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Associate memory in ageing and alzheimer's disease : |b alterations in brain activity and implications for rehabilitation techniques

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Associative memory in ageing and Alzheimer's disease: alterations in brain activity and implications for rehabilitation techniques

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SUMMARY

This thesis focused on changes in memory-related functional brain activation patterns in healthy ageing and Alzheimer's disease (AD) in order to gain a better understanding of the neural mechanisms that underlie successful memory strategies. Such information is needed in order to devise more effective cognitive intervention programmes aimed at enhancing memory function.

Current literature on brain activation changes in associative memory processes in healthy ageing and AD was reviewed and linked to results from behavioural studies that investigated different memory-enhancing learning strategies. It was suggested that semantic processing is a key aspect of improving memory in both healthy ageing and AD, and that rehabilitation strategies should target residual memory function in AD.

A second literature review explored how functional magnetic resonance imaging (fMRI) might be applied to measure treatment effects and brain plasticity in cognitive intervention aimed at people with AD. Paradigms on face-name learning in fMRI in healthy ageing, mild cognitive impairment, and AD were reviewed, and recommendations for a novel face-name learning task were made.

Study 1 compared brain activity in healthy young and older adults during a face-name learning paradigm. Results suggested that the observed hyper-activation in the older group may reflect increased effort to attain task performance similar to that of the young group.

In Study 2, brain activation during face-name learning was compared between healthy older adults and people with AD. The AD group showed hyper-activation compared to the healthy older group in posterior parietal areas during recognition. This may be an indicator of inefficient inhibition.

Study 3 compared brain activation differences in a small group of people with AD prior to and following an eight-week cognitive rehabilitation intervention. Small improvements in immediate recognition were observed. Brain activation was generally higher prior to than following treatment, which may mean more efficient inhibition of default mode network regions following treatment.

Chapter 1 – Introduction

"I'm doing this for my children... I want to help those who come after me. I hope things will be better for my daughters. I don't want anyone to have to experience what I'm going through."

[Mrs. A, who was diagnosed with Alzheimer's disease and has a familial history of the illness, explaining her reasons for taking part in the research studies presented in this thesis].

A decline in memory function has been reported in nearly 40% of older adults between 60 and 78 years (Koivisto et al., 1995). Dementia affects over 5% of all people over 65, and as prevalence increases with age, over 20% of people over 80 are thought to be affected (Hart & Semple, 1994). Alzheimer's disease (AD) is the most common form of dementia. Since the proportion of people aged 65 years and over in the United Kingdom is expected to grow over the coming decades (National Statistics, 2007), the number of people with memory difficulties is also likely to increase (Alzheimer's Society, 2007). Even in the early stages, AD leads to a dramatic decline in memory function, which can have a devastating effect on the quality of life of patients and their families. Recently the National Institute for Health and Clinical Excellence (NICE) advised health professionals that acetylcholinesterase-inhibiting medication should only be prescribed to people who are in a more advanced stage of AD (National Institute for Health and Clinical Excellence, 2006). For these reasons, it is becoming increasingly important to design appropriate non-pharmacological interventions for people who have memory difficulties (both healthy older adults and people in the early stages of AD) to assist in maintaining an optimal level of cognitive functioning. In order to develop and refine effective memory strategies, it seems sensible to combine knowledge about successful behavioural learning strategies used in healthy ageing and AD, and findings on alterations in brain activity patterns from neuroimaging studies. The purpose of this thesis is to gain a better understanding of the functional brain activation changes in healthy ageing and AD, and to explore how this information can explain the success of particular learning strategies. A better understanding of the neural mechanisms that underlie effective memory strategies is needed in order to devise more effective cognitive intervention programmes aimed at enhancing memory function.

STRATEGIES TO AMELIORATE MEMORY FUNCTION IN AGEING AND ALZHEIMER'S DISEASE

Given the large impact that impairments in memory function can have on the lives those affected, many research studies have focused on methods aimed at improving memory function. For example, recent behavioural research has shown that recollection in healthy older adults improved if they made use of semantic information during encoding (e.g. Ball et al., 2002; Luo, Hendriks, & Craik, 2007; Troyer, Häfliger, Cadieux, & Craik, 2006; Verhaegen, Marcoen, & Goossens, 1992). Learning principles that have yielded a positive outcome in people with AD include errorless learning (e.g. Clare, Wilson, Carter, & Hodges, 2003), dual cognitive support (e.g. Bird & Luszcz, 1991, 1993; Herlitz, Adolfsson, Bäckman, & Nilsson, 1991), and effortful processing (e.g. Dalla Barba & Goldblum, 1996). However, the underlying mechanisms in the brain that would account for success or failure of strategies aimed at improving memory functioning seem relatively unexplored.

APPLICATION OF NEUROIMAGING METHODS TO THE STUDY OF MEMORY FUNCTION

Imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have enabled the identification of brain areas that are activated during a particular memory paradigm so that it has now become possible to study the involvement of different brain structures in memory, and relate this to the behavioural outcome. This knowledge can add to the understanding of how memory works and may provide an insight into why people with memory impairments have difficulty with some aspects of their memory but not others. Imaging studies may also be valuable in detecting dementia at an early stage, and in tracking changes in brain atrophy in older adults with cognitive impairments to establish what sort of alterations are predictive of progression to a neurodegenerative disease (Chetelat & Baron, 2003; Fox & Schott, 2004; Rosen, Bokde, Pearl, & Yesavage, 2002). From a behavioural intervention perspective, imaging studies on memory may help to understand why certain learning strategies work better than others. For example, it has been demonstrated that if healthy older people learned words using instructions that induced deep processing, their brain activation pattern as well as their behavioural performance on the memory task became very similar to that observed in young adults (Logan, Sanders, Snyder, Morris, & Buckner, 2002).

Changes in memory-related brain activity in Alzheimer's disease have been less extensively studied. Interestingly, several neuroimaging studies have found involvement of additional brain areas in AD over and above brain regions that are typically recruited during a memory task in healthy subjects (Grady et al., 2003; Sperling et al., 2003a). Whether or not activation in the additional areas supports memory function is a matter of debate, and forms an exciting question in relation to the development of intervention programmes.

The introductory chapter will discuss a theoretical model of memory that was used in all the chapters in the thesis. Next, the neuropathology underlying AD is described to provide a background to changes in memory function and alterations in functional brain activation discussed in later chapters. Changes in memory function in healthy ageing and AD will then be covered briefly, as these are dealt with in more detail in Chapter 2.

THEORETICAL MODELS OF MEMORY

Memory plays a central role in cognitive function. It provides information needed for comprehension and production of language, perception, reasoning, goal-directed action, and problem solving. Memory is thought to be composed of multiple systems that depend on different brain structures (Schacter, 1992; Squire, 2004; Squire, Knowlton, & Musen, 1993; Squire & Zola, 1996). A distinction is made between long-term memories that are consciously accessed (explicit or declarative memory), unconscious retrieval such as knowing how to perform a motor action (implicit or non-declarative memory), and processing of visual and auditory information (working memory) (Schacter & Tulving, 1994; Squire, 2004).

Declarative memory can be divided into two components: semantic memory (information about facts and the world around us) and episodic memory (long-term, conscious learning and remembering, and knowledge of one's own experiences). In the context of conscious learning, three memory processes describe the process of acquiring, retaining and remembering knowledge. Encoding refers to the process by which information is acquired and formed into a memory. The term 'storage' is used for maintaining the memory over time. Finally, retrieval signifies the process of accessing and using the information (Haberlandt, 1999). The brain structures that are

especially important to declarative memory are the medial temporal lobe (MTL), including the hippocampus (spatial memory) and the entorhinal cortex (recognition) (Petri & Mishkin, 1994; Squire, 2004).

In contrast to declarative memory, non-declarative memory relates to unconscious learning and comprises of procedural learning (acquisition of skills and habits), priming (advantage in identifying fragments of previously seen stimuli) and classic conditioning. Habituation and motor skill learning depend largely on the involvement of the striatum (Knowlton, Mangels, & Squire, 1996). Specific structures that play an important role in classic conditioning are the amygdala and the cerebellum (Squire, 2004). Priming is associated with various areas in the neocortex, the involvement of which is largely dependent on the modality of the original stimulus (Schacter & Buckner, 1998).

Finally, working memory refers to very short-term retention of information, which is needed in higher cognitive skills such as language comprehension. It is proposed that working memory consists of three buffer systems that temporarily store auditory and visuospatial information, and one control system that manipulates attention and retrieves information from the other three systems (Baddeley, 2000). Depending on the nature of the material stored in working memory, brain structures involved may be left (verbal information) or right (visuospatial information) premotor areas, or bilateral prefrontal cortex (object information) (Smith & Jonides, 1999).

Memory is essential to executive functions as it provides the factual knowledge about the context, a set of rules, and a temporary stage for intermediate results needed to carry out the task (Haberlandt, 1999). In turn, executive functions such as directing, sustaining and switching attention to the appropriate stimulus are necessary for memory function, as memory often relies on elaborate processing and appropriate search strategies (Buckner, 2004). Brain areas underlying executive functions play a significant role in memory function. For example, the prefrontal cortex (PFC) is involved in the encoding and retrieval of information in memory (Nyberg, Cabeza, & Tulving, 1996) and forms a key structure underlying working memory function (Smith & Jonides, 1999). Memory and executive function cannot be seen separately from one another. It has been proposed that disruptions in executive functions that support memory function may be responsible for age-related memory decline that is observed in many non-demented older adults (Buckner, 2004).

CHANGES IN EPISODIC MEMORY FUNCTION IN HEALTHY AGEING AND ALZHEIMER'S DISEASE

Memory function declines with age and tends to be poorer in older adults compared to young adults (Grady & Craik, 2000; Mitrushina & Satz, 1991; Small, 2001). This change is especially prominent in verbal and non-verbal episodic memory tasks (e.g. recalling a story, a past event, or a figure), and in prospective memory function (remembering to carry out an action at a future point in time) (Buckner, 2004; Grady & Craik, 2000; Park et al., 1996). Although both young and older adults perform worse on associative memory tasks compared to item memory tasks, this discrepancy in performance is disproportionately larger in older people (Grady & Craik, 2000; Herholz et al., 2001; Naveh-Benjamin, 2000; Naveh-Benjamin, Guez, Kilb, & Reedy, 2004). Naveh-Benjamin (2000) has proposed an Associative Deficit Hypothesis (ADH) which predicts a decline in associative compared to item memory performance in older people that is larger than the difference in performance on these two forms of memory seen in young adults (Naveh-Benjamin et al., 2004).A number of studies demonstrate a large age difference in performance between older and young adults on a variety of associative learning tasks, including inter-item (word-word, picture-picture) and intra-item tasks (face-name, word-feature, item-location) (Chalfonte & Johnson, 1996; Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2004). However, if the appropriate cognitive support is provided, older adults can achieve levels of performance similar to those of young adults (e.g. Logan et al., 2002; Small, 2001).

