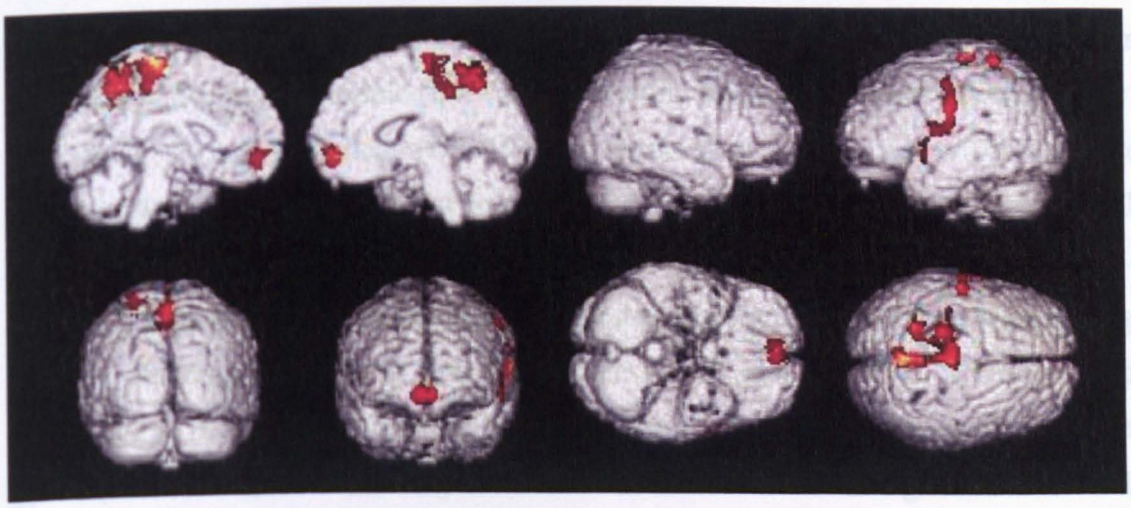

Fig 4.8: Significant differences in the comparison of the elderly group to the young group on the Pyramids and Palm Trees activation versus baseline contrast (showing corrected and uncorrected activations).

4.8.6 Discussion

4.8.6.1 fMRI Experiment 3: Regions Involved with Semantic Memory and Processing

Young Group: In the random effects analysis of the young group, significant activation was observed in the left inferior frontal gyrus (BA 45). One of the proposed functions of the left inferior frontal gyrus is considered to be in selection between competing alternatives (Thompson-Schill et al., 1997). The activation of the left inferior frontal gyrus may reflect this areas involvement in the retrieval of semantic representations.

Significant activation was also observed in the left middle temporal gyrus (BA 22). The activation in this area may have been due to lexico-semantic access, which is predicted to be needed in the activation condition. For example, the results of the Vigneau et al. (2005) study reported activation of the left middle temporal gyrus when word reading was compared to non-word reading.

Activation was observed in the left fusiform gyrus (BA 36/20). Activation of the left fusiform gyrus has been described in studies involving mental imagery, for example, Kan et al. (2003). Activation of the fusiform gyrus has also been reported during the retrieval of knowledge of form (Thompson-Schill et al., 1999), as well as in the semantic similarity judgement task by Sabsevitz et al. (2005). This structure appears to be important in the retrieval of semantic representations.

In the present comparison, activation occurred in the left precuneus (BA 19) and the left superior parietal lobule (BA 7). In the study on semantic association by Price et al. (1999), the left precuneus (BA 19) was reported to be activated. The activation found in the left superior parietal lobule in the present contrast may be related to the phonological reading of the three words as the participants completed the task.

A number of areas in the prefrontal cortex were activated. These were the right superior frontal gyrus (BA 6), the left middle frontal gyrus (BA 6), the right middle frontal gyrus (BA 46), the left medial frontal gyrus (BA 8) and the right medial frontal gyrus (BA 6). These areas may have been activated due to the greater demand for control processes that was required when completing the Pyramids and Palm Trees task compared to the baseline task. The young participants were most likely engaging higher levels of attention and manipulative processes when engaging in the activation

condition. Additional activation was observed in the right inferior frontal gyrus (BA 47). The activation of this area was also found in studies which required the inhibition of incorrect responses (Arrington et al., 2000; Garrett et al., 2000).

Activation occurred in the left middle occipital gyrus (BA 18) and the left cuneus (BA 18). The activation of these regions suggests that the activation task involved more visual processing than the baseline task. This finding may not be surprising as although the participants received similar perceptual inputs (in the activation and baseline conditions), they may not have processed the non-words to the same level as the actual words. For example, reading the non-words was not essential in order to complete the baseline task (the participants had only to search for the side the star was on), whereas in the activation task, the participants could not complete the task successfully without reading and processing the words. The activation of these brain areas have also been described in other studies on semantic retrieval. Left cuneus activation was reported in the experiment by Price et al. (1999), whereas activation of the left middle occipital gyrus was detailed in the experiment by Ricci et al. (1999) which compared semantic matching to group matching.

Activation was observed in the right parahippocampal gyrus (BA 35), the left thalamus (extending to the left medial dorsal nuclei) and the right red nucleus. Activation of the right parahippocampal gyrus may have occurred due to the mental imagery of the semantic representations. Activation in the right parahippocampal region has been reported in studies of mental imagery e.g. Howard et al. (1998). The semantic similarity study by Sabsevitz et al. (2005), which compared judgements between triads of concrete words to judgements between triads of abstract words also resulted in parahippocampal activation (this was bilateral however), as did the outcome of the study by Ricci et al. (1999) which used a variation of the Pyramids and Palm Trees task (left parahippocampal activation).

In summary, the young group activated a number of areas that would be expected in a semantic processing task such as the Pyramids and Palm Trees test. Similar patterns of activation can be seen when comparing the regions of activation found in the young group (Fig 4.5) to those that were found in the Vandenberghe et al. (1996) study (Fig 4.1). In the young group for the current comparison, activation was

observed in the left inferior frontal gyrus. The activation of this region may be related to retrieval selection. Significant activations were also observed in the left middle temporal gyrus and the left fusiform gyrus, which have been associated with the retrieval of semantic representations. Additional sites of activation were found in areas of the prefrontal cortex (which may reflect control processes) and the left superior parietal lobule (which may be related to phonological reading).

Elderly Group: The random effects analysis of the elderly group showed activation of the left inferior frontal gyrus (BA 47). The left inferior frontal gyrus was also activated in the young group and is thought to be used to guide semantic retrieval (Thompson-Schill et al., 1997). Note that the area of activation found in the young group was in Brodmann's area 45.

The elderly activated the left middle frontal gyrus (BA 6, 9 and 46) and the left superior frontal gyrus (BA 8). These areas may have been activated due to the increased demands for control processing that are likely to be incurred by the activation condition compared to the baseline condition.

Activation was observed in the left superior parietal lobule (BA 7) and the left precuneus (BA 7). Activation was also found in the left superior parietal lobule in the young group. The activation of this area may have been due to the phonological reading of the word stimuli that was occurring while the Pyramids and Palm Trees task was being completed.

Bilateral activation of the cingulate gyrus (BA 32) was detected in the elderly group. The young group did not activate these areas significantly. The activation of the cingulate gyri seen in the elderly group may have been due to increased levels of attention needed in order to complete the task. The activation might have occurred in compensation for general decrements in cognition caused by the effects of ageing. When a more liberal threshold was used, activation was also observed in the left thalamus (which encompassed the medial dorsal nucleus and the pulvinar).

In summary, the elderly group activated the left inferior frontal gyrus, which is predicted to be used to guide semantic retrieval. The elderly also activated a number of areas in the left prefrontal cortex, the left precuneus and the left superior parietal lobule.

The frontal areas may have been activated due to the increased demands on control processing incurred by the activation condition compared to the baseline. The activation of the superior parietal lobule may have been related to phonological reading processes, which are thought to be occurring during the completion of the Pyramids and Palm Trees activation condition.

4.8.6.2 fMRI Experiment 3: The Effect of Ageing on Semantic Memory and Processing

Young Group versus Elderly Group Comparison: The comparison of the young group to the elderly group showed that levels of activation in the groups differed significantly in the left superior temporal gyrus (BA 39), the left middle temporal gyrus (BA 22) and the left inferior temporal gyrus (BA 37). Regions in the left temporal cortices have been reported to be used in tasks of semantic association e.g. Price et al. (1999), Ricci et al. (1999), Sabsevitz et al. (2005) and Vandenberghe et al. (1996). The elderly group may not be able to activate these areas of the temporal cortex to the same level as the young group because of various effects of ageing. For example, elderly individuals have been reported to have decreased levels of glucose metabolism compared to the young (Petit-Taboue et al., 1998).

Elderly Group versus Young Group Comparison: This comparison showed differential levels of activation in the left medial frontal gyrus (BA 10), the right medial frontal gyrus (BA 6), the left precentral gyrus (BA 4/43) and the left postcentral gyrus (BA 43). The different levels of activation found in the precentral gyrus (BA 4) may reflect additional motor planning that is occurring in the elderly group compared to in the young group. Significantly different levels of activation also occurred in the right precuneus (BA 7). The elderly may be recruiting the right precuneus and the additional medial frontal areas in an attempt to compensate for general effects of ageing on cognition (that are not related specifically to semantic memory and processing).

Differential activation was observed in the left superior temporal gyrus (BA 38). The left superior temporal gyrus (BA 38) was activated in the study by Sabsevitz et al. (2005) when the semantic judgements concerning abstract words were compared to the judgements involving concrete words. The elderly group may be utilising the left

superior temporal gyrus (BA 38) to aid in task completion, and may be relying less on mental imagery or perceptual representations (as thought to be used by the young group).

Conclusions: In response to the Pyramids and Palm Trees Task, the young group activated a number of areas associated with semantic memory and processing e.g. the left inferior frontal gyrus, the left middle temporal gyrus, the left fusiform gyrus, and the right parahippocampal gyrus. Additional sites of activation were also found in the prefrontal cortex and in the left superior parietal lobule of the young group.

The elderly group activated the left inferior frontal gyrus, areas of the prefrontal cortex and the left superior parietal lobule. The areas that were activated in the prefrontal cortex of the elderly group were left lateralised. The pattern of activation that was found in the prefrontal cortical areas of the young group extended over both hemispheres. The HAROLD model that was proposed by Cabeza et al. (2002) would predict that elderly participants should have a more bilateral pattern of activation in the frontal areas than younger participants. This does not appear to be the case in the present comparison.

The behavioural scores of the young group were significantly higher than the elderly group. The reaction times did not differ significantly between the groups. The difference in behavioural scores between the groups was unexpected as semantic memory is thought to remain relatively constant throughout the lifespan (Stuart-Hamilton, 2000). A possible explanation for the lower mean score of the elderly group on the Pyramids and Palm Trees fMRI paradigm may be that certain members of the elderly group were in the early preclinical stages of AD. The Pyramids and Palm Trees paradigm may have highlighted deficits in these individuals, hence the lower scores. Unfortunately, the participants in the elderly group were not followed up, so there is not way of knowing if any of the individuals have since converted to AD.

It should be noted that as a group the elderly did not significantly activate any regions of the temporal cortex even at the most liberal threshold. The lack of significant activation in these regions may have contributed to the lower behavioural scores. Bilateral activation of the cingulate gyrus (BA 32) was observed. The activation of the

cingulate gyrus may be due to compensation by the elderly group in order to increase levels of attention and to inhibit irrelevant information.

Comparing the young group to the elderly group resulted in a significant difference in activation in the left superior temporal gyrus (BA 39), the left middle temporal gyrus (BA 22) and the left inferior temporal gyrus (BA 37). The lack of significant activation in these regions of the temporal cortex in the elderly group may suggest that the elderly are attempting to complete the task without retrieving perceptual representations to the same degree as the young group.

The comparison of the elderly group to the young group identified significant differences in activation in a number of areas in the prefrontal cortex, the right precuneus (BA 7) and the left superior temporal gyrus (BA 38). The differential activation in the medial areas of the prefrontal cortex and the right precuneus may be due to compensatory effects by the elderly group in an attempt to offset general age-related deficits. The differential activation in the left superior temporal gyrus may explain the ability of the elderly to complete the Pyramids and Palm Trees test without significantly activating the brain regions associated with perceptual representations.

In summary, the young and elderly groups activated similar frontal and parietal regions e.g. the left inferior frontal gyrus, the left precuneus and the left superior parietal lobule. The elderly group appeared to lack significant activation in specific regions of the left temporal cortex, which the young activated. This may have contributed to the lower behavioural scores in the elderly group. The random effects analysis showed that the elderly activated the cingulate gyrus bilaterally. The activation of this region may have aided task completion. The differential activation of the left superior temporal cortex between the elderly and the young groups may have been due to the retrieval of the semantic association in the elderly group without the use of perceptual representations (at least to the same extent as the young group).

4.9 Experiment 4: The Effect of Pathological Ageing on Semantic Memory and Processing

4.9.1 The Effect of AD on Semantic Memory and Processing

AD profoundly impairs semantic memory and processing ability as the disease progresses. The deficits that may occur can be numerous and varied. For example, the impairments might take the form of word finding difficulties (Forbes et al., 2002), problems with semantic retrieval in autobiographical memory (Ivanoiu, Cooper, Shanks, & Venneri, 2004), deficits in semantic association (Hodges & Patterson, 1995), increases in the use of irrelevant information (Croisile et al., 1996) and decreases in the range of vocabulary utilized (Garrard, Maloney, Hodges, & Patterson, 2005), amongst others. Patients with AD may therefore, exhibit a wide range of semantic impairment.

Impairments in language ability often occur due to the semantic impairments caused by Alzheimer's disease. Examples of these can be observed in the study by Garrard et al. (2005), which investigated the writings of renowned author Iris Murdoch. The last novel that the writer created, "Jackson's Dilemma", did not seem to be up to the standard of her earlier writings and was not received with enthusiasm by the critics. Not long after the book was published she was diagnosed with AD, which was later confirmed at post-mortem. The evidence suggested that Iris Murdoch composed her final novel during a period that the pathology associated with AD was already beginning to impinge on her cognition. Garrard et al. found that the vocabulary of the author, as measured by the number of distinct words relative to the overall word count, increased from her early work towards the middle of career and diminished during her final writing. Garrard et al. also found smaller increments in the proportion of distinct words to the overall number of words in Jackson's Dilemma, as the sample size was increased, compared to the two other books that were examined. The decrements in language ability that were exhibited by Iris Murdoch, illustrate an example of the semantic memory and processing impairment that can take place due to AD.

It is not only in the later stages of AD that semantic deficits can be observed, however. A study by Forbes et al. (2002) which investigated verbal descriptions of

simple and complex pictures, revealed that the responses given by the patients with minimal AD were significantly different to the normal controls on measures of word finding delay and error monitoring. Significantly different performance was also found on the measures of semantic paraphasias, response to word-finding delays and the information conveyed. The study by Forbes et al. (2002) showed that even in the minimal stages of disease, patients with AD may be impaired on measures of semantic ability (especially when a more complex task was used).

Researchers have probed various areas of semantic memory in order to attempt to understand the impairments that are induced by AD. A breakdown in the organisation of semantic memory has been suggested to occur in the presence of progressive dementia (e.g. Warrington (1975)), and specifically in Alzheimer's disease (e.g. Chertkow & Bub (1990) and A. Martin & Fedio (1983)). Semantic memory has been suggested to be organised hierarchically (Collins & Quillian, 1969). Warrington (1975) claimed that the attributes (thought to be stored at the bottom of the hierarchy) were more sensitive to dementia than superordinate information (which was considered to be stored at the top). An example of a question from the Warrington (1975) study which was used to probe attribute knowledge was "Is it heavier than a telephone directory?" Superordinate knowledge was probed with questions such as, "Is it an animal?" Examples of studies in which AD patients have been shown to be better at retrieving superordinate information as opposed to more specific knowledge are that of Chertkow and Bub (1990), and A. Martin and Fedio (1983). Various other studies, however, have revealed no differences between the degrees of breakdown of superordinate and specific semantic information in AD, for example, Cox, Bayles and Trosset (1996); Nebes and Brady (1990).

The studies on AD have also examined impairment to different types of categories e.g. living versus non-living (Silveri, Daniele, Giustolisi, & Gainotti, 1991). Silveri et al. showed that patients with AD were more impaired on items from living categories than for items from non-living categories. Other authors found that this was not always the case, for example, Gonnerman, Anderson, Devlin, Kempler and Seidenberg (1997). In the study by Gonnerman et al., heterogeneous patterns of performance were observed i.e. one of the AD patients was more impaired on living

versus non-living items and another of the patients revealed a greater deficit to non-living compared to living items.

Giustolisi, Bartolomeo, Daniele, Marra and Gainotti (1993) suggested that although patients with AD might show contrasting patterns of impairment, this is most likely to occur only in the early stages of the disease. The authors demonstrated that the three patients with AD in their study, although exhibiting a selective impairment of living things at the initial time of testing, showed no such pattern when retested six months later.

At the cognitive level the heterogeneous findings of the deficits associated with Alzheimer's disease directed the explanation for the impairments towards the damage that may be occurring to the intercorrelations and distinguishing features of semantic items. Certain concepts in memory are predicted to be accessed through one of many connections, for example, knowing that a robin has wings. Whereas, other features in memory have few connections, for example, a robin has a red breast (Gonnerman et al., 1997). It is possible to answer the first question in different ways, either by remembering via the direct route that a robin actually has wings, or for example, by remembering via the intercorrelations that are present between items i.e. a robin is a bird and like most birds, possesses wings. A distinguishing feature of a robin is the red breast and this could only be remembered if the direct pathway was activated that links red to robin.

Gonnerman et al. (1997) investigated the assumption that in AD impairments to living categories are generally greater than those to non-living categories. The authors created a model which attempts to explain this phenomena via distinguishing features and intercorrelations. Living things are generally associated with perceptual features, whereas non-living things are generally associated with functional features (Warrington & McCarthy, 1987). Living things also have more intercorrelations than non-living things (Gonnerman et al., 1997). Both living (biological) and non-living (artefact) things have distinguishing features which may be damaged due to the disease process. If the connections which link these distinguishing features to the memory concept are damaged then this feature will be lost e.g. a robin may no longer be distinguished from other birds via its red breast. This explains why certain distinguishing features are lost from both living and non-living things.

The model suggests that as there are numerous intercorrelations between living things, compensation may be available to offset the effects of disease. For example, a robin can be inferred to have wings even if this connection is lost because wings are highly intercorrelated with other features of birds and the basic knowledge that a robin is a bird may still be present. Non-living things are considered to be different however. For example, a vehicle generally only has one distinct function e.g. an aeroplane flies. If this connection is lost there may be no other intercorrelations for aeroplane and the recall of this item may be lost. The model proposes that artefacts are lost in a linear fashion, whereas biological things are lost along a non-linear trajectory. The loss in biological things is thought to be compensated for by the relatively large number of intercorrelations, at least up to a certain point, when the damage to these is so great that there is a loss of an entire category. The model, when applied to AD, appears to fit well with the data collected in the Gonnerman et al. (1997) study. The artefacts showed greater impairment early in the disease process, but this pattern was reversed later in the course of the disease, as the terminal drop of biological items was predicted to occur due to damage to the intercorrelations. The model also predicts that later in the disease process both impairment to biological and artefact categories should be stabilised as the patients proceed towards complete anomia (due to the extensive damage to the connections and intercorrelations).

Impairments to the connectivity of the semantic memory system provide an explanation for the breakdown of semantic knowledge that occurs due to Alzheimer's disease. The widespread atrophy that is characteristic of the disease most likely causes damage to occur both in the areas that information is stored and also to the connections that make the information available. In patients with Alzheimer's disease the semantic memory system appears to break down with the loss of specific information (distinguishing features) and associative information (connections and intercorrelations), preceding the breakdown of superordinate information. This pattern is most likely observed because of the relatively large number of connections which must be damaged before a deficit is predicted to occur in superordinate knowledge.

The effect of AD appears therefore, to impair semantic memory processing and storage. By studying the semantic memory system with neuro-imaging techniques, it may be possible to distinguish the effects of pathological ageing at a very early stage.

4.9.2 Neuro-imaging Evidence of the Differences between AD and Normal Ageing

Using fMRI, Grossman et al. (2003) investigated the differences in brain activation patterns between patients with AD and normal controls on a semantic task which involved rating either animals or implements for pleasantness. Grossman et al. found that a number of differences existed between the AD group and elderly controls. When both types of category were combined in the analysis, the AD group had reduced activation in the left posterolateral temporal-parietal (BA 22/39), the left lateral frontal (BA 44/46), the left occipital (BA 17/18), the right ventral temporal (BA 22/20) cortices and the right caudate. When the categories were investigated individually, the AD patients showed a lack of activation in the left posterolateral temporal and inferior parietal cortices. The lack of activation in these regions was common to both categories.

Grossman et al. (2003) proposed a two-component model of semantic memory which contained (1) long term knowledge of features associated with word meaning (2) a category neutral process which is involved in integrating semantic features. The authors suggested that the reduced levels of activation found in the AD patients were associated with impairment to both the availability of feature knowledge and the integration of semantic features. The areas that lacked activation in the AD group which were common to the rating of both categories of knowledge (animals and implements) were considered to be linked to deficits in integrating semantic features. The areas that lacked activation which were category-specific (animals or implements), however, were suggested to be related to an impairment of feature knowledge.

The AD group had increased activation in the left inferior temporal region compared to the controls (when categories were combined). The increased area of activation was in a region very close to that activated by the controls. Grossman et al. (2003) suggested that the increased activation was due to compensation on behalf of the patient group.

In summary, the results of the Grossman et al. (2003) study suggest that in AD, impairment is occurring to multiple components of the semantic system. The authors suggest that the impairments are associated with the underactivations that were

observed in the AD group. The experiment also appears to provide evidence of compensation by the AD group.

4.9.3 The Association between Functional Problems in AD and Semantic Memory Impairment

The level of activation of the neuronal networks in response to semantic processing tends to be lower in the AD brain than in the normal elderly brain, most probably resulting from the inability of the AD patients to use those areas that have been subject to atrophy (Almkvist, 2000).

Using SPECT, a widespread decrease in blood flow can be observed, in particular in the temporo-parietal regions bilaterally (Holman, Johnson, Gerada, Carvalho, & Satlin, 1992; Messa et al., 1994). These decreases in blood flow can often be correlated with mental status, and are related to semantic memory function. There may also be frontal lobe involvement or asymmetrical abnormal perfusion patterns. The findings are similar in PET, in which widespread decreased glucose metabolism can be observed, especially around the temporo-parietal association cortex and prefrontal cortex (Pietrini, Alexander, Furey, Hampel, & Guazzelli, 2000; Silverman et al., 2001), with sparing of the visual and motor cortices, in addition to the striatum and cerebellum (Herholz, 1995).

In summary, the use of various brain imaging techniques have revealed considerable differences between the brains of patients with AD and normal elderly brains. Decreases in perfusion and metabolism have been described to occur in specific regions in the brains of patients with AD. Semantic memory impairment is thought to be associated with these changes.

4.9.4 The Effect of AD Pathology on Semantic Memory

The medial temporal lobes and the hippocampal region are amongst the first to degenerate in AD. These structures are linked explicitly with memory. In the

examination of semantic dementia, which is a disorder in which the patients cannot remember semantic information but tend to remember personal episodes well (until up to approximately one year before the symptoms of the disease), a pattern usually emerges which reveals that the difficulty lies in the inability of the patient to transfer details of association from the medial temporal lobes to the anterior temporal neocortex regions (Mayes & Montaldi, 2001). This deficit may be similar to the problem in AD. The neural pathways that run between the medial temporal lobes and the neocortex might not be functioning correctly. To exasperate the problem in AD, the neurons in the neocortex are also degenerating, in addition to those in the medial-temporal lobes. These alterations to the AD brains may produce impairments of semantic processing that are dependent on the stage and topography of the disease.

One of the first signs of AD is usually an impairment of recent memory. This is thought to occur because of atrophy to the hippocampal region. Other very early impairments tend to be subtle personality changes, difficulties in finding the appropriate words (in particular nouns and names) or arithmetic problems. These other possible deficits are not dependent on the hippocampal structures. One theory that accounts for the depletion of these abilities very early in the disease and can also lend support for very early semantic impairment focuses on metabolic alterations within the neuronal somata (Terry, 2000). This theory accounts for the prevalence of neurofibrillary tangles in the entorhinal cortex and their absence from the neocortex at very early stages of the disease process, even though damage is occurring to both areas. The theory states that the large neurons in the entorhinal cortex have relatively few terminals, whereas neurons in the neocortex have hundreds or even thousands of terminals. This means that when a neuron in the entorhinal cortex loses more than a few of the terminals that it possesses, it becomes useless, lacking the ability to be a neurotransmitter. The neuron also ceases to pick up essential trophic factors, which results in degeneration. The trophic factors are the food or nourishment that the neurons require. Neocortical neurons however, can lose some terminals with no major consequence to the uptake of the trophic factors. This means that no degeneration or formation of plaques occur until later in the course of the disease. The neurons do, however, lose synapses which makes them less effective. This process probably occurs simultaneously to the beginning of the terminal loss in the entorhinal cortex (Terry, 2000).

Structural MRI shows that atrophy to regions other than the hippocampal structures generally occurs later in the disease process. This means that in patients that are in the very early stages of AD, extensive atrophy may not be observed in the areas contributing to semantic memory function (with the limitations of current neuro-imaging facilities). It may be possible to see behavioural or functional deficits however, if a sensitive enough test is employed.