In AD, a severe deficit in episodic memory is the most striking feature. Impairments occur on both visual and verbal memory tasks for immediate as well as delayed recall and recognition, and include memory for faces, names, simple geometric shapes, and short stories (Graham, Emery, & Hodges, 2004; Greene, Baddeley, & Hodges, 1996; Perry, Watson, & Hodges, 2000). Some aspects of semantic memory (naming objects and category fluency) are also impaired from the onset of the disease, while others, such as making judgments on semantic category relations between objects, remain relatively intact in the early and mild stages of AD (Graham, Emery, & Hodges, 2004). Implicit memory such as priming (responding faster and / or more accurately to stimuli that involve unconsciously acquired knowledge and skills) and habit learning remains relatively intact until the later stages of AD (Eldridge, Masterman, & Knowlton, 2002; Lustig & Buckner, 2004;

Verfaellie, Keane, & Johnson, 2000). It is widely acknowledged that attention, executive function, and memory are closely intertwined and that appropriate functioning of each of these components depends on the other. It has been suggested that attentional deficits may underlie the difficulties with everyday tasks that people with AD often demonstrate (Perry & Hodges, 1999).

In order to understand the cognitive deficits that occur in AD, the neuropathology which underlies the disease will be discussed in the next section.

NEUROPATHOLOGY IN ALZHEIMER'S DISEASE

The hallmark of neuropathology in AD consists of cytoskeletal changes, formed by neurofibrillary tangles (NFTs) and neuropil threads (NTs) in pyramidal nerve cells and cells forming long cortico-cortical connections in the neocortex. The entorhinal cortex and the subiculum in the hippocampus are the areas first and most heavily affected (Hyman, Van Hoesen, Damasio, & Barnes, 1984). The development of NTs and NFTs is thought to take place in stages and follows a specific pattern (Braak & Braak, 1997; Hansen & Samuel, 1997; Hyman, 1998). Braak and colleagues (1999) have distinguished three phases in the progression of AD pathology, which have been supported by other reports in literature (Scahill, Schott, Stevens, Rossor, & Fox, 2002; Smith, 2002). In the 'preclinical' phase of the disease, before any clinical symptoms are apparent, the entorhinal cortex in the MTL is the first to exhibit neuronal changes. At a later stage, when the first functional disturbances may be observed, the atrophy extends from the entorhinal cortex into the hippocampal area and temporal and insular regions. This causes deficits in the exchange of information between parietal secondary association areas and components of the limbic system (hippocampus, amygdala, thalamus), and leads to largely reduced input of the limbic loop to the prefrontal cortex (PFC). Finally, the brain exhibits severe and widespread cortical atrophy, ventricular widening and loss in weight. In the last phase even the primary motor cortex and the primary sensory field, which remain virtually intact throughout the course of the disease, are affected. Although tangle-bearing cells can live up to several years, it is likely that their entangled state negatively influences their functionality (Braak et al., 1999). Smith (2002) proposed that perhaps deprivation of input from MTL connections is related to development of tangles and neuronal death in other parts of the brain to which the

MTL projects. Reduced activity of neurons in the projection areas may lead to slower metabolism, reduced blood flow, and ultimately to the inability of a brain structure to function properly.

Independently of the growth of NTs and NFTs, but generally occurring at a later stage, neuritic plaques are formed (e.g. Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992; Braak & Braak, 1991). Many studies of anatomical brain changes in AD have shown symmetrical gray matter volume loss in bilateral hippocampal areas (Karas et al., 2003; Karas et al., 2004; Krasuski et al., 1998; Rombouts, Barkhof, Witter, & Scheltens, 2000). A number of longitudinal (Mungas et al., 2005; Petersen et al., 2000; Visser, Verhey, Hofman, Scheltens, & Jolles, 2002) as well as cross-sectional (Pantel et al., 1997) studies has demonstrated that hippocampal volume was positively correlated with memory function and that atrophy in the MTL plays an important role in predicting the rate of cognitive decline. It has been suggested that the size of the hippocampus may be a crucial factor in the early detection of AD. Of note, neuropathology may be present without expression of behavioural symptoms of AD (Katzman et al., 1989). It is thought that factors such as large head circumference and high educational level protect against symptom expression (Mortimer, Snowdon, & Markesbery, 2003; Stern et al., 2000). Nevertheless, the degree of neuropathology in AD generally corresponds well with the amount of cognitive impairment (e.g. Morris, 2004).

Although the onset and course vary across individuals, broad clinical stages of AD have been identified. Reisberg (1988) proposed a seven-scale Functional Assessment Staging scale, which distinguishes no or some functional decline (scales 1 and 2), noticeable deficits in cognitively demanding situations (scale 3 – early AD), requiring assistance with complicated tasks such as finances and event planning (scale 4 – mild AD), substantial cognitive deficits and required assistance in choosing proper attire (scale 5 – moderate AD), severe cognitive deficits and dependency on others for grooming and personal hygiene (scale 6 – moderately severe AD), and finally, very severe cognitive deficits, loss of motor abilities, and complete dependency on the care of others (scale 7 – severe AD). In this thesis, where people with AD are included, the focus will be on early to mild AD (scales 3 and 4).

STRUCTURAL CHANGES IN THE BRAIN IN HEALTHY AGEING

The healthy ageing process is thought to be characterised primarily by loss of grey matter in the prefrontal cortex (PFC) and the striatum, while less substantial changes occur in inferior temporal, fusiform, and superior parietal regions (Raz et al., 1997). The striatum is a structure in the basal ganglia that projects to the PFC and is involved in dopamine production. Indeed, decreased levels of dopamine have been associated with age (Antonini et al., 1993). Increased damage to white matter has also been reported in relation to increasing age (Raz et al., 2005; Ylikoski et al., 1995), and this was most prominent in the frontal lobe (O'Sullivan et al., 2001). Thus, in healthy ageing anatomical changes occur mainly in the frontal lobe (Greenwood, 2000), and these changes involve grey and white matter loss as well as decreased neurotransmitter levels.

RESEARCH QUESTIONS ADDRESSED IN THIS THESIS

In an attempt to draw together findings from the field of neuroimaging and evidence from behavioural studies on effective learning strategies, the following questions will be addressed in this thesis:

1. What activation differences characterise differences between healthy young and old people during associative memory processes?
2. What are the main changes in brain activation pattern between healthy older adults and people with AD during encoding and recognition of associations?
3. In both these cases, what is the nature of these activation differences? Do they represent the use of additional brain areas to compensate for neural loss, or are they indicative of dysfunction of a particular brain region?
4. What constitutes a good paradigm to study associative memory in healthy ageing and Alzheimer's disease with fMRI?
5. Can knowledge about functional brain activation changes be used to make recommendations for more effective cognitive strategies to ameliorate memory functioning in healthy ageing and Alzheimer's disease?
6. What changes can be observed in people with Alzheimer's disease on the level of brain activation patterns following a cognitive rehabilitation intervention programme? Is it possible to identify biomarkers of treatment success?

STRUCTURE OF THE THESIS

This thesis follows the format of two literature review chapters, three experimental chapters, and a discussion. As adapted versions of the literature reviews and the empirical study chapters were or will be submitted for publication, these are presented as a series of papers in journal article format.

Chapter 2 is a literature review in which the changes in memory function and in brain activation related to associative memory in healthy ageing and AD are considered, and an attempt is made to link these findings to results of behavioural intervention strategies that aim to ameliorate memory functioning to identify promising approaches for cognitive rehabilitation. A version of Chapter 2 has been submitted for publication (Van Paasschen, Clare, & Linden, *Brain activation during associative memory in aging and Alzheimer's disease: implications for rehabilitation techniques,* submitted to Neuropsychology Review).

Chapter 3 reviews how functional magnetic resonance imaging (fMRI) can be applied to study associative memory function in healthy ageing and AD, and makes recommendations for a face-name learning paradigm that can be used in the scanner. Chapter 3 also calls for the need to identify biomarkers to explain the success of particular cognitive intervention strategies to maximise treatment outcome. Based on findings from the literature and results from a behavioural pilot study, it introduces a novel face-name learning task for use in three experimental studies (Chapters 4, 5 and 6). Chapter 3 served as the basis for a review article that has been submitted for publication to a special issue on plasticity in Restorative Neurology and Neuroscience (Van Paasschen, Clare, Woods, & Linden, *Can we change the brain with cognition-focused intervention in AD? The role of functional neuroimaging,* submitted to Restorative Neurology and Neuroscience).

In Study 1 (Chapter 4), functional activation differences during encoding and recognition of face-name associations are studied in healthy young and older people, using fMRI. It is noted that some of the age-related hyperactivation described in previous studies as being beneficial in task performance, may in fact represent differential use of brain areas comprising a resting state network. A version of Chapter 4 has been submitted for publication (Van Paasschen, Clare, Woods, & Linden, *Age differences during a simple associative memory paradigm,* submitted to Neuropsychologia).

Study 2 (Chapter 5) examined functional activation differences between

healthy older adults and people with AD during encoding and recognition of unfamiliar face-name associations. It is important to understand what key changes occur during such processes in AD, as this may suggest that the focus of intervention strategies should either be on making the most of residual memory function (if people with AD make use of the same networks as the healthy older adults) or on targeting alternative networks of brain regions.

Study 3 (Chapter 6) is a longitudinal study in which six participants with early stage AD took part in an eight-week cognitive rehabilitation programme. Participants were scanned using the face-name association task described in Chapter 3 prior to and following their participation in the programme in order to explore whether any changes in brain activity could be observed during an associative memory task, and whether it would be possible to identify biomarkers underlying the potential success of the treatment.

Finally, Chapter 7 is a discussion chapter which draws together the findings, implications and limitations from the empirical chapters and makes recommendations for future research.

Chapter 2 – Brain activation during associative memory processing in ageing and Alzheimer's disease: implications for rehabilitation techniques.

ABSTRACT

Although there is promising behavioural evidence to suggest that memory performance can be improved to some extent in healthy ageing and in Alzheimer's disease, little is known about the mechanisms that underlie the strategies used to achieve improvements. This knowledge is important in order to establish the most effective strategies for maintaining or rehabilitating memory function. The current review examines changes in brain activation that occur during associative memory processes in healthy ageing and in Alzheimer's disease, and considers how the findings relate to results of behavioural intervention strategies aimed at improving memory. The nature of these neural changes is discussed with a view to identifying promising strategies for cognitive rehabilitation.