The semantic memory decline may be much more subtle than the episodic memory decline, as the brain regions involved are better designed to cope with the problem, effectively concealing it. To examine the subtle semantic memory impairments tests with high sensitivity must be used.

4.9.5 Tests for Semantic Memory in AD

Semantic memory appears to be impaired much earlier in the AD process than once thought. Not all semantic memory measures are sensitive enough to demonstrate the impairments found in AD however, and with no definite path of neuronal damage some memory tests might be able to detect a deficit in one AD patient but not another.

Impairments in semantic memory have been observed in patients with minimal AD (i.e. Mini Mental State Exam (MMSE) scores over twenty-three). Hodges and Patterson (1995) found decreased performance on category fluency, the naming of line drawings, answering semantic feature questions, the naming to verbal descriptions, and on the Pyramids and Palm Trees test (which assesses semantic association). Note that not all the patients were impaired on the full range of semantic memory tasks, some were impaired on a subset only.

In the Hodges and Patterson (1995) study, the Pyramids and Palm Trees Test was not the most sensitive of the semantic memory tasks, but it showed the same pattern of discrimination as category fluency, naming to description and picture naming (which were the most sensitive).

Despite not being the most sensitive task, the scores on the Pyramids and Palm Trees Test yielded highly significant group differences between the minimal AD patients and the controls. Post hoc testing also revealed these highly significant group

differences: controls > minimal (MMSE > 23) = mild (MMSE 17-23) > moderate (MMSE < 17) (Hodges & Patterson, 1995). The Pyramids and Palm Trees Test can be seen therefore, to be efficient at demonstrating semantic impairment at a very early stage of the disease process when this type of impairment is present.

4.9.6 Experiment 4: Hypotheses

The hypotheses were formulated with respect to the areas of activation that occurred in the elderly group in experiment 3.

For the patients with AD:

1) The left inferior frontal gyrus will be activated (BA 47). This region is thought to be used to guide retrieval processes.
2) Activation should be observed in the left precuneus and the left superior parietal lobule (BA 7). Activation of the left precuneus appears to be related to semantic retrieval, whereas activation of the left superior parietal lobule may be associated with the phonological reading of the word stimuli.
3) No activations will occur in the left temporal cortex that will reach significance, even at a liberal threshold.
4) The cingulate gyrus (BA 32) may be activated bilaterally.

For the individuals with MCI:

1) The left inferior frontal gyrus will be activated (BA 47) (retrieval processes).
2) Activation is expected in the left precuneus and the left superior parietal lobule (BA 7) (Semantic retrieval and phonological reading of the word stimuli).
3) No activations will occur in the left temporal cortex that will reach significance, even at a liberal threshold.
4) The cingulate gyrus (BA 32) may be activated bilaterally.

4.9.7 Methods

4.9.7.1 Participants

The participant groups consisted of 9 elderly participants, 17 patients with AD and 6 individuals with MCI. The elderly control group included 3 males and 6 females between the ages of 72 and 77. The mean age of the elderly controls was 75.11 (SD 1.62). The AD group consisted of 9 males and 8 females between the ages of 69 and 90. The mean age of the AD group was 79.24 (SD 5.85). The MCI group was composed of 4 males and 2 females between the ages of 66 and 87. The mean age of the MCI group was 76.33 (SD 7.61).

The participants were all British and English was their first language. All the participants recruited for the study were right handed. Ethical approval for this study was granted by the Grampian Health Board and the University of Aberdeen Joint Ethics Committee.

4.9.7.2 Patient Selection

Seventeen patients in the early stages of AD and six individuals with MCI were selected for the fMRI adapted Pyramids and Palm Trees study. The patients with AD and individuals with MCI were selected from approximately one hundred patients with memory problems that were referred to an old age psychiatry memory clinic in Aberdeen to be screened for participation in this study. Exclusion criteria included claustrophobia, vascular risk factors (a Hachinski Ischaemia score (Hachinski et al., 1975) greater than four), or Mini Mental State Examination (MMSE) scores of less than eighteen. The patients that were selected for the study fulfilled the NINCDS-ADRDA criteria for probable AD (McKhann et al., 1984) of minimal to mild severity. The diagnosis of MCI was made using the R. C. Petersen (1997) criteria for amnestic MCI. A summary table of the neuropsychological assessment scores for the AD patients and individuals with MCI is included below (Table 4.6). Note all the patients with AD performed reasonably well on the pencil and paper version of the Pyramids and Palm

Trees Test. The lowest score that was obtained was thirty-eight out of fifty-two (seventy-three percent correct).

Table 4.6

The means and standard deviations for the neuropsychological test scores of the patients with AD and the individuals with MCI

Neuropsychological Test	AD group		n	MCI group		n
	Mean	(SD)		Mean	(SD)	
Mini Mental State Exam (MMSE)	23.94	(2.01)	17	27.00	(3.63)	6
ADAS Cog	18.00	(4.56)	17	NA	NA	0
Confrontational Naming	17.35	(1.50)	17	17.83	(1.47)	6
Verbal Paired Associates	8.13	(2.90)	16	9.00	(2.00)	6
The Pyramids and Palm Trees Test	46.86	(3.76)	14	50.00	(3.46)	3
Rey's Complex Figure Test (Copy)	19.50	(9.20)	6	25.50	(0.00)	1
Rey's Complex Figure Test (Delay)	1.08	(1.56)	6	0.00	(0.00)	1
Semantic Fluency	27.13	(10.41)	15	40.33	(15.92)	6
Phonemic Fluency	28.07	(10.95)	15	42.00	(23.87)	6
Digit Span Forward	6.47	(1.19)	15	6.17	(1.47)	6
Digit Span Backward	4.40	(0.91)	15	4.67	(1.21)	6
Logical Memory: Immediate	5.85	(3.48)	13	5.00	(1.73)	3
Delayed (10 minutes)	3.38	(4.13)	13	6.67	(2.52)	3
Raven's Progressive Matrices	22.82	(4.29)	17	27.33	(4.84)	6
Stroop task (Error Interference)	8.03	(11.03)	17	0.90	(1.02)	5
Stroop task (Time Interference)	38.06	(21.20)	17	27.70	(8.89)	5
Digit Cancellation	42.47	(10.27)	15	48.67	(14.74)	3
Visuoconstructive Apraxia Test	12.57	(1.90)	7	12.33	(1.15)	3
Token Task	31.06	(2.17)	9	28.50	(0.00)	1

Note: NA - Not Available
ADAS - cog: Alzheimer's Disease Assessment Scale - cognitive subscale
Not all the AD patients or individuals with MCI did all the tests. The numbers that comprise each mean and standard deviation have been included.

4.9.7.3 Materials

The same materials were used as in experiment 3.

4.9.7.4 fMRI paradigm

Exactly the same fMRI version of the Pyramids and Palm Trees Test was employed as described in experiment 3. The baseline task was also the same.

4.9.7.5 Procedure

The individuals with MCI and the patients with AD underwent the same procedure as the elderly controls (described in experiment 3).

4.9.7.6 fMRI methods

The fMRI acquisition was carried out using the equipment and acquisition sequence reported in experiment 3.

4.9.7.7 fMRI data analysis

The statistical design consisted of three different participant groups (elderly controls, individuals with MCI and patients with early AD) which performed the Pyramid and Palm Tree Test procedure. A between subjects design was used in order to examine the effects of pathological ageing (elderly versus both the patients with AD and the individuals with MCI). The fMRI data were analysed using the same technique as reported in experiment 3.

4.9.8 Results

4.9.8.1 Analysis of behavioural data

The ages, educations and Mini-Mental State Exam scores of the elderly, MCI and AD groups were investigated (see Table 4.7). ANOVA showed that the groups did not differ significantly on either age, $F(2,29) = 1.872$; p = ns, or education, $F(2,29) = 1.813$; p = ns. A main effect of MMSE was observed, however, $F(2,29) = 16.084$; $p < 0.001$. Planned contrasts revealed that the mean MMSE scores of the elderly group

were significantly higher than the AD group ($p < 0.001$). The MMSE scores of the MCI group were also significantly higher than the AD group ($p < 0.01$).

Table 4.7

The means (and standard deviations) for the ages, educations and MMSE scores of the elderly, MCI and AD groups.

Group	N	Age	Education (yrs)	MMSE
Elderly	9	75.11 (1.62)	11.67 (2.29)	28.89 (0.93)
MCI	6	76.33 (7.61)	13.83 (3.60)	27.00 (3.63)
AD	17	79.24 (5.85)	11.06 (3.23)	23.94 (2.01)

Note: The maximum attainable score on the MMSE is thirty

The mean performance scores of the elderly, MCI and AD groups on the fMRI adapted Pyramids and Palm Trees paradigm can be seen in Table 4.8. ANOVA showed that the groups were significantly different, $F(2,29) = 11.536$; $p < 0.001$. Planned contrasts revealed that the scores of the elderly group were significantly higher than the scores of the AD group ($p < 0.001$). The scores of the MCI group were also significantly higher than the AD group ($p < 0.05$). The scores of the elderly group and the MCI group did not differ significantly.

Table 4.8

The mean behavioural scores (and standard deviations) for the elderly, MCI and AD groups on the Pyramids and Palm Trees Test Activation Condition

Pyramids and Palm Trees Test Activation Condition		
Group	N	Mean (SD)
Elderly	9	45.78 (3.46)
MCI	6	41.67 (5.35)
AD	17	37.41 (4.26)

Note: The maximum score achievable on the paradigm was 54

The mean reaction times of the groups can be seen in Figure 4.9. These were compared using ANOVA. The reaction times were significantly different between the groups, $F(2,29) = 6.971$; $p < 0.01$. Planned contrasts revealed that the mean reaction times of the AD group were significantly longer than the elderly group ($p < 0.01$). No significant differences in reaction times occurred for the other group comparisons.

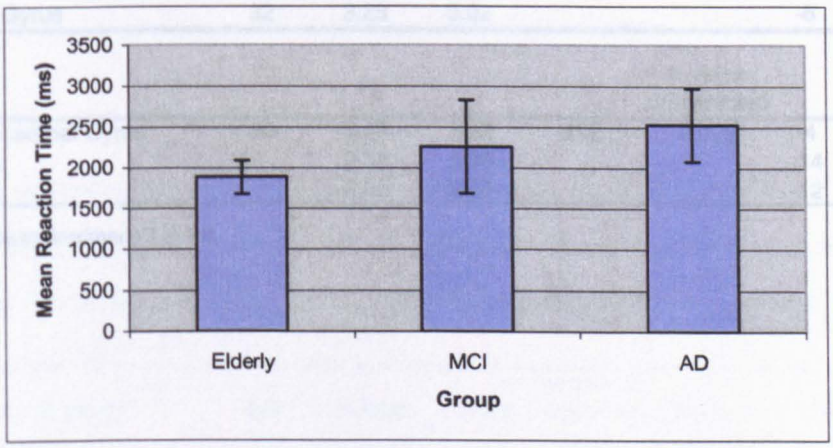

Fig 4.9: The mean reaction times for the young, elderly, MCI and AD groups on the Pyramids and Palm Trees Activation Condition (error bars of the standard deviations are provided).

4.9.8.2 fMRI Experiment 4: Detection of the Areas Used in Semantic Memory and Processing

AD Group: Activation was found in the left inferior frontal gyrus (BA 44), the left middle frontal gyrus (BA 49/9), the left superior frontal gyrus (BA 6) and the left cingulate gyrus (BA 32), ($p < 0.01$, corrected). At the uncorrected level of significance, activation was also detected in the left parahippocampal gyrus (BA 30) and the left thalamus (including the ventral lateral nucleus). All the activations can be seen in Table 4.9, and are shown on a 3D rendering of the brain in Figure 4.10.

Table 4.9

Areas of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, corrected (a) and uncorrected (b), for the Pyramids and Palm Trees activation versus baseline contrast in the AD group.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Middle Frontal Gyrus	46	7.16	5.46	1838	0.000	-46	19	21
	9	6.99	5.38			-48	15	29
Left Inferior Frontal Gyrus	44	5.29	4.43			-51	9	20
Left Cingulate Gyrus	32	4.96	4.22	822	0.019	-6	21	41
Left Superior Frontal Gyrus	6	4.72	4.07			-4	7	55
Left Cingulate Gyrus	32	3.28	3.02			-6	27	32
b)					p-value uncorrected			
Left Parahippocampal Gyrus	30	3.68	3.32	292	0.023	-4	-37	4
Left Thalamus		3.38	3.09			-14	-13	12
Left Thalamus		3.06	2.84			-12	-14	1

Note: * BA refers to Brodmann's Areas.