Impairments in episodic memory are a hallmark of Alzheimer's disease (AD), but a less dramatic memory decline is also observed in healthy ageing. There is a considerable literature on instructional techniques that have demonstrated improvement in memory function or performance for both healthy older adults (e.g. Ball et al., 2002; Craik et al., 2007; Derwinger, Stigsdotter Neely, & Backman, 2005; Luo, Hendriks, & Craik, 2007) and people with AD (e.g. Bäckman, 1992, 1996; Bird, 2001; Bird & Luszcz, 1991, 1993; Clare et al., 2003; Dunn & Clare, 2007; Herlitz et al., 1991; Karlsson et al., 1989; Lipinska & Bäckman, 1997; for a full review, see Clare, 2007).

While these studies provide valuable behavioural evidence of changes in performance, very little is known about the patterns of brain activity that might account for the effectiveness of these strategies. In turn, neuroimaging studies focusing on brain activation differences between groups of people rarely link their findings to cognitive intervention methods. The theory of cognitive reserve (Stern, 2002) proposes that the amount of pathology or damage in the brain does not necessarily correlate with a person's cognitive functioning. Instead factors such as higher intelligence seem to have a protective role and allow certain individuals to maintain a higher level of cognitive functioning than would be expected based on pathology level. Therefore, it is important to understand what neuro-cognitive factors help to predict success of certain techniques for a given individual. Understanding more about the relationship between memory-related brain activation changes in healthy ageing and AD on the one hand and successful learning strategies on the other could help us develop more effective intervention strategies and may help identify predictors of success for a given individual.

CHANGES IN MEMORY FUNCTION IN HEALTHY AGEING

Age-associated memory impairment has been reported in nearly 40% of older adults between 60 and 78 years (Koivisto et al., 1995). Generally, memory performance of healthy older adults is poorer than that of young adults (Grady & Craik, 2000; Mitrushina & Satz, 1991; Small, 2001). Although performance on implicit (where material is studied without participants being aware that it is a memory task) and short-term (e.g. repeating strings of numbers or words) memory tasks decreases only slightly with increasing age, a substantial age-related decline in performance is

observed for both verbal and non-verbal episodic memory (e.g. recalling a story, a past event, or a figure), and prospective memory (remembering to carry out an action at a future point in time) (Buckner, 2004; Grady & Craik, 2000; Park et al., 1996). Although memory function commonly changes with increasing age, memory decline is not inevitable and some individuals may continue to show high cognitive performance at advanced age (e.g. Buckner, 2004; Small, 2001). When provided with the appropriate cognitive support, older adults can achieve levels of performance similar to those of young adults, but the underlying functional activation in the brain often varies to a greater extent among older individuals than among younger people (Logan et al., 2002; Small, 2001).

CHANGES IN MEMORY FUNCTION IN ALZHEIMER'S DISEASE

In AD, a severe deficit in episodic memory is typically the most striking feature early in the disease process, although the onset and course may vary across individuals. Impairments occur on both visual and verbal memory tasks for immediate as well as delayed recall and recognition, and can affect memory for a wide range of stimuli such as faces, names, simple geometric shapes, and short stories (Graham, Emery, & Hodges, 2004; Greene, Baddeley, & Hodges, 1996; Perry, Watson, & Hodges, 2000). Implicit memory functions such as priming and habit learning (Eldridge, Masterman, & Knowlton, 2002; Lustig & Buckner, 2004; Verfaellie, Keane, & Johnson, 2000) and the encoding of affective dispositions (Blessing, Keil, Linden, Heim, & Ray, 2006) remain relatively intact until the later stages of AD. Some aspects of semantic memory, including object naming and category fluency, may be impaired from the onset of the disease, while others, such as judgments on semantic category relations between objects, remain relatively intact in the early and mild stages of AD (Graham, Emery, & Hodges, 2004). Whereas category fluency requires self-generation of words and depends heavily on executive function, deciding whether a word represents, for example, a living or a nonliving thing relies predominantly on semantic memory. This suggests that brain structures subserving semantic memory are relatively spared in the initial stages of AD. They could play an important role in cognitive interventions aimed at improving or maintaining memory function in patients with early dementia or individuals at risk.

MEMORY DECLINE IN DEMENTIA: ACCELERATED AGEING OR A DISTINCT PROCESS?

Some of the memory problems experienced by many healthy older adults may be qualitatively similar to those experienced by people with AD. At the level of changes in functional activation and brain structures, there has been an ongoing debate about whether AD constitutes one extreme end of the spectrum in the normal ageing process, or whether a separate mechanism underlies the disease process (e.g. Buckner, 2004; Huppert, 1994; Ohnishi, Matsuda, Tabira, Asada, & Uno, 2001; Sperling et al., 2003a). These views have been captured in two proposed explanatory frameworks. A unitary factor framework suggests that similar processes that cause mild cognitive change in normal ageing are, in accelerated form, responsible for the severe memory impairments seen in AD (Huppert, 1994). In such a framework, all ageing would ultimately result in severe cognitive decline if only time would allow for it. The competing multiple factor model introduces several distinct age-related processes that affect different neural systems and vary in their level of progression (e.g. Gabrieli, 1996). These processes may occur independently of each other. A number of studies have demonstrated that processes that cause memory decline in AD are separate from those seen in healthy ageing, thus supporting the idea that multiple factors are responsible for cognitive alterations in ageing (e.g. Golby et al., 2005; Hedden & Gabrieli, 2004; Ohnishi et al., 2001; Sperling et al., 2003a). A rapidly progressing decline in memory such as that observed in AD is viewed as a process that is distinctively different from the memory difficulties that may be experienced by healthy older adults. In a recent review, Buckner (2004) pointed out that if older adults do experience a decline in memory function, two differential effects could be causing this change: reduced executive functioning due to changes in the fronto-striatal circuits, and disrupted medial temporal lobe (MTL) functioning caused by AD-associated neurodegeneration in brain structures in the MTL, such as atrophy, cellular pathology and cell loss in the MTL, in particular in the entorhinal cortex and the hippocampus. These pathological processes have indeed been shown to precede the onset of AD by years or decades (Braak et al., 1999; Braak & Braak, 1997), and vulnerability of these areas even in healthy older people is therefore likely.

AIM OF THE CURRENT REVIEW

Imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have made it possible to identify brain areas that are activated during a particular memory paradigm and thus to study the involvement of different brain structures in memory function, and relate this to the behavioural outcome. Imaging studies have typically investigated memory function when participants were asked to study words (Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003a, 2003b; Morcom, Good, Frackowiak, & Rugg, 2003), pictures (Gutchess et al., 2005), or associations, for example between faces and names (Dickerson et al., 2005; Sperling et al., 2003a) or an object and its background (Gutchess et al., 2007). Instructions for the tasks have varied in that some studies have asked people to learn the stimuli for a later memory test, whereas others have instructed participants to make semantic judgments about the stimuli after which they received a surprise memory test. The majority of studies have focused on brain activation changes during the encoding process, both in healthy ageing and in AD, but some have incorporated both encoding and retrieval processes (e.g. for healthy aging Daselaar et al., 2003a; for AD Pariente et al., 2005). This review will first focus on the changes in memory-related brain activity in healthy ageing and AD that have been demonstrated in studies employing associative memory paradigms, and consider the nature of these changes. The implications of this knowledge for intervention strategies that aim to improve memory function will then be discussed. Specifically, the aim is to answer the following questions: 1) How do patterns of brain activity during associative memory differ between healthy ageing and AD? 2) Are these differences more pronounced during specific memory processes (i.e. encoding or retrieval) 3) Are any of these functional activation differences compensatory in nature? 4) Can the knowledge about functional changes in healthy ageing and AD be utilised to devise new or more effective memory strategies? 5) What are the practical implications of these findings for rehabilitation strategies?

Although of interest to research into AD, it is beyond the scope of this review to discuss studies that have focused on alterations in brain activity in people with mild cognitive impairment (MCI) or carriers of the Apolipoprotein E (APOE) allele. Cognitively, MCI falls between healthy ageing and AD, and per annum approximately 5–16% of people with MCI convert to AD (e.g. Jack et al., 2005; Petersen et al., 1999). Carriers of APOE are genetically at high risk of developing

AD (e.g. Corder et al., 1993; Raber, Huang, & Ashford, 2004), and show a different pattern of brain activity *before* the onset of AD compared to non-carriers (Bookheimer et al., 2000; Lind et al., 2006; Smith et al., 1999).

METHODS

Literature searches were conducted using PubMed, PsycInfo, Medline, and Web of Science on 22 February 2008. The key words 'aging / ageing', 'age difference', 'age', 'old', 'older', 'Alzheimer*', and 'dementia' were combined with 'fMRI or PET' and 'associative memory', 'relational memory', or 'contextual memory' to identify studies of differences in memory-related brain activation related to healthy ageing and AD. Studies were included if 1) functional brain activation during an associative memory task was studied using fMRI or PET, and 2) the study compared the population of interest to a control group. Studies were excluded if they were not written in English. The focus was on associative memory as deficits occur here in healthy older adults before a decline in memory for single items takes place (e.g. Naveh-Benjamin, 2000). Associative memory is also an area relevant to neuropsychological rehabilitation, and (re)learning faces and names of acquaintances or members of a social group may be a chosen therapy goal for people with AD (e.g. Clare, Wilson, Breen, & Hodges, 1999; Clare et al., 2000). Although there is a large body of literature on imaging studies exploring age differences in episodic memory in healthy ageing, few studies have examined age-related changes in *associative* memory function. Only seven studies relating to functional activation changes in associative memory in healthy ageing met the inclusion criteria. These are summarised in Table 2.1. With regards to functional brain activity alterations in AD during a memory task, the search yielded nine studies that met the inclusion criteria. These are summarised in Table 2.2.

Studies related to healthy ageing

Three studies employed PET to compare healthy older adults with young adults on memory for word pairs (Anderson et al., 2000; Cabeza, Anderson, Locantore, & McIntosh, 2002; Cabeza et al., 1997). The other four used fMRI to study age differences in brain activation during memory processes relating to object-location associations (Gould, Brown, Owen, Bullmore, & Howard, 2006b; Kukolja, Thiel,

Wilms, Mirzazade, & Fink, 2007), objects on a meaningful background (Gutchess et al., 2007), or face-name associations (Sperling et al., 2003a). Three studies explored both encoding and retrieval processes (Anderson et al., 2000; Cabeza et al., 1997; Kukolja et al., 2007), two studies looked at retrieval processes only (Cabeza et al., 2002; Gutchess et al., 2007), and Sperling and colleagues (2003a) only investigated encoding. Gould et al. (2006b) explored the amount of *deactivation* compared to baseline during encoding and retrieval processes in young and older adults. The majority of studies reported brain activation differences between young and older adults. During encoding, a number of studies found reduced activation in the older group in prefrontal areas (Anderson et al., 2000; Cabeza et al., 1997; Sperling et al., 2003a). Gutchess and colleagues (2007) also reported reduced activity in frontal regions during a recognition task in older adults. In some cases the older adults recruited frontal areas during memory processing that were not recruited by the young group (Anderson et al., 2000; Cabeza et al., 2002; Cabeza et al., 1997). These results were interpreted as reflecting compensatory neural activity in the older group. However, other studies made no mention of compensatory activation and found only small group differences. For example, Kukolja et al. (2007) observed higher activity for successfully encoded than for unsuccessfully encoded object-location pairs in the left fusiform gyrus in young adults, whereas no difference was detected in the same region in the older group. Gould and co-workers (2006b) detected no differences between groups in an analysis of the whole brain, and found less deactivation in the left anterior cingulate in the young group compared to the older group only when activity patterns in a specific region of interest were explored. One of the reasons for these apparently incongruent findings between studies may be that group differences are very small or non-existent when only successful memory processes are studied.