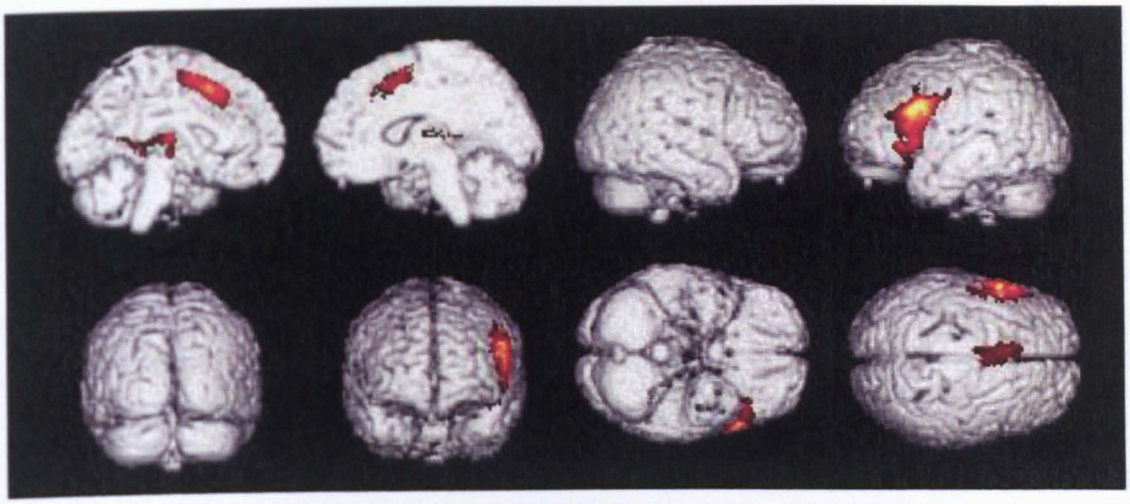

Fig 4.10: Significant activation found in the AD group for the Pyramids and Palm Trees activation versus baseline contrast (displaying corrected and uncorrected activations).

Using a less conservative threshold of significance ($p < 0.05$), additional activation occurred in the left medial frontal gyrus (BA 6).

AD Group versus Elderly Group Comparison: This comparison revealed significant differences in the left anterior cingulate (BA 33) and the left caudate, ($p < 0.01$, uncorrected). Table 4.10 lists the differences, which are portrayed in Figure 4.11.

Table 4.10

Sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the comparison of the AD group to the elderly group on the Pyramids and Palm Trees activation versus baseline contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Anterior Cingulate	33	4.14	3.80	317	0.016	-6	20	16
Left Caudate		3.07	2.92			-4	11	18

Note: * BA refers to Brodmann's Areas.

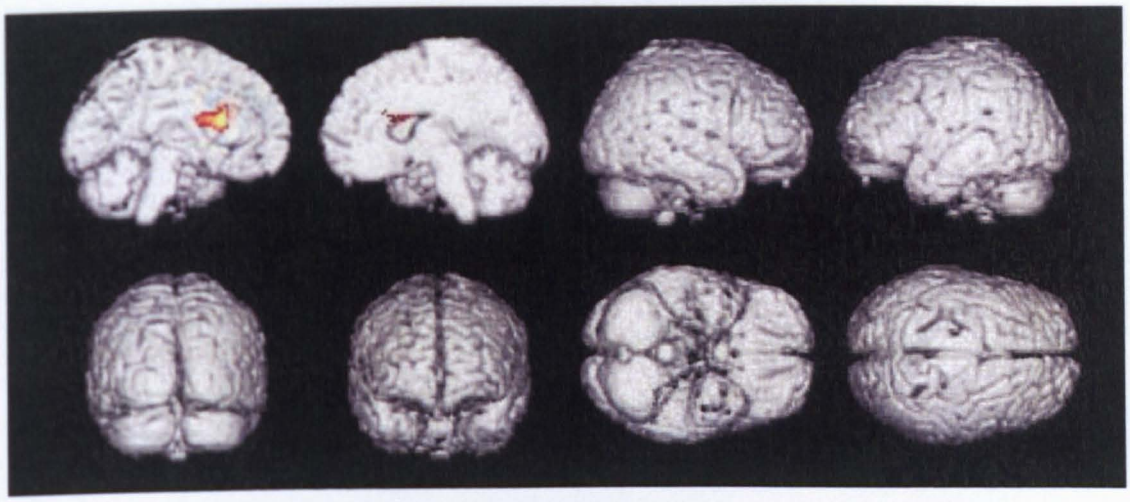

Fig 4.11: Significant differences in activation for the comparison of the AD group to the elderly group on the Pyramids and Palm Trees activation versus baseline contrast.

When a less conservative threshold was used, further significant differences in activation were observed in the medial frontal gyrus (BA 6) bilaterally, ($p < 0.05$).

Elderly Group versus AD Group Comparison: Significant differences were present in the left middle frontal gyrus (BA 9/46) at the $p < 0.05$ level of significance, uncorrected (See Table 4.11 and Figure 4.12).

Table 4.11

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the comparison of the elderly group to the AD group on the Pyramids and Palm Trees activation versus baseline contrast.

Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Middle Frontal Gyrus	9	3.53	3.31	768	0.040	-40	20	32
	46	3.43	3.22			-40	31	20

Note: * BA refers to Brodmann's Areas.

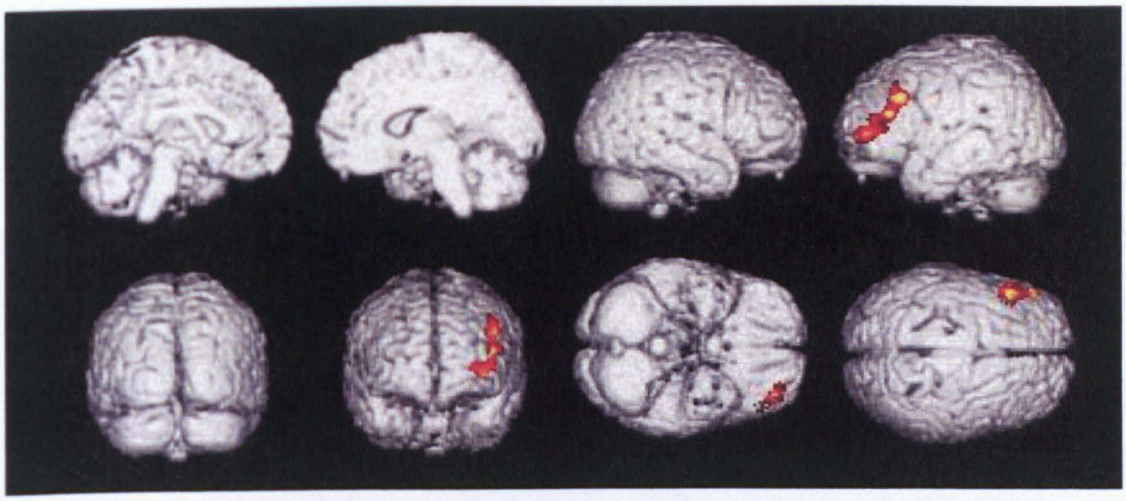

Fig 4.12: Significant differences in activation for the comparison of the elderly group to the AD group on the Pyramids and Palm Trees activation versus baseline contrast.

MCI Group: A cluster of significant activation was present in the left middle frontal gyrus (BA 46/9), ($p < 0.01$, corrected). No additional areas of activation were detected when an uncorrected level of significance was chosen. The activations are presented in more detail in Table 4.12. These can be seen in a visual format in Figure 4.13.

Table 4.12

Areas of activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the Pyramids and Palm Trees activation versus baseline contrast in the MCI group.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value corrected	Co-ordinates x	y	z
Left Middle Frontal Gyrus	46	6.16	3.97	570	0.031	-44	18	20
	9	4.49	3.32			-44	11	32

Note: * BA refers to Brodmann's Areas.

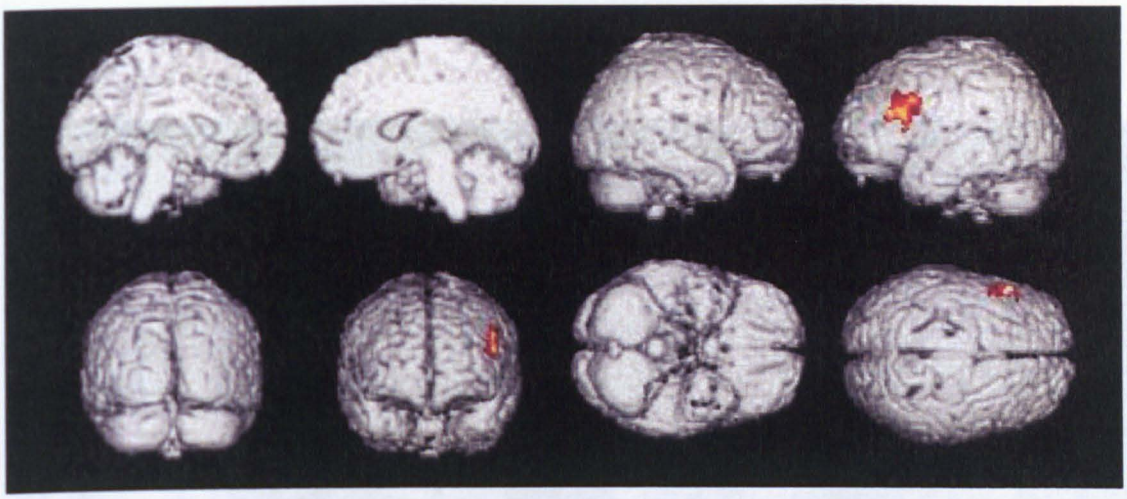

Fig 4.13: Significant activation found in the MCI group for the Pyramids and Palm Trees activation versus baseline contrast.

When a more liberal threshold was used, additional activations were found in the left inferior frontal gyrus (BA 9), the left middle frontal gyrus (BA 6), the left thalamus and the caudate body bilaterally ($p < 0.05$).

MCI Group versus Elderly Group Comparison: Significant differences in activation were seen in the right anterior cingulate (BA 32/24), the right inferior frontal gyrus (BA 9) and the right precentral gyrus (BA 6), ($p < 0.01$, uncorrected). The differences are presented in Table 3.13 and Figure 4.14.

Table 3.13

The areas of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the comparison of the MCI group to the elderly group on the Pyramids and Palm Trees activation versus baseline contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Right Anterior Cingulate	NA	3.97	3.49	204	0.030	0	39	0
	32	3.79	3.37			18	39	0
	24	2.60	2.44			8	27	-1
Right Inferior Frontal Gyrus	9	3.49	3.14	185	0.037	59	7	25
Right Precentral Gyrus	6	3.37	3.06			46	-8	34
	6	2.92	2.70			53	-3	24

Note: * BA refers to Brodmann's Areas.

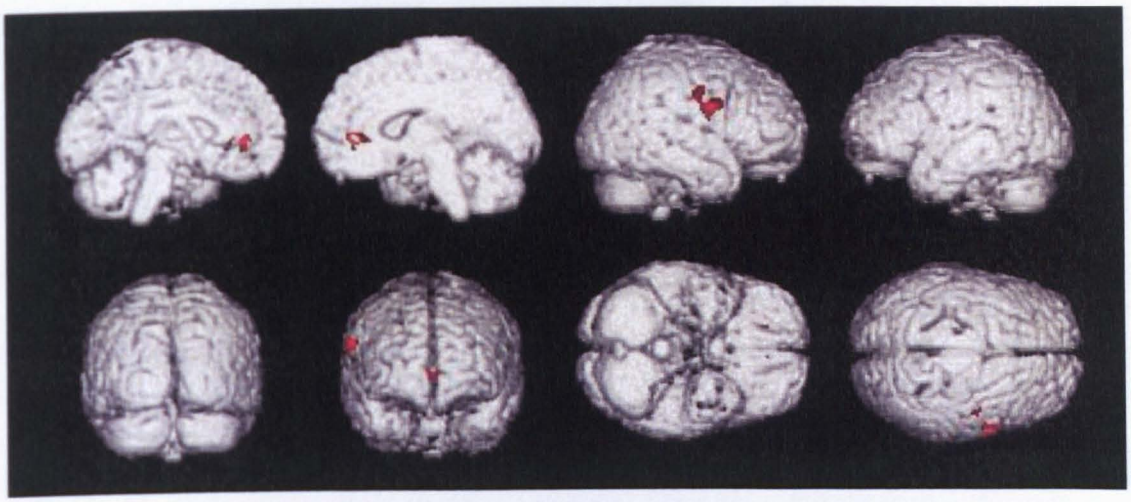

Fig 4.14: Significant differences in activation for the comparison of the MCI group to the elderly group on the Pyramids and Palm Trees activation versus baseline contrast.

Additional differences in activation were found in the left medial frontal gyrus (BA 11), the left anterior cingulate (BA 32) and the caudate body bilaterally, when a less conservative threshold was used ($p < 0.05$).

Elderly Group versus MCI Group Comparison: Differences in activation were observed in the left middle frontal gyrus (BA 10/11) and the left superior frontal gyrus (BA 10), at the $p < 0.01$ level of significance, uncorrected (see Table 4.14 and Figure 4.15).

Table 4.14

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the elderly group versus the MCI group comparison on the Pyramids and Palm Trees activation versus baseline contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Middle Frontal Gyrus	10	4.24	3.68	201	0.031	-38	57	0
	11	3.16	2.89			-38	55	-10
Left Superior Frontal Gyrus	10	3.11	2.85			-13	53	-3

Note: * BA refers to Brodmann's Areas.

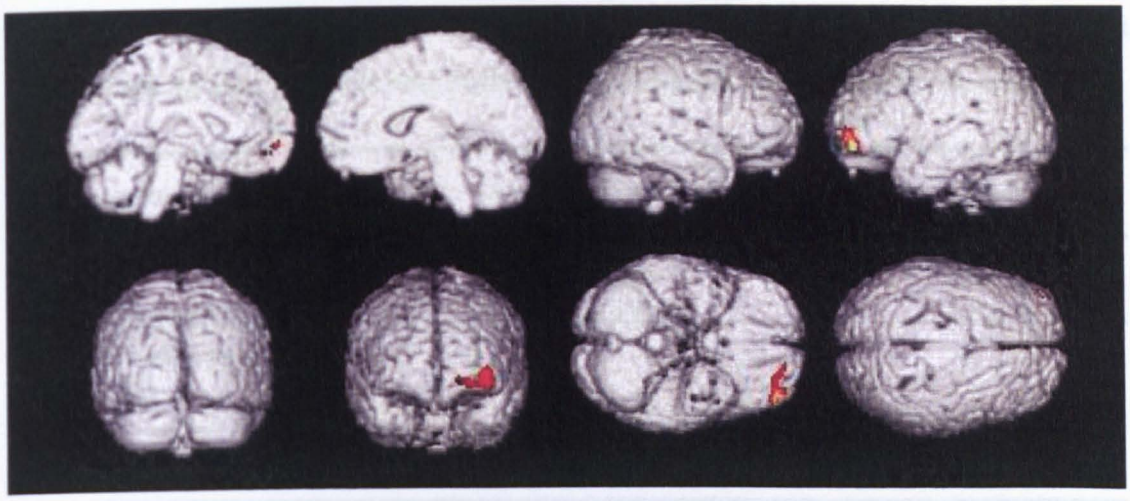

Fig 4.15: The significant differences in activation for the comparison of the elderly group to the MCI group on the Pyramids and Palm Trees activation versus baseline contrast.

Further differences in activation were seen in the left inferior frontal gyrus (BA 46), the right medial frontal gyrus (BA 6), the right cingulate gyrus (BA 23/31), the right cuneus (BA 19), right superior temporal gyrus (BA 22), the right middle temporal gyrus (BA 39), the right superior occipital gyrus (BA 19) and the right parahippocampal gyrus (BA 36) when a more liberal threshold was used ($p < 0.05$). Significant differences were also present in the left claustrum, left thalamus, right thalamus (pulvinar) and right lentiform nucleus (putamen).

MCI group versus AD Group Comparison: No significant differences in activation were observed at the $p < 0.01$ level of significance. At a more liberal threshold, significant differences in activation were seen in the left superior frontal gyrus (BA 10) and the left anterior cingulate (BA 32), ($p < 0.05$, uncorrected). These differences can be viewed in Table 4.15 and Figure 4.16.

Table 4.15

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the MCI group versus the AD group comparison on the Pyramids and Palm Trees activation versus baseline contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Superior Frontal Gyrus	10	3.17	2.99	909	0.035	-32	51	14
	10	3.09	2.92			-21	50	21
Left Anterior Cingulate	24	3.08	2.91			-1	32	1

Note: * BA refers to Brodmann's Areas.

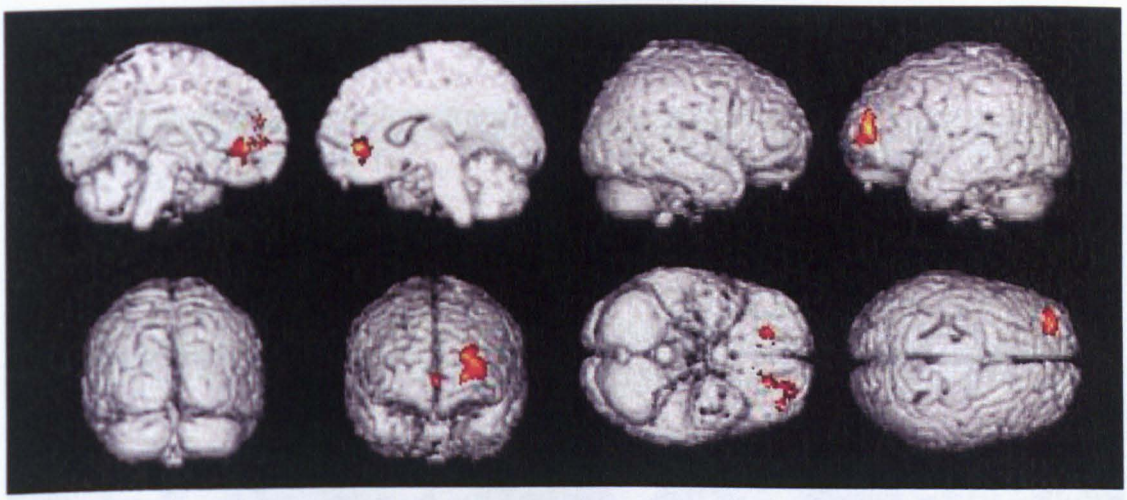

Fig 4.16: The significant differences in activation for the comparison of the MCI group to the AD group on the Pyramids and Palm Trees activation versus baseline contrast.

AD Group versus MCI Group Comparison: No significant differences were observed between the groups at the $p < 0.01$ level of significance. At a less conservative threshold, however, significant differences in activation were present in the left inferior frontal gyrus (BA 44/45), the left superior temporal gyrus (BA 22), the right transverse temporal gyrus (BA 41) and the left thalamus ($p < 0.05$, uncorrected). Table 4.16 provides additional information on the differences in activation and Figure 4.17 illustrates the locations of these differences.

Table 4.16

The sites of differential activation, Talairach co-ordinates, Brodmann's Areas, T-values, Z-values, cluster sizes, and p-values, for the AD group versus the MCI group comparison on the Pyramids and Palm Trees activation versus baseline contrast.

a) Site of activation	BA*	T-value	Z-value	Number of Voxels in Cluster	p-value uncorrected	Co-ordinates x	y	z
Left Inferior Frontal Gyrus	44	3.91	3.59	815	0.045	-51	7	20
	45	3.49	3.25			-57	13	20
Left Superior Temporal Gyrus	22	3.31	3.10			-57	-2	-2
Right Transverse Temporal Gyrus	41	3.26	3.06	2097	0.003	38	-31	11
Left Thalamus		2.83	2.69			-12	-23	14
		2.82	2.68			-20	-18	-2

Note: * BA refers to Brodmann's Areas.

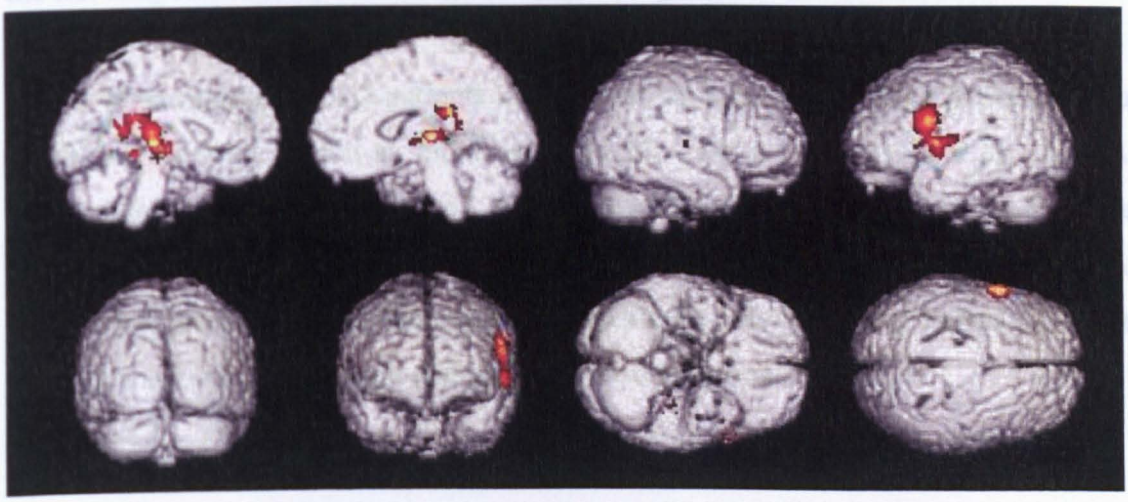

Fig 4.17: Significant differences in activation for the comparison of the AD group to the MCI group on the Pyramids and Palm Trees activation versus baseline contrast.

4.9.9 Discussion

4.9.9.1 fMRI Experiment 4: Areas of Activation in AD Involved with Semantic Memory and Processing

The random effects analysis of the AD group revealed activation in the left inferior frontal gyrus (BA 44), the left middle frontal gyrus (BA 49/9) and the left superior frontal gyrus (BA 6). The activation of the left inferior frontal gyrus (BA 44)

may be due to the AD patients subvocalising the word stimuli as they search for the semantic association. The activation of the other frontal areas may have been due to the increased demands for control processing that are produced by the Pyramids and Palm Trees task compared to the baseline task.

The AD group activated the left parahippocampal gyrus (BA 30) and the left thalamus. Activation of the left parahippocampus is not unusual during semantic matching tasks. This area was activated in the study by Ricci et al. (1999) and the right parahippocampal gyrus was activated in the young group for the present contrast.

Similar to the elderly group, activation was observed in the left cingulate gyrus (BA 32). Note that the activation of this region in the elderly group was bilateral however. At a more liberal threshold, further activation was identified in the left medial frontal gyrus (BA 6), but no significant clusters of activation were observed in any of the left temporal or left parietal regions in the AD group.

In summary, the AD patients activated an area in the left inferior frontal gyrus, albeit not the same region as found in either the young or elderly groups. The AD group also activated a number of other areas of the prefrontal cortex and the left parahippocampal gyrus. Similar to the pattern of activation found in the elderly, the AD group activated the left cingulate gyrus. Interestingly, the AD group lacked significant activation in both the temporal and parietal cortical regions.

4.9.9.2 fMRI Experiment 4: The Effect of AD on Semantic Memory and Processing

AD group versus Elderly Group Comparison: Significantly different levels of activation were found in the left anterior cingulate (BA 33) and the left caudate body. The difference in activation that was seen in the left anterior cingulate may have been related to the recruitment of additional attentional areas by the AD group in order to aid in task completion.

When a more liberal threshold was adopted, significant differences were also observed in the medial frontal gyrus (BA 6) bilaterally. The differential activation found in these frontal areas may be associated with certain compensatory mechanisms that might have been implemented by the AD group. The activation that was found in the prefrontal cortex of the elderly group was left lateralised. It appears that the AD

group may have been employing bilateral regions of the prefrontal cortex to aid in task completion.

Elderly Group versus AD Group Comparison: The comparison of the elderly group to the AD group revealed significant differences in the left middle frontal gyrus (BA 9/46). The differential activation found in these regions suggests that the elderly group are activating the left middle frontal gyrus to a significantly higher level than the AD group. Greater levels of activation in these left prefrontal regions may help the elderly to handle the increased demands on control processing that are placed by the Pyramids and Palm Trees task compared to the baseline task. This may be one of the reasons that the elderly group outperform the AD group on the Pyramids and Palm Trees task.

It should be noted that although the random effects analysis of the elderly group showed significant activation in the left precuneus and in the left superior parietal lobule, (and the random effects analysis of the AD group did not reveal any significant activation in these regions), when the activation patterns of the two groups were statistically compared, no significant differences were present in these regions. This finding suggests that the AD group may have sub-threshold activation in the left parietal areas i.e. underactivation is occurring.

Conclusions: The patients with AD activated the left inferior frontal gyrus (BA 44). This area has been activated in other semantic matching tasks such as that of Ricci et al. (1999). The AD group activated the left middle frontal gyrus, the left superior frontal gyrus and the left parahippocampal gyrus. The activation of these areas does not appear to be uncommon in semantic memory tasks. Similar to the elderly group, the AD group activated the left cingulate gyrus (BA 32).

The AD group did not have any significant activation in the left precuneus or the left superior parietal lobule. These areas were activated in both the elderly and the young groups. The absence of significant activation in the left precuneus and the left superior parietal lobule in the AD group may have contributed to the lower scores on the Pyramids and Palm Trees task when compared to the elderly group. The AD group had significantly lower behavioural scores and significantly longer reaction times than the elderly group.