Table 2.1 – Imaging studies comparing brain activity in healthy young and older adults during associative memory tasks.

Study	Objective	Participants	Method	Outcome
Anderson et al. (2000)	To investigate brain activity in young and older adults during encoding and retrieval under full and divided attention conditions, using PET.	12 young adults (9 female; mean age 24.4 yrs; mean education 16.7 yrs; mean MMSE score unknown); 12 older adults (9 females; mean age 68.5 yrs; mean education 15.9 yrs; mean MMSE score unknown).	20 moderately related words were presented at a rate of 5 seconds per pair. Subjects were instructed to mentally create a visual image connecting the words. During retrieval the first word of a pair was shown and subjects recalled the second word. A low tone was presented every two seconds (full attention condition) and subjects pressed a button. In condition 2 (divided attention), subjects performed the same task but indicated via two buttons whether the tone was high or low. The divided attention condition was administered either during encoding or during retrieval.	Behavioural outcome: full attention condition - young adults recalled 79% of word pairs correctly; older adults correctly recalled 60%. Divided attention condition - young adults (DA during encoding: 58% correct; DA during retrieval: 75% correct); older adults (DA during encoding: 36% correct; DA during retrieval: 51% correct). PET data: during full attention the older adults showed reduced activity in prefrontal regions that younger adults recruited during either encoding or retrieval. The older group also recruited the prefrontal areas not activated in the young group. During encoding DA reduced memory performance behaviourally in both groups, and also reduced brain activation in left prefrontal and medial temporal areas. During retrieval, the DA condition seemed to have relatively little effect on both behavioural performance and brain activation in the two groups. Activation in left inferior prefrontal cortex was reduced similarly by age as well as the DA condition, which may reflect a reduced ability to engage in effective encoding strategies.
Cabeza et al. (2002)	To explore whether the neural basis of different ageing patterns in PFC is one of compensation or dedifferentiation, using PET.	12 young adults (5 females; mean age 25.3 yrs; mean education unknown; mean MMSE unknown); 8 older high-performing older adults (4 females; mean age 68.0 yrs); 8 older low-performing older adults (4 females; mean age 69.9 yrs). The high-performing older adults performed comparable to the young group on a series of neuropsychological tests, whereas the low-performing older group scored significantly lower than the young and the old-high group.	Task 1 (word pairs): subjects studied 24 unrelated word pairs presented for 3 seconds each. They were scanned during recall, in which they were presented with the first word of each pair and were asked what the second word was. Task 2 (source memory): participants studied two lists of single words that were either viewed or heard. At a recognition test participants were asked whether they had heard or seen the word.	Behavioural outcome: recall performance - young group .75; old-high group .86; old-low group .64. These scores are adjusted for chance but the paper contains no information on how this is done. Across Tasks 1 and 2 young and old-high subjects performed better than old-low but there was no difference between young and old-high. PET results: during the associative recall task, the young group recruited left dorsolateral (BA 9) and ventrolateral (BA 44/47) areas, whereas the two older groups only recruited the left ventrolateral regions. The old-high group showed significantly less activity in this region compared to the young and the old-low group. In the source memory task, the young and the old-low group recruited the right PFC whereas the high-OC group recruited both right and left PFC during the task. This pattern in the high-OC group was interpreted as compensatory.
Cabeza et al. (1997)	To compare regional cerebral blood flow in young and older adults while they were encoding, recognising, and recalling word pairs, using PET.	12 young adults (6 females; mean age 25.7 yrs; mean education 17.8 yrs; mean MMSE score unknown); 12 older adults (7 females; mean age 70.5 yrs; mean education 16 yrs; mean MMSE score unknown).	Encoding task: 192 unrelated word pairs were presented in blocks of 24 pairs for 4 seconds each. Subjects were instructed to note a meaningful relation between the two words to remember the pair. Recognition: subjects viewed pairs of words, and if they thought the second word was the original one they read it out loud. Recall: subjects saw the first word and were asked to recall the second word. After the PET procedure subjects were tested on delayed recall and recognition.	Behavioural outcome: immediate recognition (hits – false alarms) – young adults .86; older adults.86. Delayed recognition – young adults .82; older adults .74. Immediate recall – young adults.78; older adults .76. Delayed recall – young adults .39; older adults .26. Differences between groups are non-significant. PET results: during encoding older adults showed higher activation in bilateral insular and right occipital regions compared to young adults. Increased activity in the older group compared to the young group was also observed in the cuneus/precuneus during recognition, and in the left PFC during recall. The young group showed more left frontal activation during encoding coupled with more right frontal activity during retrieval, whereas the older group did not show this lateralisation pattern. The older adults showed reduced activation in areas recruited by the young group, and instead recruited other regions.

Table 2.1, continued

Study	Objective	Participants	Method	Outcome
Gould, Brown et al. (2006b)	To examine task-induced fMRI deactivations during successful encoding and retrieval of visuospatial paired associates in young and older adults.	12 young adults (6 females; mean age 28.7 yrs; mean education 17.9 yrs; mean MMSE score 30); 12 healthy older adults (6 females; mean age 64.4 yrs; mean education 14.8 yrs; mean MMSE score 29.4). There was a significant difference between the groups in age, education, and MMSE scores.	3, 4 or 6 everyday objects appeared one by one in one of a white box on the screen for 2.5 seconds. Difficulty level was adjusted for each subject individually by varying the number of objects. One second after all objects had been presented, two objects appeared in one of the locations and subjects indicated which object had been in this location during encoding.	Behavioural outcome: the young adults needed significantly less attempts than the older adults on the 4 and 6 object-location pairs. fMRI results: common deactivations for the two groups were observed in prefrontal , temporal, and limbic regions as well as in the claustrum and the lateral cerebral sulcus. There were no significant group differences when correcting for multiple comparisons across the whole brain. An ROI analysis revealed that the young adults showed significantly less deactivation in the left anterior cingulate than the older adults during retrieval.
Gutchess et al. (2007)	To investigate age differences during the processing of contextual information, using event-related fMRI.	21 young adults (11 females; mean age 21.1 yrs; mean education 14.9 yrs; mean MMSE score 29.1); 20 older adults (14 females; mean age 68.1 yrs; mean education 15.0 yrs; mean MMSE score 29.3).	Participants encoded 96 colour photographs of an object on a meaningful background, each presented for 4 seconds. The encoding data are not discussed in this study. Subjects then performed a recognition task in which they decided whether the object was old or new. The object (Old or New) could be presented on a previously seen (OO or NO condition) or on a new background (ON or NN condition).	Behavioural outcome: there was no difference in A' (hits – correct rejections) between the young group (.84) and a subgroup of high performing older adults (.83), but a subgroup of low performing older adults scored significantly lower (.76) than the other two groups. fMRI results: young adults showed greater activation than the older group in bilateral dorsolateral PFC, left anterior cingulate, left middle frontal gyrus, left lingual gyrus, left precuneus, and left inferior parietal cortex. The high performing older group showed less differentiated activation to different conditions than the young adults in DLPFC. They also showed greater differential activation between NO and NN conditions in a number of frontal areas than the low performing older group. This may be a compensatory mechanism.
Kukolja et al. (2007)	To investigate neural correlates of age-related changes during encoding and retrieval of spatial contextual memory, using fMRI.	18 young adults (8 females; mean age 23.9 yrs; mean education 16.4 yrs; mean MMSE score 29.9); 17 older adults (7 females; mean age 59.0 yrs; mean education 14.8 yrs; mean MMSE score 29.3).	64 pictures of objects appeared randomly in one of four quadrants for 1 second. Subjects indicated for each one whether it was man-made or natural. During recognition, 96 objects (64 old, 32 novel) were presented one by one. Subjects made old / novel judgments and if they had seen it before, also indicated in which quadrant the object had appeared.	Behavioural outcome: older and young adults did not differ in their ability to recognise items as 'old' (young: 81.5%; old: 79.8%) but the young subjects made significantly more correct spatial context judgments than older adults. fMRI findings: young adults showed higher activation than the older group in the left fusiform gyrus and the left inferior occipital gyrus during encoding of object-location pairs. In the left fusiform gyrus, the older group showed no difference between falsely and correctly encoded spatial locations, while the young group showed higher activity for the correct vs incorrect locations. During recognition, the older group showed higher activation for unsuccessful than for successful retrieval of location compared to the young group in the left anterior hippocampus. The young group showed the opposite pattern.
Sperling et al. (2003a)	To examine alterations in brain activation pattern for associative encoding in healthy ageing and AD using fMRI.	10 young controls (6 females; mean age 24.9 yrs; mean education unknown); 10 healthy older controls (8 females; mean age 74.1 yrs; mean education and MMSE unknown); 7 AD (mean age 80.6; mean education and MMSE unknown).	Participants encoded 84 novel face-name pairs (presented for 5 seconds each), seven pairs per block; and two repeated face-name pairs that were shown 49 times each over the course of the session. Following the scan participants did a recognition test for the faces, and were also tested for free recall on 6 face-name pairs, 4 novel pairs, and the two repeated pairs.	Behavioural outcome: recognition for faces was tested outside the scanner. Young controls: 94% correct; older controls: 78% correct; AD: 60%. Free recall of names: young controls 58% correct; older controls 40% correct; AD 12% correct. fMRI results: when activation for novel stimuli was contrasted with that for a fixation cross, the older controls showed higher activation in bilateral superior and inferior parietal regions, and in the anterior cingulate, than the young group. The young adults showed higher activity in left superior prefrontal regions.