Neither the random effects analyses of the elderly or AD groups showed any significant clusters of activation in the temporal cortex. Perfusion and metabolism abnormalities have been observed in the temporo-parietal regions of patients with AD (Holman et al., 1992; Messa et al., 1994; Pietrini et al., 2000; Silverman et al., 2001). These functional deficits may well be related to the lack of activation that occurred in the temporal and parietal regions of the AD group in the current comparison. Note that although the elderly group did not show any significant activation in the left temporal cortex, they did activate the left precuneus and the left superior parietal lobule significantly.

The study on semantic processing that was carried out by Grossman et al. (2003), which investigated the patterns of activation that were found in patients with AD and normal elderly, showed that the patients underactivated the posterolateral temporal and inferior parietal cortices. This finding is relevant to the present comparison as the AD patients from this study also appear to underactivate regions of the temporal and parietal cortex.

Comparing the AD group to the elderly group identified significantly different levels of activation in the left anterior cingulate (BA 33), the left caudate, and the medial frontal gyrus bilaterally. The greater activation of these regions may reflect mechanisms of compensation that are taking place in the AD group. These areas may be activated due to the lack of activation found, for example, in the left precuneus and the left superior parietal lobule of the AD group.

When the elderly group was compared to the AD group differential activation was observed in the left middle frontal gyrus. The lower levels of activation in this area by the AD group compared to the elderly group may explain the need of the AD group to recruit bilateral medial frontal areas. The AD group may be compensating for decreased levels of left frontal activation (compared to that found in normal elderly).

In summary, a number of interesting differences appear to exist between the AD group and the elderly group. The AD group appeared to underactivate the left precuneus and the left superior parietal lobule, compared to the pattern of activation observed in the elderly group. The AD patients also seemed to recruit additional areas, for example, the left anterior cingulate (BA 33) and the medial frontal gyri. When the

elderly were compared to the AD group differential activation was observed in the left middle frontal gyrus. The regions of greater activation in the AD group may have been utilized in order to compensate for those areas that are undergoing dysfunction due to disease.

4.9.9.3 fMRI Experiment 4: Areas of Activation in MCI Associated with Semantic Memory and Processing

The random effects analysis of the MCI group showed activation of the left middle frontal gyrus (BA 46/9). Additional activation was detected in the left inferior frontal gyrus (BA 9) and the left middle frontal gyrus (BA 6) when a less conservative threshold was used. The MCI group did not activate the same regions of the left inferior frontal gyrus as seen in the young group (BA 45) or the elderly group (BA 47). Neither did they activate the left precuneus or the left superior parietal lobule (as seen in the young and elderly groups). Note that significant activation in these areas was also absent in the AD group. Activation occurred in the left thalamus and the caudate body bilaterally in the MCI group at the more liberal threshold. No significant activations were observed in any regions of the temporal cortex.

In summary, similar to the AD group, the MCI group appeared to lack significant activation in specific areas of the left inferior frontal gyrus, the left temporal cortex and the left parietal cortex.

4.9.9.4 fMRI Experiment 4: The Effect of MCI on Semantic Memory and Processing

MCI Group versus Elderly Group Comparison: Significant differences in activation were present in the right anterior cingulate (BA 32/24), the right inferior frontal gyrus (BA 9) and the right precentral gyrus (BA 6). The MCI group may have activated the right prefrontal hemispheric areas to higher levels than the elderly group in order to aid task performance. Significant differences were also observed in the left medial frontal gyrus (BA 11), the left anterior cingulate (BA 32) and the caudate body bilaterally when the comparison between groups was explored with a more liberal threshold. It appears that the MCI group are activating the cingulate cortex bilaterally, to higher levels than

the elderly group. The greater cingulate activation may be due to compensation in the MCI group as they attempt to perform at the same behavioural level as the normal elderly.

Elderly Group versus MCI Group Comparison: Significant differences were identified in the left middle frontal gyrus (BA 10/11) and the left superior frontal gyrus (BA 10). This finding suggests that the elderly group were managing to activate these left prefrontal areas to higher levels than the MCI group. The greater activation of these areas may have aided performance by the elderly group on the Pyramids and Palm Trees task. The significantly different activation found in the cingulate areas for the previous comparison (MCI group versus elderly group), may be in compensation for the lower levels of activation found in the left middle frontal gyrus and the left superior frontal gyrus of the MCI group, when compared to the elderly. No significant differences were found in the precuneus or the left superior parietal lobule. This finding implies that the MCI group may be activating these areas to a subthreshold area in order to complete the task.

A number of areas exhibited differential activation when a less conservative threshold was used. Significantly different activation was observed in the left inferior frontal gyrus (BA 46), the right medial frontal gyrus (BA 6), the right middle temporal gyrus (BA 39), the right parahippocampal gyrus (BA 36), the right superior temporal gyrus (BA 22), the right superior occipital gyrus (BA 19), the right cuneus (BA 19) and the right cingulate gyrus (BA 23/31). It appears that the elderly activated the left inferior frontal gyrus to a significantly higher level than the MCI group, whereas the result of the previous comparison suggested that the MCI group activated the right inferior frontal gyrus to a significantly higher level than the elderly group. This finding might reflect the inability of the MCI group to activate specific left hemispheric areas, resulting in compensatory activation of the right hemisphere. The differential activation that was observed in the right middle temporal gyrus, the right superior temporal gyrus, the right superior occipital gyrus and the right cuneus was a more unusual finding, as the activation of the left hemispheric homologues of these areas tend to be reported in tasks of lexical and semantic processing. The activation of these regions in the right hemisphere does not appear to be as common, however. The difference in activation

that was found in the right parahippocampal gyrus may reflect greater semantic processing by the elderly group than the MCI group. Activation of the right parahippocampal gyrus was reported in the study by Sabsevitz et al. (2005). The differential activation that was observed in the right cingulate gyrus seems to be in a more posterior location to any of the activations found in the previous semantic memory and processing comparisons. The MCI group appear to be underactivating this area compared to the elderly group. Differential activation also occurred in the left claustrum, the left thalamus, the right thalamus (pulvinar) and the right lentiform nucleus (putamen).

In summary, when the elderly group were compared to the MCI group, significantly different levels of activation were observed in the left middle frontal gyrus, the left superior frontal gyrus, the left inferior frontal gyrus and the right parahippocampal gyrus. These areas seem to have been underactivated by the MCI group. Significant differences in the levels of activation were also observed in a number of more unusual locations, for example, the right middle temporal gyrus, the right superior temporal gyrus, the right superior occipital gyrus and the right cuneus. A significant difference in activation was also seen in the right posterior cingulate gyrus.

MCI Group versus AD Group Comparison: Significant differences in activation were observed in the left superior frontal gyrus (BA 10) and the left anterior cingulate (BA 32). The AD group may have underactivated these regions due to greater dysfunction related to the disease process.

AD Group versus MCI Group Comparison: Significant differences were found in the left inferior frontal gyrus (BA 44/45), the left superior temporal gyrus (BA 22), the right transverse temporal gyrus (BA 41) and the left thalamus. The differential activation observed in the left inferior frontal gyrus (BA 44) may reflect more subvocalisation of the word stimuli by the AD group compared to the MCI group. An alternative explanation for the difference in activation in this area may be that the area was recruited by the AD group to aid in semantic memory retrieval processes. Buckner (2003) suggested that the left inferior frontal gyrus (BA 44/45/47) is used in guiding

long term memory retrieval. The differential activation in Brodmann's area 44/45 found in the present comparison, therefore, may also be due to semantic memory retrieval processes. Activation of the left superior temporal gyrus was described in the study on semantic association by Price et al. (1999). The difference in activation that was found in this region for the present comparison may reflect the need for the AD group to activate this region to higher levels than the MCI group in order to attempt similar performance scores. The right transverse temporal gyrus was not activated in any of the studies on semantic association that have been described e.g. Price et al. (1999), Ricci et al. (1999), Sabsevitz et al. (2005) and Vandenberghe et al. (1996). The differential activation of this area seems unusual for an fMRI semantic processing paradigm such as the Pyramids and Palm Trees test.

In summary, the comparison of the AD group to the MCI group revealed significantly different activation in the left inferior frontal gyrus (BA 44/45), the left superior temporal gyrus (BA 22) and the right transverse temporal gyrus. Neither the left inferior frontal gyrus (BA 44), nor the left superior temporal gyrus (BA 22) were activated by the young or elderly groups when completing the Pyramids and Palm Trees task in the current study. The AD group may have activated these regions to a higher level than the MCI group in an attempt to keep performance at as high a level as possible. An alternative explanation for the differences in activation could be that the activation seen in these regions provided no real benefit to the AD group when performing the Pyramids and Palm Trees task. Note that the mean score on the task was significantly higher for the MCI group than the AD group.

Conclusions: The random effects analysis of the MCI group showed activation in the left middle frontal gyrus and the left inferior frontal gyrus (BA 9). The activation of these areas is likely to contribute to the retrieval of semantic associations. The MCI group did not activate the left inferior frontal gyrus in the same areas as seen in the young group (BA 45) or the elderly group (BA 47), nor did they activate the left precuneus or the left superior parietal lobule as seen in both the young and elderly groups. The MCI group still managed to perform the Pyramids and Palm Trees task despite the lack of significant activation in these areas. The mean score of the MCI

group fell between the elderly group and the AD group, differing significantly only from the AD group.

Comparing the MCI group to the elderly group revealed significantly different levels of activation in the right inferior frontal gyrus (BA 9), the right precentral gyrus and the cingulate cortex bilaterally. A number of the individuals in the MCI group may have been activating these cingulate areas and right hemispheric regions to higher levels than the elderly in order to compensate for dysfunction related to the very early stages of Alzheimer's disease. Differential activation was also seen in the left medial frontal gyrus (BA 11) and the caudate body bilaterally.

The comparison of the elderly group to the MCI group showed significantly different activations in the left middle frontal gyrus and the left superior frontal gyrus. Additional differences in activation were observed in the left inferior frontal gyrus and the right parahippocampal gyrus, although only at a less conservative p-value. Higher levels of activation in these regions may have supported the trend of better performance in the elderly group compared to the MCI group. Differential activation was also seen in a number of right hemispheric areas and the right cingulate gyrus (BA 23/31).

The comparison of the MCI group to the AD group showed differential activation in the left superior frontal gyrus and the left anterior cingulate. These areas may have been underactivated by the AD group compared to the MCI group. This may have been one of the causes for the lower behavioural scores in the AD group.

Finally, the comparison of the AD group to the MCI group revealed significantly different activations in the left inferior frontal gyrus (BA 44/45), the left superior temporal gyrus (BA 22), the right transverse temporal gyrus and the left thalamus. The activation of the left inferior frontal gyrus (BA 44/45) and the left superior temporal gyrus are considered to be related to semantic processing. Neither the young group nor the elderly group activated the left inferior frontal gyrus (BA 44) or the left superior temporal gyrus (BA 22) significantly in the current study, however.

In summary, the MCI group differed from the young and elderly groups in a number of ways. The random effects analysis of the MCI group revealed underactivation of the left inferior frontal cortex and the left parietal cortex. Certain brain areas such as the left superior frontal gyrus appeared to be activated to higher levels in the elderly than the MCI group and to higher levels in the MCI group than the

AD group. This finding might suggest that regions of the prefrontal cortex such as the left superior frontal gyrus may be related to more efficient semantic retrieval. The differential activation that was observed in the anterior cingulate regions when the MCI group was compared to the elderly group and when the MCI group was compared to the AD group, might suggest that compensatory mechanisms are recruited in the MCI group, which are not available to the AD group, at least to the same extent, because of the extensive damage that is characteristic of the disease process. The MCI group may also be seeking compensation by activating the right inferior frontal gyrus and the right precentral gyrus to significantly higher levels than the elderly group.

4.9.9.5 The Effect of Pathological Ageing on Semantic Memory and Processing

The behavioural scores showed a decreasing trend running best to worst from the elderly group, to the MCI group, to the AD group. The mean behavioural score of the elderly group was significantly higher than the AD group, as was the mean score of the MCI group when compared to the AD group. The mean reaction times of the groups showed an increasing trend from the elderly group, to the MCI group, to the AD group. The mean reaction times of the AD group were significantly longer than the mean reaction times of elderly group.

The fMRI analysis of the Pyramids and Palm Trees task relative to the baseline showed that the young and elderly groups activated the left inferior frontal gyrus (BA 45 and 47, respectively), the left precuneus and the left superior parietal lobule. Both the MCI and the AD groups lacked significant activation in these areas. The MCI and AD groups did activate regions of the left inferior frontal gyrus, BA 9 and BA 44, respectively, but these were different in location to the sites of activation seen in the young and elderly groups. The lack of significant activation in the left parietal regions of the AD and MCI groups may be due to the hypometabolism and decreased perfusion that is commonly found in the temporo-parietal regions of patients with AD. The metabolic deficits that are found in the temporo-parietal regions of AD patients have been described for example, in the studies by Pietrini et al. (2000) and Silverman et al. (2001). The perfusion abnormalities have been reported, for example, in the study by Hashikawa et al. (1995).

The comparison of the elderly group to the MCI group revealed significantly different activation in the left superior frontal gyrus (BA 10). Furthermore, the comparison of the MCI group to the AD group also showed significantly different activation in the left superior frontal gyrus (BA 10). The level of activation in the left superior frontal gyrus (BA 10) appears therefore to increase from the AD group to the MCI group and from the MCI group to the elderly group. The behavioural scores of the groups also followed a trend of impairment, in which the scores increased from the AD group to MCI group and from the MCI group to the elderly group. Increased levels of activation in the left superior frontal gyrus may enable more efficient retrieval of semantic associations.

The levels of activation in the left middle frontal gyrus were significantly different for the elderly group versus MCI group comparison (BA 9/46), and for the elderly group versus AD comparison (BA 10/11). The significantly different patterns of activation in the regions of the middle frontal gyrus may reflect more effective semantic retrieval mechanisms in the elderly group than in either the MCI or AD groups.

The comparisons of the elderly to each of the pathological groups seem to reveal differential activation in lateral areas of the left prefrontal cortex. This is in contrast to the comparisons of the pathological ageing groups to the elderly, in which differential activation occurs in more medial areas of the prefrontal cortex. The comparison of the MCI group to the elderly group revealed differential activation of the left medial frontal gyrus (BA 11), whereas the comparison of the AD group to the elderly group showed differential activation in the right medial frontal gyrus (BA 6). The pathological ageing groups may have recruited these medial frontal areas in attempts to compensate for dysfunction due to disease. Note that differential activation of the medial frontal gyrus (bilaterally) was observed in the elderly versus young comparison. This differential activation was thought to reflect compensatory efforts by the elderly.

The comparison of the MCI group to the elderly group revealed significantly different levels of activation in the right inferior frontal gyrus (BA 9) and the right precentral gyrus (BA 6). These differences are in contrast to those seen when the elderly group were compared to the MCI group e.g. left middle and superior frontal gyri. The MCI group may be recruiting the right prefrontal hemispheric regions to

attempt to compensate for underactivation in left hemispheric areas of the prefrontal cortex.

Investigation of the levels of activation in the anterior cingulate cortex showed that significant differences occurred in this region when the MCI group were compared to the elderly group (BA 24/32), and when the MCI group were compared to the AD group (BA 32). The pattern of activation in this area suggests that the MCI group may be compensating (possibly for the presence of disease related pathology in a number of the individuals) by activating this region to a higher level than the elderly group. It may be the case that due to disease progression the AD group are no longer able to recruit the help of this region, at least to the same extent as the MCI group. This explanation may be strengthened by the observation that no significant difference in anterior cingulate activation was observed when the AD group was compared to the elderly group (i.e. the AD group were not activating the anterior cingulate (BA 32) to a significantly higher level).

A different area of the anterior cingulate cortex (BA 33) exhibited differential activation when the AD group were compared to the elderly group. This difference in activation may reflect an attempt by the AD group to compensate for disease related impairments. The finding that the AD group seem to be able to activate this region of the anterior cingulate to higher levels than the elderly group, but not the region that incorporates Brodmann's area 32 suggests that disease pathology in this population may not be as well established in Brodmann's area 33 as it is in Brodmann's area 32. Another explanation is that the differential activation in Brodmann's area 33 is not beneficial to the AD group and it is an example of non-selective overactivation.

Comparing the elderly to the MCI group identified a number of right hemispheric regions that were activated differentially by the groups e.g. the right middle temporal gyrus, the right superior temporal gyrus, the right superior occipital gyrus and the right cuneus. The areas that showed this pattern of differential activation appear to be the homologous areas to those in the left hemisphere that have been described to be used in semantic processing and retrieval. The MCI group may be failing to activate these regions to the same level as the elderly group.

The comparison of the AD group to the MCI group showed significant differences in activation in the left inferior frontal gyrus (BA 44/45), the left superior temporal gyrus (BA 22) and the right transverse temporal gyrus (BA 41). The behavioural scores of the AD group were significantly lower than the MCI group, suggesting that the differential activation in these regions may have been created due to compensatory efforts on behalf of the AD group, in an attempt to offset the effects of disease related pathology in other regions. Judging by the behavioural scores the differences in activation do not reflect better semantic processing strategy, however. Furthermore, although the left inferior frontal gyrus (BA 44) and the left superior frontal gyrus (BA 22), have been described in other studies of semantic processing e.g. in the experiments of Price et al. (1999) and Ricci et al. (1999), respectively, neither of these regions were activated by the young or elderly groups in the current study.

Significant differences were also present in the caudate body. A difference was observed in the left caudate body when the AD group were compared to the elderly group, and in the caudate body bilaterally when the MCI group was compared to the elderly group. Grossman, Cooke, et al. (2002) suggested that activation of the caudate may be related to resource demanding tasks. The level of activation in the caudate body appears to be higher in the AD and MCI groups compared to the elderly group. This difference in activation may be associated with greater effort on behalf of the groups that are undergoing pathological ageing. It is likely that these groups are finding the Pyramids and Palm Trees task more demanding than the elderly (as suggested by the pattern of behavioural scores).

In summary, both the AD group and the MCI group underactivated regions that were activated by the young and elderly control groups e.g. regions of the left inferior frontal gyrus, the left precuneus and the left superior parietal lobule. A differential pattern of anterior cingulate (BA 32) activation appeared to suggest compensatory efforts by the MCI group that were no longer available (at least to the same extent) in the AD group. The activation of left middle and superior frontal gyri appears to be related to more efficient semantic processing. The results showed that these areas were activated to higher levels in the elderly group than in the MCI or AD groups. Both the AD and MCI groups appeared to activate regions of the medial frontal cortex and the caudate to significantly higher levels than the elderly group. The MCI group also

seemed to activate the right inferior frontal gyrus and the right precentral gyrus to higher levels than the elderly group. These differences in activation may be due to compensation. The findings described above seem to be related to the pathological effects of disease on semantic processing, as they appear to differ substantially and look to be more extensive than the effects of normal ageing that were reported in experiment 3 (e.g. lower levels of activation in the elderly group in regions of left temporal cortex). The differences between the MCI and AD groups compared to the elderly group suggest that the use of semantic paradigms with fMRI may provide a beneficial method of discriminating normal from pathological ageing in the very early stages.

CHAPTER 5: GENERAL DISCUSSION

The results of the set of studies in this thesis indicate that the cognitive deficits caused by normal ageing and pathological ageing do not appear to fall along the same continuum. Although behavioural performance appeared to decrease in a linear fashion in the semantic task, and showed no significant differences in the vigilance and working memory tasks, there were marked differences in the brain activation patterns of the participant and patient groups on each of the experimental paradigms that were used. The combination of the locations and levels of activation appear to discriminate normal from pathological ageing.

5.1 The Effect of Normal Ageing

In the vigilance and working memory conditions, the behavioural scores and reaction times of the young and elderly groups were very close and did not differ significantly from one another.

The young group in the present study activated similar regions to those found in previous functional imaging studies of vigilance and working memory. For example, the vigilance studies of Lawrence et al. (2003), Lewin et al. (1996) and Pardo et al. (1991) and the working memory studies of Braver et al. (1997) and Veltman et al. (2003). The elderly group, although showing similar patterns of activation to the young group on these tasks, demonstrated important differences. The comparisons showed that the elderly often lacked significant activation in areas activated by the young group (even at a liberal threshold), or underactivated regions that were activated by the young. For example, in the vigilance task the elderly appeared to lack significant activation in the right middle frontal gyrus. In the working memory task with a light load, the elderly underactivated parietal regions, such as the left inferior parietal lobule (BA 40), and lacked significant activation, for example, in the right inferior parietal lobule (BA 40). The more demanding working memory task again showed underactivation by the

elderly group, for example, in the left inferior parietal lobule (BA 40), and a lack of significant activation in the anterior cingulate (BA 32) bilaterally.

Despite all these areas of altered activation, the elderly still managed to perform the tasks successfully. The additional areas of activation that were found in the elderly group may be in compensation for the lack of significant activation and underactivations that were observed in certain regions. For example, in the vigilance task the elderly activated the posterior cingulate bilaterally (BA 24) to higher levels than the young group. This additional activation may have been in compensation for the lack of activation in the right frontal/parietal areas that was found in the elderly group. In the task that involved a light working memory load, the elderly differentially activated right hemispheric areas such as the lingual gyrus, the parahippocampal gyrus and the inferior frontal gyrus, compared to the young group. The activation of these regions of the right hemisphere may have compensated for the shortcomings in the levels of activation in other areas in the elderly group. During the task with a higher working memory load, the elderly activated the left parietal cortex (BA 39), areas associated with visual processing and the posterior cingulate (amongst other areas), to significantly higher levels than the young group. The activation of these regions may have enabled the elderly to perform at the same behavioural level as the young group. Alternatively, some (or all) of the increased levels of activation in the elderly group may have been due to non-selective over-activations (i.e. activation with no real benefits). The explanation that all of the increased areas of activation in the elderly group are due to non-selective over-activation is unlikely, however. Previous studies have supported the compensatory construct by showing that the recruitment of brain areas increases, both as task difficulty increases (e.g. Anderson et al. (2002) and Klingberg et al. (1997)) and as the age of the participants increases (e.g. DiGirolamo et al. (2001) and Langenecker, Nielson and Rao (2004)).

The mean behavioural scores on the semantic memory and processing task were significantly lower for the elderly group than the young group. The reaction times did not differ significantly between the groups. The lower mean behavioural performance score of the elderly group was not expected in the current experiment as semantic memory has been shown to remain relatively constant throughout the lifespan (Nilsson, 2003; Stuart-Hamilton, 2000). The difference suggests that certain individuals in the elderly group may be exhibiting early preclinical effects of AD, despite showing no other obvious symptoms, being still fully active and leading independent normal lives.

It is not known whether the elderly people that participated in this study will go on to develop AD or not.

In the semantic memory and processing task, the elderly group lacked significant activation in the left superior, middle and inferior temporal gyri, compared to the young group. The absence of significant activation in these regions may have contributed to the lower behavioural scores in the elderly group. The elderly had significant activation in the cingulate gyrus (BA 32) bilaterally. The young group did not activate this area significantly during the semantic memory task. The elderly group also appeared to activate the medial frontal gyrus bilaterally, the right precuneus, and the left superior temporal gyrus (BA 38) to higher levels than the young group. These areas may have helped to compensate for the areas that lacked significant activation in the elderly group.

The models of ageing that were investigated i.e. the HAROLD (Cabeza, 2002) and the hemi-ageing hypothesis (Dolcos et al., 2002) did not receive a great deal of support in either the n-back and Pyramid and Palm Trees tests. Partial support was often available for HAROLD e.g. the elderly activated right sided regions to higher levels than the young, but without a clear picture of bilateral activation in the elderly group, concrete conclusions were difficult to make. The most support for the right hemi-ageing hypothesis came from the results of the working memory task with a light load. This task showed more right hemispheric activations in the young than the elderly group, which may provide evidence of hemi-ageing. The finding was not replicated in the working memory task with a higher load however. The support for the models of ageing remains inconclusive in this study and further research is required. Morphometric studies may shed light upon the validity of the right hemi-ageing hypothesis. The HAROLD appears to have more support in the literature, but this study did not fully support the predictions.

Many age-related changes may help to explain the differences in the patterns of activation that were observed between the young and elderly groups. A decrease in working memory capacity has been reported with ageing (Salthouse, 2000). A failing central executive has been described to be one of the causes of this decline (Salthouse, 2000). Ageing has also been shown to be related to failing context representations (Braver & Barch, 2002), slower processing ability (Salthouse, 1991), and problems switching attention (Verhaeghen & Basak, 2005), to name some possible causes for impairments in working memory. Semantic memory on the other hand has been

reported to be relatively resistant to the effects of ageing compared to other types of memory (Nilsson, 2003). One of the reasons that the differences in the patterns of activation between the elderly group and the young group on the Pyramids and Palm Trees test may have been due to the potential contamination of the "normal" elderly group with preclinical cases of AD. It cannot be entirely ruled out, that although not having any obvious symptoms, some of these individuals might still develop AD in the future. Other more general effects of ageing might also have contributed to the altered activation patterns of the elderly group.

The effects of ageing are wide-ranging and it is likely a combination of factors may contribute to differences in the brain activation patterns of young and elderly controls. A modest decline in cortical cholinergic innervation has been reported to occur during the ageing process (Mesulam, 2000). Cholinergic deficits of this kind have been described to impair attention (Mesulam, 2000). One of the reasons for the decreased levels of activation in the elderly group during the vigilance/working memory tasks in the present study may be dysfunction through cholinergic impairment. Context representations and the ability to maintain items in working memory over a delay have been linked to dopaminergic activity (Braver & Barch, 2002). Braver and Barch (2002) reported that the prefrontal cortex and the dopaminergic system are amongst the earliest areas to be affected by age. Ageing also decreases the rate of resting brain glucose utilisation by approximately six percent every ten years (Petit-Taboue et al., 1998). Some of the most significant effects in the Petit-Taboue et al. (1998) study were found in the inferior and posterior-lateral frontal regions, the anterior temporal regions, the temporoparietal areas and the anterior cingulate cortex. There are more effects of ageing, but those that have been described show that important neurobiological alterations are taking place in the brains of elderly people. The age-related deficits that have been reported to occur in elderly brains appear to be related to the differences in the patterns of activation (revealed by fMRI) that can be observed between the young and the elderly groups in the present study.