Studies related to AD

All of the studies comparing people with AD to healthy older adults discussed here employed fMRI and used either face-name associations (Celone et al., 2006; Dickerson et al., 2005; Pariente et al., 2005; Petrella et al., 2007; Sperling et al., 2003a) or object-location pairs as stimuli (Gould et al., 2006a; Gould et al., 2005). In one study, participants studied line drawings of object pairs (Rombouts, Barkhof, Veltman et al., 2000). Five studies examined the encoding process only (Celone et al., 2006; Dickerson et al., 2005; Pariente et al., 2005; Petrella et al., 2007; Sperling et al., 2003a) and three studies assessed both the encoding and retrieval phase (Golby et al., 2005; Gould et al., 2006a; Pariente et al., 2005). One study investigated differences in deactivation between healthy older adults and people with AD during encoding and retrieval (Gould et al., 2006b, as discussed above).

Given that a key neuropathological process in AD originates in the hippocampal formation in the MTL, it is not surprising that one of the main alterations in memory-related brain activity AD compared to healthy ageing is decreased activity in the hippocampus (Celone et al., 2006; Dickerson et al., 2005; Pariente et al., 2005; Petrella et al., 2007; Sperling et al., 2003a). Some studies reported that this decrease in hippocampal activation was coupled with an increased signal in frontoparietal regions (Celone et al., 2006; Pariente et al., 2005; Petrella et al., 2007; Sperling et al., 2003a). However, some of the studies discussed here have found no, or only minor, differences in memory-related brain activity in people with AD compared to healthy older adults (Gould et al., 2006a; Gould et al., 2005; Rombouts, Barkhof, Veltman et al., 2000). Of note, these studies have employed a different paradigm to study associative memory, but nonetheless their paradigm involved associative learning and is thus comparable to the five previously mentioned studies that used face-name associations. Importantly, some studies matched behavioural performance between the people with AD and the healthy older adults, and compared only correct trials (Gould et al., 2006a; Gould et al., 2005). These latter results suggested that when a memory is formed successfully, people with AD make use of very similar brain areas to healthy older adults. Indeed, a key question in fMRI studies exploring brain activation *changes* in AD compared to healthy ageing is whether these alterations reflect the recruitment of an alternative network of brain areas. The next sections will consider findings from neuroimaging studies investigating memory function in healthy ageing and in AD.

Table 2.2 – Imaging studies comparing brain activation in healthy older adults and people with AD during associative memory tasks.

Study	Objective	Participants	Method	Outcome (AD group compared to control group)
Celone et al. (2006)	To use independent component analyses to investigate memory-related brain activation in people with MCI, people with AD, and healthy older controls, with fMRI.	15 healthy older controls (8 females; mean age 75.5 yrs; mean education 16.5 yrs; mean MMSE 29.5); 15 MCI with low sum of box scores on CDR (7 females; mean age 75.1 yrs; mean education 17.1 yrs; mean MMSE 29.3); 12 MCI with high sum of box scores on CDR (6 females; mean age 80.0 yrs; mean education 15.3 yrs; mean MMSE 28.6); 10 AD (7 females; mean age 77.6 yrs; mean education 12.5 yrs; mean MMSE 21.1)	Activation paradigm: see Sperling et al., 2003a. Participants were instructed to try to remember the name associated with the face, and to make a decision as to whether they thought the name 'fit' the face or not. Post-scan memory task: subjects recognised 12 'old' faces, the 2 repeated faces, and 8 novel faces. Then 12 different previously studied faces were shown paired with two previously seen names and subjects picked the correct name for that face.	Behavioural outcome: face-recognition - older controls 74.8%; low-SB MCI group 78.8%; high-SB MCI group 75.3%; AD group 64.6%. Forced-choice name recognition: older controls 87.7%; low-SB MCI group 83.0%; high-SB MCI group 87.0%; AD group 65.7%. There was a strong relationship between activation in the hippocampus and de-activation in the precuneus, bilateral parietal regions, and the posterior cingulate. A 'nonlinear' trajectory was found across the four subject groups with activation during encoding highest in the low-SB MCI group > healthy older controls > high-SB MCI group > AD group.
Dickerson et al. (2005)	To investigate whether hippocampal and entorhinal activation during learning is altered in the earliest phase of MCI, using fMRI.	10 healthy older adults (6 females; mean age 71.5 yrs; mean education 14.9 yrs; mean MMSE score 29.7); 9 MCI (4 females; mean age 73.9; mean education 18.4 yrs; mean MMSE score 29.6) 10 AD (7 females; mean age 77.6 yrs; mean education 13.0 yrs; mean MMSE score 21.1). The MCI group had a significantly higher education than the older controls or the AD group.	See Sperling et al. (2003a) for the face-name learning task. After scanning subjects underwent a brief forced-choice recognition task in which 14 of the faces they had studied were presented with the correct name and one name that had been paired with another face during encoding.	Behavioural outcome: the older controls recognised 87% of the names associated with the faces, compared to 85% correct in the MCI group and 66% correct in the AD group. fMRI results: in the hippocampal formation, MCI patients demonstrated a greater extent of activation than the older control subjects, while the AD group showed a lesser extent of hippocampal activity compared to the older controls and the MCI group. The AD group showed a lesser extent also in the entorhinal cortex compared to the other two groups. There was no difference between the older controls and the MCI group. Across the entire group of 29 subjects there were significant correlations between recognition performance and MTL activation in the right entorhinal cortex and the left hippocampal formation.
Gould, Arroyo et al. (2006a)	To determine whether compensation in AD takes place by recruiting the same brain regions as a control group or recruiting different regions, using fMRI.	12 healthy older adults (7 females; mean age 77.3 yrs; mean education 11.4 yrs; mean MMSE score 29.1); 12 AD (7 females; mean age 77.3 yrs; mean education 11.3 yrs; mean MMSE score 26.3). [this are the same groups of participants who also took part in Gould et al. (2005)]	See Gould et al. (2005). For this study, only those trials comprising two and three objects are included in the analyses.	Behavioural outcome: the AD group performed worse both on the two- and the three object-location pair trials compared to the controls. fMRI results: no significant differences were found between the groups during successful encoding and retrieval of object-location pairs in a whole-brain analysis. Within functional ROIs, the AD group showed higher activation compared to the controls in left medial PFC and right middle frontal gyrus during successful encoding of two object-location pairs.

Table 2.2, continued

Study	Objective	Participants	Method	Outcome (AD group compared to control group)
Gould, Brown et al. (2006b)	To examine task-induced fMRI deactivations during successful encoding and retrieval of visuospatial paired associates in older adults with and without mild AD.	12 healthy older adults (7 females; mean age 77.3 yrs; mean education 11.4 yrs; mean MMSE score 29.1); 12 AD (7 females; mean age 77.3 yrs; mean education 11.3 yrs; mean MMSE score 26.3). [this are the same groups of participants who also took part in Gould et al. (2005)]	3, 4 or 6 everyday objects appeared one by one in one of a white box on the screen for 5 seconds. The number of white boxes (locations) could vary from trial to trial. Six seconds after all objects had been presented, a single object appeared in one of the locations and subjects indicated whether this object had been in this location during encoding. Difficulty level was adjusted for each subject individually.	Behavioural outcome: at the hardest difficulty level, AD subjects needed more attempts (2.16) to successfully complete the trial than the control group (1.45). fMRI results: common deactivations for the two groups were observed during encoding and retrieval in the right posterior cingulate left anular and supramarginal gyri, right temporal gyrus, left claustrum and bilateral insula. There were no significant group differences when correcting for multiple comparisons across the whole brain.
Gould et al. (2005)	To develop a strategy that overcomes confounds as a result of performance differences in patient and comparison groups in functional imaging.	12 healthy older adults (7 females; mean age 77.3 yrs; mean education 11.4 yrs; mean MMSE score 29.1); 12 AD (7 females; mean age 77.3 yrs; mean education 11.3 yrs; mean MMSE score 26.3).	2, 3, 4 or 5 everyday objects appeared one by one in one of six white boxes on the screen for 5 seconds. The number of white boxes (locations) could vary from trial to trial. Six seconds after all objects had been presented, a single object appeared in one of the locations and subjects indicated whether this object had been in this location during encoding. Difficulty level (=how many object-location pairs were studied in one trial) was adjusted for each subject individually.	Behavioural outcome: at the hardest difficulty level, AD subjects needed more attempts (2.16) to successfully complete the trial than the control group (1.45). fMRI results: no differences between the groups were found when corrected for multiple comparisons. Group differences were then assessed uncorrected for multiple comparisons. The AD group showed higher activation than the controls in left medial and middle frontal gyri during encoding, and in the lentiform nucleus during retrieval. The control group showed higher activity than the AD group in the right cerebellum during encoding, and in the right superior temporal gyrus during retrieval.
Pariente et al. (2005)	To better understand the alternative brain networks activated by a face-name task during encoding and retrieval in AD and healthy ageing, using event-related fMRI.	17 healthy older adults (13 females; mean age 70.6 yrs; mean education 13.2 yrs; mean MMSE score 29); 12 AD (8 females; mean age 70.9 yrs; mean education 12.9 yrs; mean MMSE score 25.1).	Subjects studied 48 face-name pairs in the scanner, each presented for 6.4 seconds and blocked in sets of 12 pairs at a time. Recognition followed directly after each encoding block. In the recognition phase participants viewed a previously seen face with four previously viewed names and were asked to pick the one that was associated with that face.	Behavioural outcome: in the forced-choice recognition task, the older controls scored 61.5% correct, compared to 39.5% in the AD group (random response rate was 25%). fMRI results: encoding - when correct versus incorrect trials were contrasted, the control group showed higher activity in bilateral hippocampi than the AD group. The AD group showed higher activity in bilateral precuneus, and bilateral superior lobule. Recognition - when correct versus incorrect trials were contrasted, the older controls showed higher activation in right hippocampus, right middle temporal gyrus, and bilateral inferior temporal gyrus than the AD group. In contrast, the AD group showed higher activation in te right fusiform gyrus. Thus, there was hypoactivation in the hippocampus in the AD group during encoding and recognition, combined with hyperactivation by the same group in a frontoparietal network.

Table 2.2, continued

Study	Objective	Participants	Method	Outcome (AD group compared to control group)
Petrella et al. (2007)	To identify brain regions in which task-related changes correlate with degree of memory impairment in AD, MCI, and healthy older adults, using fMRI.	28 healthy older controls (14 females; mean age 71.96 yrs; mean education 16.3 yrs; mean MMSE score 28.25); 34 MCI (18 females; mean age 74.5 yrs; mean education 15.1 yrs; mean MMSE score 26.6); 13 AD (6 females; mean age 71.4 yrs; mean education 12.7 yrs; mean MMSE score 24.6). The three groups differed significantly in years of education and MMSE scores.	Participants studied 60 novel face-name pairs and two familiar faces, each presented for 5 seconds. The novel faces were grouped into blocks of 10 at a time. Participants performed a forced-choice recognition task in which they chose which out of two faces matched a name.	Behavioural outcome: older controls - 71% correct; MCI - 59% correct; AD - 46% correct. fMRI results: there was a decrease in activation from controls to AD in left medial frontal gyrus, left anterior cingulate and left MTL, including hippocampus and fusiform gyrus. However, there was a signal increase from AD to MCI to the control group in bilateral precuneus (BA 7/31) and left posterior cingulate, with smaller increases in right prefrontal gyri, and right superior temporal gyrus.
Rombouts et al. (2000)	To test the hypothesis that brain activation is decreased in the medial temporal lobe memory system in AD compared with healthy volunteers.	10 healthy older adults (5 females; mean age 61.5; mean education unknown; mean MMSE score 30); 12 AD (5 females; mean age 65.1; mean MMSE score 21.67 (range 16-28))	Task 1: encoding of 40 novel colour pictures and 2 familiar pictures (not associative). Task 2: encoding of 40 line drawings representing pairs of unrelated objects, and 2 familiar pairs, each presented for 4 seconds. After scanning, participants engaged in a forced-choice recognition task where one of the objects was presented and participants chose which out of two possibilities was originally shown with that object.	Behavioural outcome: recognition for pairs of objects was scaled from 0.0 (50% correct) to 1.0 (100% correct). The older controls scored 0.73 whereas the AD group scored 0.01. fMRI results: only 8 AD patients were able to complete task 2 in the scanner. In task 1, the AD group showed decreased activity in the left hippocampus and bilateral parahippocampal gyrus. However, in task 2 a whole brain random effects analysis revealed no significant differences between the groups. A region of interest analysis in the MTL also did not reveal any differences between the groups. One reason for this may be that the groups were small and there was a lot of variation within groups (e.g. the MMSE scores in the AD group ranged from 16 to 28, suggesting a variety in disease progression).
Sperling et al. (2003a)	To examine alterations in brain activation pattern for associative encoding in healthy ageing and AD using fMRI.	10 young controls (6 females; mean age 24.9 yrs; mean education unknown); 10 healthy older controls (8 females; mean age 74.1 yrs; mean education and MMSE unknown); 7 AD (mean age 80.6; mean education and MMSE unknown).	Participants encoded 84 novel face-name pairs (presented for 5 seconds each), seven pairs per block; and two repeated face-name pairs that were shown 49 times each over the course of the session. Following the scan participants did a recognition test for the faces, and were also tested for free recall on 6 face-name pairs, 4 novel pairs, and the two repeated pairs.	Behavioural outcome: recognition for faces was tested outside the scanner. Young controls: 94% correct; older controls: 78% correct; AD: 60%. Free recall of names: young controls 58% correct; older controls 40% correct; AD 12% correct. fMRI results: when activation for novel stimuli was contrasted with that for a fixation cross, the older controls showed higher activation in the right inferior frontal gyrus (BA 45), bilateral hippocampus, and left superior parietal lobule (BA 7). The AD group showed higher activation than the controls in left superior frontal gyrus (BA 9), left middle temporal gyrus (BA 21), right superior temporal gyrus (BA 41), right posterior cingulate (BA 29), and bilateral precuneus (BA 31)

FUNCTIONAL ACTIVATION CHANGES IN HEALTHY AGEING

Studies of age-related changes during associative memory processes have reported mixed results. To make sense of these equivocal findings, the studies will be considered in the light of existing models of age-related changes in memory. The review will first describe commonly reported age-related changes in encoding and retrieval, and then focus on specific factors that could explain contradictory findings in the literature.

Neural systems models of age-related changes in memory

In memory processing, it has been suggested that young adults show a hemispheric encoding / retrieval asymmetry in terms of functional activation patterns (Nyberg, Cabeza, & Tulving, 1996), i.e. there is higher left prefrontal activation during encoding, whereas retrieval elicits higher right prefrontal activation (see Figure 2.1). This hemispheric asymmetry can be observed for both verbal and visual material (Habib, Nyberg, & Tulving, 2003). For example, during encoding of word pairs in an intentional learning paradigm, where participants are explicitly instructed to memorise the items and are left to choose their own learning strategy, older adults have been found to show an age-related decrease in left prefrontal cortex (PFC) activity, coupled with an increase in right PFC activity, compared to young controls (Anderson et al., 2000; Cabeza et al., 1997).

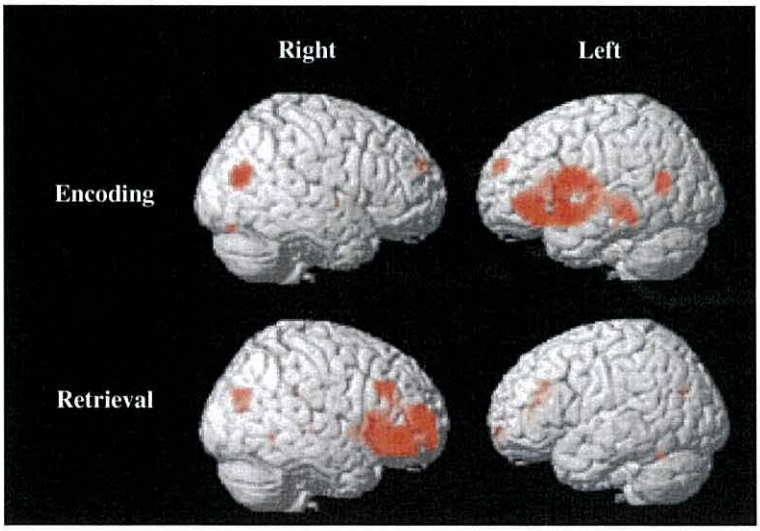

Figure 2.1 – The HERA model. In healthy young adults, brain activity is larger in the left than in the right prefrontal cortex during encoding, and larger in the right than the left prefrontal cortex during retrieval. Adapted from Habib, Nyberg, & Tulving (2003).

Some have argued that in older adults, this asymmetry is reduced (Bäckman et al., 1997; Cabeza, 2002; Cabeza et al., 1997; Rajah & D'Esposito, 2005). Cabeza (2002) referred to this more symmetrical distribution of prefrontal activity in older adults as the HAROLD model (hemispheric asymmetry reduction in older adults). This model is illustrated in Figure 2.2. The additional activations seen in the HAROLD phenomenon have been interpreted in several different ways. Cabeza (2002) argued that these activation differences may be compensatory and can assist with processing in older adults. Rajah and D'Esposito (2005) argued that the differences are the result of dedifferentiation, whereby processes that were functionally different in young adults come to require similar organising resources in older adults, but that in response to this dedifferentiation process some compensatory activity in frontal cortex can occur.

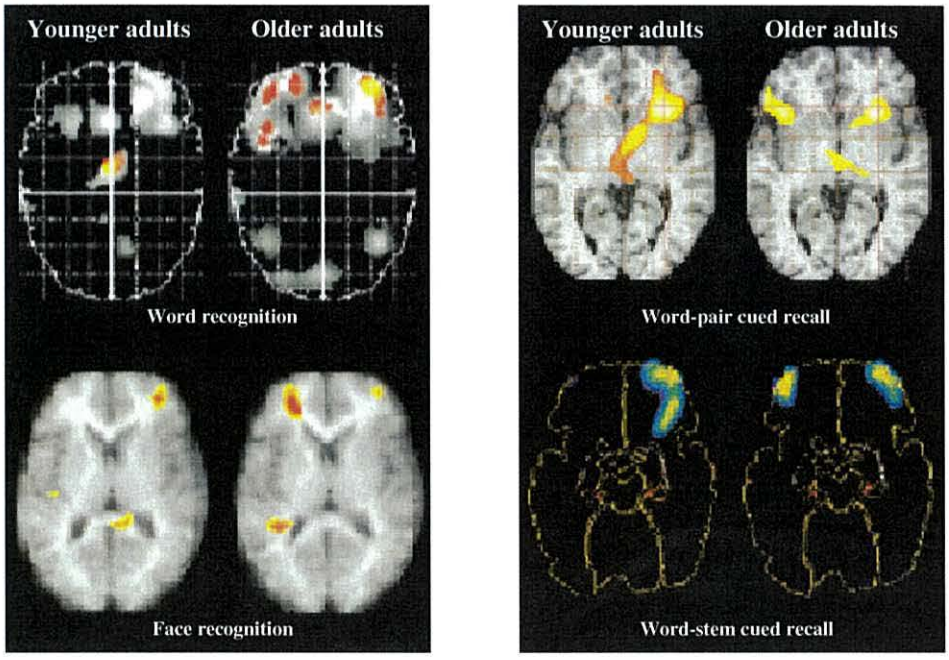

Figure 2.2 – The HAROLD model. Brain activation in prefrontal cortex in younger and older adults during episodic memory retrieval is right lateralised in younger adults and bilateral in older adults. Adapted from Cabeza (2002).

Others have distinguished two types of age differences in brain activation in frontal regions: under-recruitment and nonselective recruitment of brain regions by older adults (Logan et al., 2002). Under-recruitment occurs as a result of inefficient

strategies to encode information and can be reversed when effective learning strategies are used. Nonselective recruitment is thought to reflect a breakdown in the selection of areas appropriate to task performance, rather than representing compensatory neural activation. Recently, it has been proposed that increases in frontal activity are coupled with a reduction in occipito-temporal activation in older adults (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008).

Functional activation during associative encoding

Anderson and colleagues (2000) asked subjects to learn word pairs under conditions of full and divided attention (pressing buttons in response to high- or low-pitched tones). They found reduced memory performance and reduced left PFC activity in the divided attention condition in both the younger and the older group, but no difference between groups in this condition. However, in the full attention condition, the older group showed reduced left PFC activity compared to the young group, suggesting reduced ability to engage in effective encoding strategies. Sperling and colleagues (2003a) also found differences between older and young adults during intentional encoding of face-name associations: the older group showed reduced activation in left prefrontal areas compared to the young group. Kukolja, Thiel, Wilms, Mirzazade and Fink (2007) observed higher activation during encoding of object-location pairs in the left fusiform and left inferior occipital gyrus in a group of young adults compared to older adults.