In summary, a number of differences have been identified between the patterns of activation found in the brains of the young and elderly groups on all the paradigms that have been investigated in this thesis. Some of these have been quantitative differences i.e. the elderly group have activated the area, but the young group have activated the area to a higher level. Other differences have taken the form of possible non-selective over-activations, areas that lack significant activation, and activations

thought to be due to compensation. The behavioural scores of the elderly participants showed no significant impairments on the vigilance and working memory tasks compared to the younger participants. The results show that at this stage the elderly are managing to cope with the changes that are taking place in their brains, and are compensating effectively. On the semantic memory task the elderly were impaired compared to the young. This deficit may have been due to the contamination of the elderly group with early preclinical cases of AD.

5.2 The Effect of Pathological Ageing

No significant differences were seen between the elderly group, the MCI group and the AD group on either the mean behavioural scores or the mean reaction times on the vigilance task or the working memory task.

A number of differences were present between the brain activation patterns of the pathological groups and the group of normal elderly participants. For example, both the MCI and the AD groups lacked significant activation in specific areas that are thought to be used to complete tasks of vigilance. The AD group lacked activation in the right middle frontal gyrus. This area is considered to be used during sustained attention (Posner & Raichle, 1997). The MCI and AD groups both under-activated the left fusiform gyrus. This area is thought to be used during the visual processing of the letters. The young and the elderly groups both activated this region. A possible reason that the left fusiform gyrus was underactivated in the pathological groups may be due to the disease related formations that are associated with AD. Further differences between the groups could also be observed. Additional activations in regions of the left temporal cortex were found in the MCI and AD groups. These were not seen in either the young group or the elderly group and may suggest compensation or non-selective over-activation is occurring in the pathological groups. The areas that showed the underactivations and increased activations in the MCI and AD groups may be useful when attempting to discriminate normal from pathological ageing. One of the problems of the vigilance task however, was that certain activations occurred in the MCI group (which contained at least four preclinical AD cases) that were similarly activated by the

young or the elderly groups, or were within the normal limits (i.e. between the activation levels of the young and the elderly groups).

Many more differences could be identified between the elderly group and the pathological groups when using the working memory task (1-back) as opposed to the vigilance task (0-back). Areas that appeared to be useful at distinguishing normal from pathological ageing were the left inferior and superior parietal cortices. The AD and MCI groups appeared to under-activate these regions. The MCI and AD groups also seemed to lack activation in parahippocampal regions, and the right fusiform gyrus. The lack of activation in these regions may have been related to the presence of underlying disease pathology. Right hemispheric regions such as the right inferior parietal lobule were recruited by the MCI and AD groups. The activation of these right hemispheric areas may have been in compensation for the decreased levels of activation in other areas. The left parietal cortex has been reported to undergo greater AD related atrophy than the right (Boxer et al., 2003). This may be one of the reasons that the pathological groups activated right hemispheric regions, such as the inferior parietal lobule. Furthermore, the predominantly left-sided atrophy that is found in AD may be the reason that the working memory task with a light load yielded more differences between the normal and pathological groups than the vigilance task. The working memory task (1-back) is thought to involve mainly left-lateralised brain regions, whereas the vigilance task is considered to engage a right-lateralised attentional network. The individuals in the preclinical stages of AD may therefore, be experiencing more problems with the working memory task than the vigilance task because of the underlying atrophic changes.

In both the vigilance and the working memory task, the AD group activated the anterior cingulate (BA 32) to significantly higher levels than the elderly and MCI groups. This differential activation may suggest greater compensation is needed in the AD group due to the increased impact of disease related impairment.

On the behavioural scores of the semantic memory task, the elderly group performed significantly better than the AD group. The reaction times of the AD group were also significantly longer than the reaction times of the elderly group. The Pyramids and Palm Trees paradigm appears therefore to be sensitive to semantic impairment. The fMRI results showed that the AD and MCI groups seemed to have problems activating the left middle and superior frontal cortex. These cortical areas are considered to be related to the control processes that are involved in retrieving semantic

knowledge and the greater activation of these may have enabled the elderly group to score significantly higher on the Pyramids and Palm Trees paradigm than the AD group. Note that the mean score of the elderly group was also higher than the mean of the MCI group but the difference was not significant. Further differences in the activation patterns found in normal and pathological groups were also present. The pathological groups activated different areas in the left inferior frontal gyrus, compared to the young and elderly control groups. Under-activation also occurred in regions of the left parietal cortex in the MCI and AD groups. The young and the elderly groups activated these areas. One of the methods of compensation available to the pathological groups appeared to be to activate medial frontal regions.

The effects of pathological ageing, in all the tasks (vigilance, working memory and semantic memory) show underactivation, lacks of activation and areas of increased activation (thought to be due to either compensation or non-selective activation). The areas in which these differences in activation were found appear to be different to the areas that undergo change in normal ageing. The findings provide evidence that pathological ageing (in the form of AD) and normal ageing do not fall along the same continuum, but impair the brain in separate ways. The MCI group, of which the majority was composed from cases of preclinical AD, also exhibited clear differences in brain activation compared to the normal elderly group. The patterns of brain activation found in the MCI group did not appear to look like the normal elderly, but rather resembled the AD group.

Individual examination of the activation patterns in the people with MCI, showed that the most useful diagnostic cognitive paradigm appeared to be the semantic memory and processing task. The activation patterns found in the vigilance task demonstrated a mixture of effects that were difficult to interpret. The working memory task showed that in one of the individuals that converted to AD, a lack of significant activation occurred in vital regions activated by the elderly group. The other three converters appeared to activate the appropriate regions, but two of the converters had much more widespread activation (which left the activation of one of the converters looking relatively normal). Turning now to the semantic task, behaviourally the non-converters performed at substantially higher level than the converters (within the range of the normal elderly). This finding highlights the sensitivity of the semantic memory paradigm in diagnosis. Furthermore, the brain activation patterns induced by this task showed abnormalities in all of the converters. These abnormalities took the form of a

lack of significant activation in relevant areas (i.e. temporal structures) and activation that was more widespread. Of the two individuals that did not convert, the activation pattern on the semantic paradigm seemed relatively normal. Although the semantic memory and processing task appeared to differentiate the converters from non-converters more successfully than the other two tasks, a combination of fMRI paradigms may have the best diagnostic potential.

The differences in the brain activation patterns of the AD patients and the individuals with MCI compared to the normal elderly group are likely to be related to the pathological attributes of AD. Alzheimer's disease alters the brain in many different ways compared to the effects of normal ageing. For example, cholinergic deficits can cause impairments in vigilance. These may be reflected in the areas of decreased activity that are found in the pathological ageing groups. Cholinergic problems may be present in normal ageing but the deficits are much more severe in AD (Mesulam, 2000). Cholinergic innervation is associated with the nucleus basalis of Meynert, which undergoes extensive neurofibrillary tangle formation due to AD (Mesulam, 2000). The decrease in cholinergic innervation of the limbic system is considered to affect both vigilance and memory.

The under-activations which are found in the working memory task and the semantic memory task are paralleled by the deficits in glucose metabolism (G. S. Smith et al., 1992) and perfusion abnormalities (Hashikawa et al., 1995) which have been observed in the temporo-parietal regions of the brains of patients with AD. The decreased activations observed in the fusiform gyri and the parahippocampal areas of the AD and MCI groups may be related to the neurofibrillary tangle formation which develops in both these areas at relatively early stages of the disease process. Figure 1.3 illustrates the formation of neurofibrillary tangles in the fusiform regions of individuals with MCI. The presence of neurofibrillary tangles and senile plaques in the brains of AD patients are thought to impair brain functioning, as is the build up of amyloid, which can be observed in widespread brain areas (including the prefrontal cortex) of AD patients at even early stages of the disease process.

AD patients have also been reported to have decreased amounts of prefrontal grey matter than age matched controls (Salat et al., 2001). Another study has illustrated significantly lower amounts of frontal lobe white matter in AD patients compared to age and gender matched controls (Bartzokis et al., 2003). The decreases of grey and white matter in the prefrontal cortex may contribute to less efficient central executive

functioning which is important for vigilance and working memory. The changes in the prefrontal cortex of AD patients may also contribute to impairments in semantic processing by damaging areas associated with retrieval selection and control functions. The semantic memory problems that AD patients have in the current study are also reflected in their behavioural scores as well as their brain activation patterns.

The combination of these changes to the brains of patients with AD and individuals with MCI (of whom a large proportion are in the preclinical stages of AD) may help to explain the irregular patterns of activation that can be seen in these groups during the current experiments.

Differences between the pathological ageing groups and the normal elderly controls were observed on all three of the tasks. It may be possible therefore, to use any of the tasks with fMRI to attempt to distinguish pathological from normal ageing. The scanning of additional elderly people, individuals with MCI and patients with AD may be beneficial in order to improve the reliability of the results.

5.3 Overall Conclusions

The effects of normal ageing that were observed in the current experiments took the form of under-activations and lacks of significant activation in specific areas. A number of the effects appeared to be quantitative e.g. the young group had higher levels of activation in certain brain regions than the elderly group, but the elderly were still activating these regions. Additional activations also occurred in areas not activated by the young. These activations may have been due to compensatory mechanisms, non-selective over-activation, or a combination of both of these explanations. There are many effects of ageing which may have contributed to these differences in brain activation. None of the effects of normal ageing are as severe, however, as the neurobiological and anatomical changes that may take place due to AD.

A range of similar effects on the brain activation patterns were observed in the groups that were undergoing pathological ageing, for example, under-activation, lack of significant activation, and additional activations (due to compensation, non-selective over-activation, or both), but these changes appeared to be much more extreme and tended to affect different areas to those seen in normal ageing. Comparing the normal

elderly group to the young group showed that in a number of areas used to complete the tasks, the elderly had lower levels of activation compared to the young. The groups that were undergoing pathological ageing however, seemed to be unable to recruit the same networks as the young and elderly groups and instead had to resort to alternative cortical networks. Note that at least four out of the six individuals with MCI were in the preclinical stages of AD at the time of testing and so this group was also considered to represent pathological ageing. The vigilance task did not appear to discriminate pathological from normal ageing as well as the working memory task (with a light load) on account of the overlap in levels of activation that the MCI group had with the young and elderly groups. The very slight increase in working memory load (1-back task) however, enabled many more differences to be detected between the pathological groups and the normal elderly group. Importantly, the differences in brain activation patterns were present even when no behavioural impairments on the task were seen in the pathological groups i.e. neither the scores nor the reaction times differed significantly from the normal elderly group.

The semantic memory task may have been expected to show more differences between the pathological groups and the normal elderly group given the view that semantic memory remains unimpaired (relative to other types of memory) throughout the lifespan (Nilsson, 2003). In the present study, the behavioural performance followed an increasing trend which ran from the AD group, to the MCI group, to the elderly group, to the young group. Significant differences were present between the young group and the elderly group, between the elderly group and the AD group, and between the MCI and the AD group. As well as having lower behavioural scores than the normal elderly group, the pathological groups presented differences in brain activation patterns, which may be used to attempt to discriminate the groups. A combination of results from the light working memory task and the the Pyramids and Palm Trees test might provide the best diagnostic potential. The scanning of additional volunteers may improve the diagnostic power of the Pyramids and Palm Trees paradigm.

In the future, an interesting approach to discriminate preclinical AD from normal ageing may be to use regions of interest. These would involve the same procedures as detailed in this thesis, but a different type of statistical analysis. Specific regions of the brain would be defined in which the groups are expected to differ. Judging by the

differences in the patterns of activation that were identified between the pathological ageing groups and the normal elderly groups on the tasks that were used in the current study, the areas that showed these changes would be a good place to begin. After whole brain scanning, the signal changes in these areas alone would be examined and as there are less voxels contained in these areas, as opposed to doing a comparison over the whole brain, the statistical power would be increased. A combination of the signal changes from multiple regions of interest could then be used to attempt to distinguish those people that are ageing pathologically.

Further investigation is needed, but the results reported in this thesis suggest that the use of fMRI along with sensitive cognitive testing may provide a useful diagnostic tool to discriminate pathological from normal ageing. The tasks used in this study identified distinct differences in the brain activation patterns of the group of MCI (in which at least 4/6 people had preclinical AD) and the group of normal elderly. This means that when future diagnosis is questionable, examination of the patterns of activation in the concerned individual, while they perform specific cognitive paradigms (such as those used in the present studies), may be of assistance in resolving diagnostic uncertainty.

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