Functional activation differences in retrieval of associations

Age-related differences in neural circuitry have been identified during both recall and recognition, although these appear to be less pronounced than at encoding (Cabeza et al., 2004; Cabeza et al., 1997; Daselaar et al., 2003a). The reduced right PFC activation that led to the HAROLD model may reflect altered retrieval operations in older adults (Cabeza et al., 2002; Cabeza et al., 1997). The possibility of altered control processes in recognition is supported by a study looking at correct rejection of novel objects presented on a familiar scene (Gutchess et al., 2007). Kukolja et al. (2007) also studied recognition processes in healthy older and young adults but used object-location pairs. They demonstrated higher activity for successful than unsuccessful retrieval in the left hippocampus in young adults, compared to the opposite pattern of activation in the older adults. Irrespective of retrieval success,

they reported less deactivation in older than young adults in the so-called default mode network, which comprises regions that are more active during rest than during goal-directed behaviour (Raichle et al., 2001) and includes the medial frontal gyrus, anterior and posterior cortex, inferior parietal cortex and the precuneus. They proposed that activity in areas that are not specifically necessary in a given task, such as those in the default mode network, can negatively interfere with successful retrieval of object-location information. Conversely, in a different study, difficulty level was adjusted for each individual so that object-location pairs could be recalled in approximately the same number of retrieval attempts (Gould et al., 2006a). The authors reported no differences in deactivation between young and older adults in a whole brain comparison, and only found greater deactivation in the anterior cingulate during retrieval in the older group compared to the young group when the analysis was restricted to a previously defined region of interest

The role of instructions in memory processing

Logan and colleagues (2002) pointed out that similarity in functional activation and in behavioural performance between age groups can be achieved when older subjects are instructed to use a semantic encoding strategy. Logan and colleagues showed that in comparison to young adults, healthy older adults demonstrate under-recruitment and nonselective recruitment of frontal areas during intentional memory encoding. They suggested that under-recruitment occurs when areas typically involved in the encoding process are intact, but are not spontaneously engaged fully during an encoding condition, possibly because older participants rely on self-initiated, ineffective strategies. Nonselective recruitment refers to additional, atypical activation of areas involved in encoding in older adults compared to young adults. When choosing their own encoding strategy, older adults demonstrated a more bilateral frontal activation pattern for both verbal and non-verbal stimuli compared to young adults. Notably, the under-recruitment could be reversed when subjects were, by the nature of the task (e.g. judging whether a word is abstract or concrete), forced to engage in a suitable encoding strategy. Under these circumstances, older adults engaged brain areas in a very similar way to the younger adults, and their behavioural performance nearly reached the level observed in young adults.

The importance of performance: differentiating between good and poor performers

Mixed results have thus emerged from the existing literature on age differences in neural activity during associative memory. Some of this variability may be explained by performance differences across participant groups, especially as most studies did not distinguish between high and low performers in the adult group. Cabeza, Anderson, Locantore and McIntosh (2002) administered a battery of memory tests to participants and selected an older group of eight high performers (old-high) and eight low performers (old-low) based on these test results, in addition to a group of young adults. When activation for source memory was contrasted with that of free recall, the old-high group demonstrated bilateral prefrontal activity compared to the right lateralised prefrontal recruitment by the young and the old-low group. Cabeza and colleagues argued that the high performing older group showed a pattern of reduced hemispheric asymmetry. Because only the high and not the low performing older group showed this pattern, it was interpreted as being compensatory in nature and thus helping the older group with task performance. In another example, Daselaar and colleagues (2003a) differentiated between strong and weak performers during an incidental learning task in which participants rated nouns as pleasant or unpleasant. There were no significant differences in activation levels between a normally-performing older group and their young counterparts. However, in the reduced-performance group, activation levels in the left anterior MTL were significantly reduced compared to the young group. It has been suggested that the amount of MTL activity relates to the number of associations formed during encoding (Henke, Weber, Kneifel, Wieser, & Buck, 1999). The MTL is thought to form associations between the cognitive, sensory, and emotional processes that make up an episode in memory (Alvarez & Squire, 1994; Eichenbaum, Schoenbaum, Young, & Bunsey, 1996). Given that even the older reduced-performance group had reasonable scores in the retrieval condition, the reduced MTL activation pattern would imply that this group merely formed fewer memory associations.

Familiarity versus remembering

Recognition can be attained through strong as well as weak recollection. Strong recollection ("remembering") is based on many memory associations and involves judgment with ease and confidence. Weak recollection ("feeling of knowing / familiarity") is thought to yield less brain activation compared to strong recollection

in frontal, parietal, and MTL regions (e.g. Maril, Simons, Mitchell, Schwartz, & Schacter, 2003). There is a positive relation between MTL activation and the number of associations formed during encoding (Henke, Buck, Weber, & Wieser, 1997; Henke et al., 1999). This led Daselaar et al. (2003a) to propose that during poor performance relatively few associations may underlie recognition, leading to a decision made with less confidence. When making their responses, members of the reduced-performance group in the Daselaar et al. study may have relied more on a feeling of knowing rather than actually being certain of the response, perhaps because of the MTL dysfunction during encoding. This interpretation would be supported by the finding of Cabeza and co-workers (2004) that older adults showed significantly fewer 'remember' responses and more 'know' (familiarity) responses than young adults when asked to make decisions on whether they had seen a word before in a list. The hippocampus showed an age-related decrease in activation, while activity was increased in the parahippocampal gyrus, which has been associated with a "feeling of knowing" (e.g. Aggleton & Brown, 1999).

The importance of performance: distinguishing between success and failure

Some studies have investigated whether age-related differences would remain when only successfully encoded or remembered items were taken into account for both young and older adults (Gould et al., 2006a; Kukolja et al., 2007). Both studies found minimal differences between age groups when comparing only successful trials. However, age-related alterations in brain activation during retrieval may differ for items that can be remembered and items that cannot. Daselaar and colleagues (2003a) investigated this by distinguishing between successful retrieval (correct recognition) and retrieval attempts (correct rejection) on a verbal incidental learning task. Age-related activation differences seemed to occur mainly during retrieval attempts, but disappeared when only the activation related to successful retrieval was taken into account (Daselaar et al., 2003a). These differences were interpreted as indicating that participants were compensating for the encoding deficit with increased effort. Similar activation occurred in all three groups during successful retrieval, with common areas including the left anterior PFC, left inferior / superior parietal cortex and posterior cingulate. Daselaar and colleagues argued that these regions are particularly relevant to successful retrieval and that ageing apparently does not affect those processes related to the actual recovery of information. Based

on these findings, it has been suggested that older adults recruit similar neural circuits to young adults during the encoding of new memories, and that the processes that support the actual recovery of information are not affected by ageing (Daselaar et al., 2003a; Morcom et al., 2003).

CHANGES IN BRAIN ACTIVATION IN ALZHEIMER'S DISEASE

Many studies investigating alterations in memory-related brain activity in AD compared to healthy ageing focus on whether or not people with AD recruit additional brain areas to compensate for dysfunction in the hippocampal areas that play a major role in memory formation. The outcomes of these studies are ambiguous. Here, functional activation changes in AD compared to healthy ageing during encoding and retrieval will be discussed, after which the possible mechanisms underlying the contradictory findings will be considered.

Functional activation changes at encoding

The most important and consistent finding in functional imaging studies on AD is an activation decrease in the MTL during encoding of novel items (Celone et al., 2006; Dickerson et al., 2005; Pariente et al., 2005; Petrella et al., 2007; Sperling et al., 2003a). The regional atrophy in the hippocampus in AD partly explains reduced activity in this area (Rombouts, Barkhof, Veltman et al., 2000), but Sperling et al. (2003a) also noted dysfunction in the remaining tissue. However, one study found partially preserved activation in the MTL in people with AD during an episodic memory task (Golby et al., 2005). It is unclear what factors explain the different findings reported by Sperling et al. and Golby et al. There are some methodological differences in the paradigms and instructions used in the studies that may account for these contradictions. For example, Golby and colleagues instructed participants to judge whether scenes in a picture were outdoors or not, while Sperling et al. asked subjects to learn face-name pairs. The first instruction forces participants to process the semantic aspects of the picture, while the latter instruction does not guide participants into the use of a particular learning strategy. In healthy older adults, making semantic judgments about words significantly improved their performance on a subsequent memory task compared to intentional learning, and also increased brain activity in an area that was related to successful encoding in young adults

(Logan et al., 2002). A semantic strategy may also be beneficial to memory performance in AD, as behavioural studies suggest that people with AD have particular difficulty at encoding (e.g. Greene, Baddeley, & Hodges, 1996).

A series of different associative learning studies (Gould et al., 2006a; Gould et al., 2006b; Gould et al., 2005) used object-location pairs to study associative memory in AD. They matched AD participants and healthy older people for behavioural performance to control for the amount of effort put in by each group that may lead to differences in activation. When participants were compared on a task in which performance was *not* matched, higher activity was detected in the AD group compared to the healthy older group in medial and prefrontal regions (Gould et al., 2006a; Gould et al., 2005). Interestingly, when the successful matched performance trials were compared between the groups, these differences disappeared. Thus, it was suggested that during successful memory formation, people with AD make use of very similar networks compared to healthy older adults. People in the early stages of AD may need to work harder than healthy older adults, as expressed by increased activity when the task was more difficult. This compensation mechanism probably collapses with the progression of AD pathology (Prvulovic, Van de Ven, Sack, Maurer, & Linden, 2005). Important caveats are that the three different publications appear to have been based on results from the same subjects participating in the object-location task on a single occasion, which limits the generalisability of these findings, and that no correction for multiple comparisons was applied, raising the possibility of false positive results.

Functional activation changes at retrieval

Four of the studies reviewed here investigated the retrieval process (Gould et al., 2006a; Gould et al., 2006b; Gould et al., 2005; Pariente et al., 2005). As mentioned previously, Gould and colleagues matched performance levels between the AD and the healthy group and compared only successful trials of object-location recall. They reported no differences in memory-related brain activity between the groups under these circumstances. Pariente and colleagues compared the AD group and the healthy older group by contrasting successful versus unsuccessful trials of face-name recognition. They reported that during recognition, the AD group showed decreased activity in the right hippocampus compared to the healthy older group, whereas the opposite pattern was observed in the right fusiform gyrus.

Diminished activation in hippocampal areas in people with AD compared to healthy older adults has been reported previously in episodic memory studies that did not employ an associative memory paradigm (e.g. Desgranges et al., 2002; Garrido et al., 2002; Remy, Mirrashed, Campbell, & Richter, 2005). Desgranges and colleagues (2002) found that during an episodic memory task (story recall), a less severe AD group recruited MTL areas such as entorhinal and retrosplenial cortex, whereas a more severe group employed more widely distributed and predominantly left-hemispheric association cortices. Desgranges et al. suggested that as the level of impairment progresses, regions subserving episodic memory shift from limbic structures to areas that are usually devoted to semantic memory, and that these regions may aid episodic memory when the typical network supporting this function is impaired.

Some studies in this area have related memory performance (both recognition and retrieval) to regional atrophy or to resting state glucose metabolism (e.g. Desgranges et al., 2002; Garrido et al., 2002), and found that behavioural performance on a verbal episodic memory task correlated negatively with the degree of atrophy in hippocampal areas and in posterior cingulate cortices. These findings support the idea of a disrupted network of regions relevant to episodic memory, including the posterior cingulate and retrosplenial cortex, in addition to the medial temporal lobe (Buckner, 2004).

IS RECRUITMENT OF ADDITIONAL BRAIN REGIONS COMPENSATORY?

Recruitment of additional neural networks seems to occur in the normal ageing process as well as in AD and might represent a general response to functional loss of varying origin (Grady et al., 2003). People with early-stage AD have been shown to recruit additional brain areas during encoding and retrieval, the involvement of which is likely correlated to the (mal)function of the hippocampus and other structures in the MTL that typically support memory processes. However, the involvement of additional brain regions may not be compensatory in nature, but merely indicate inability to recruit the appropriate area (Logan et al., 2002).

A number of imaging studies have described increased activation of additional brain regions adjacent to the 'typical' network of memory areas in early-stage AD

compared to healthy older controls during memory task performance (Desgranges et al., 2002; Garrido et al., 2002; Grady et al., 2003; Pariente et al., 2005; Remy et al., 2005; Sperling et al., 2003a). Areas showing hyper-activation during encoding as well as retrieval in AD compared to healthy ageing comprise bilateral prefrontal cortex, bilateral medial parietal cortex (precuneus), posterior cingulate, retrosplenial cortices, and superior, middle and inferior temporal gyri. Some of these areas comprise a resting state network (Raichle et al., 2001). Similarly, in healthy ageing studies it has been suggested that older adults may recruit additional mainly prefrontal regions compared to young adults, and that the involvement of these areas contributes to task performance. In all cases, the main argument in favour of the supportive nature of these areas is that this activation is positively correlated with task performance. However, there appears to be a divide in the studies reporting compensatory memory-related activity in AD. While some have suggested that hyper-activation in both prefrontal cortex and posterior parietal areas is compensatory (Desgranges et al., 2002; Grady et al., 2003; Pariente et al., 2005), others concluded that increased activity in parietal areas may represent impaired inhibition of the default mode areas (Garrido et al., 2002; Remy et al., 2005; Sperling et al., 2003a).

Support for the latter view comes from a number of recent studies investigating the so-called default mode network in AD. Parietal midline areas such as the precuneus and posterior cingulate gyrus are thought to be part of this network of areas that is more active during rest than during deliberate cognitive processes (Raichle et al., 2001). Lustig et al. (2003) reported marked alterations in the medial parietal cortex (BA 31) in people with AD compared to healthy young and older adults, with the patient group showing a signal increase in this region during encoding (making living / nonliving judgments about words) whereas the young group demonstrated significant deactivation of this area. Celone and colleagues (2006) compared healthy older adults, people with mild cognitive impairment (MCI) and participants with AD on a face-name learning paradigm, and argued that hippocampal activity is positively correlated to the deactivation in parietal regions that form part of a resting state network. Moreover, hyperactivity in parietal and prefrontal regions separated those with minor pathology (MCI) from those in whom the pathology was more advanced (AD). Some researchers have proposed that recruitment of additional areas is only likely to be beneficial to memory function if

the recruited regions already subserve a cognitive function that may complement task performance (Colcombe, Kramer, Erickson, & Scalf, 2005). Analogous to these reports, Buckner (2004) suggested that there may be concurrent loss of neurons in the MTL and in regions reciprocally connected to the MTL, in particular the posterior parietal cortex. Thus, instead of representing a compensatory mechanism, functional changes in AD in parietal regions may be an early indicator of dysfunction in this area.

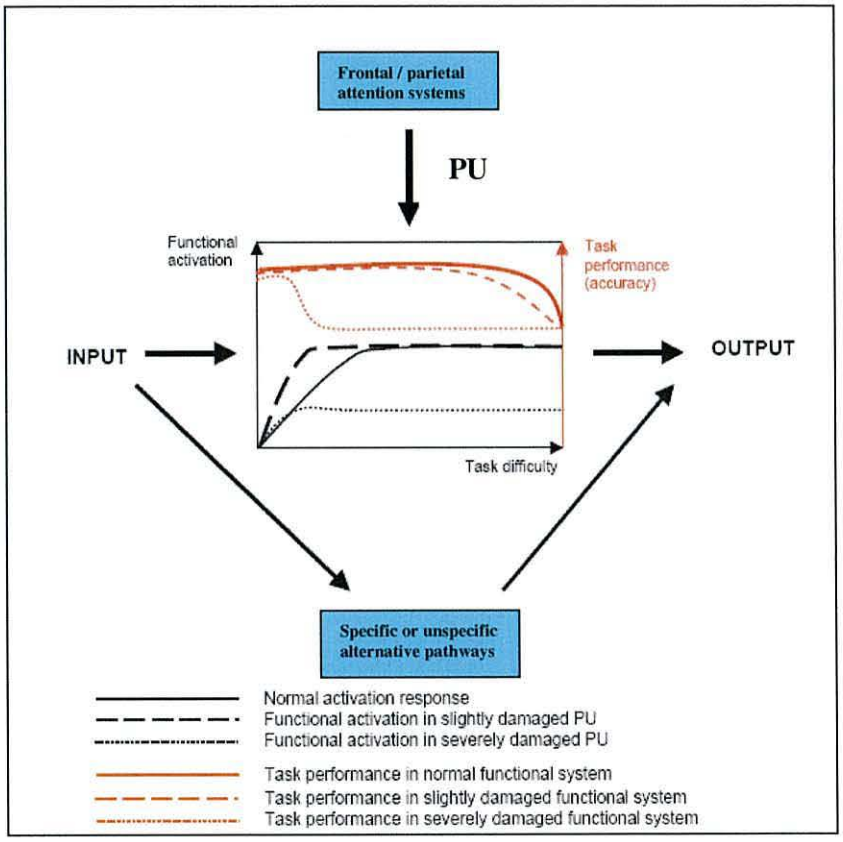

Figure 2.3 – An integrated model of possible relations between a damaged processing unit and its relation to observed brain activation patterns at different levels of task difficulty. PU = processing unit. Adapted from Prvulovic, Van de Ven, Sack, Maurer and Linden (2005).

It is proposed that some of the hyper-activation in AD, rather than reflecting compensation, represents altered activity in the brain and, in relation to the default mode areas, may merely be a marker for less efficient processing. The degree of impaired inhibition is perhaps an indicator of the amount of cognitive impairment. One of us has proposed a model of neural response to damage to a so-called

'processing unit' – a specific area of the cortex engaged in the task at hand – where a slightly damaged system will yield a greater neural response compared to a normal system until the maximum processing capacity is reached (Prvulovic et al., 2005). A severely damaged unit in this model (see Figure 2.3) shows equal activation compared to a normal unit initially when the task is easy, but quickly becomes overburdened. In that case, activation in the severely damaged unit levels off whereas the healthy unit continues to show increased activity in response to task difficulty until a much higher level of difficulty is reached. It is argued that activation in the processing unit depends on its processing efficiency, its capacity, task difficulty, the individual performance on the task, and the quality of the input signal. Under conditions in which people can still perform a cognitive task, slightly impaired areas show a higher than normal activation because the processing efficiency is decreased while its capacity is still largely intact.

The interpretation of differences in memory-related brain activity in healthy ageing and AD has important implications for rehabilitation strategies. If recruitment of additional areas is indeed compensatory and able to assist in task performance then cognitive strategies could be targeted at activating and stimulating these new, alternative neural circuits. However, recent findings suggest that higher brain activity and involvement of atypical structures may also reflect the onset of cognitive decline. If this is the case then strategies aimed at stimulating residual capacity in the damaged network would be more beneficial to people with AD.

IMPLICATIONS FOR REHABILITATION TECHNIQUES

Effective learning strategies in healthy ageing

Several reports indicate that when only successfully encoded items are compared, older adults use very similar networks to a young control group (Daselaar et al., 2003a; Gould et al., 2006a; Gould et al., 2006b; Gould et al., 2005). This suggests that with the right cognitive strategy, older adults are able to use the typical structures underlying memory function at least to some extent, and that the actual neural networks that support retrieval of information are not affected by ageing. Evidence from neuroimaging studies implies that older adults can perform as well as young adults on episodic memory tasks when they use semantic information to encode the stimuli (Logan et al., 2002). These results are supported by recent

behavioural research exploring the effects of different mnemonic strategies on recollection in older adults (e.g. Ball et al., 2002; Luo, Hendriks, & Craik, 2007; Troyer et al., 2006; Verhaegen, Marcoen, & Goossens, 1992). Troyer and colleagues conducted a series of experiments in which older adults learned names, or face-name associations, using a variety of instructions. Only when participants were required to attend to physical, phonemic or semantic characteristics of the names during encoding, were there no differences in subsequent memory performance between the older and young adults. Older adults also had better recollection of faces and names when they learned the associations intentionally as opposed to incidentally. In addition, name recall was best when participants had themselves generated a semantic meaning for the person's name, noted a prominent feature in the face, and created a link between the name and the face. Although this procedure requires effort and time, and may be difficult to apply in real-life settings, Troyer et al. (2006) pointed out that even partial use of a strategy, such as semantic processing of the name without creating a link to the face, is more helpful than not using a strategy at all.

If these results are joined together with the findings from neuroimaging studies, it becomes apparent that semantic processing is a key aspect of improving memory in healthy older adults. Both functional imaging and behavioural studies have found that, although older people find it difficult to engage in semantic encoding spontaneously, they are perfectly capable of doing so, and that the relevant neural circuits in frontal areas are intact.

Effective learning strategies for people with Alzheimer's disease

Compared to an older control group, people with AD showed hypo-activation of the hippocampal regions, while superior parietal areas were hyper-activated during encoding (Pariente et al., 2005). This is suggestive of more widespread disruptions in the network of structures underlying memory formation, a finding that can be expected in view of the disease process. This can help to explain why, for people with AD, more cognitive support is needed in order to demonstrate enhanced memory functioning (Bäckman, 1992; Bird & Luszcz, 1991, 1993). People with AD who made indoor / outdoor decisions about pictures of scenes during encoding showed activity in the hippocampus (Golby et al., 2005), while people with AD who encoded face-name associations without specific strategy guidance did not (Sperling

et al., 2003a). It would appear that rehabilitation strategies emphasising deep processing and semantic association or elaboration are most likely to be effective. Behavioural reports demonstrate that making decisions about semantic category during encoding (Herlitz et al., 1991; Lipinska & Bäckman, 1997) and forming semantic associations between items (Bird & Luszcz, 1991, 1993; Dalla Barba & Goldblum, 1996) aids memory function in people with AD. Providing support at both encoding and retrieval, as opposed to giving semantic cues at encoding only, enhanced recall in people with AD, whereas in a healthy older control group the added support at retrieval had no additional benefit compared to when semantic cues were available at encoding only (Bird & Luszcz, 1991). These findings link in well with the proposition that memory difficulties in healthy ageing stem from impairments in fronto-striatal circuits, while AD pathology affects MTL regions in the first instance (Buckner, 2004). Drawing together these ideas with findings from behavioural studies, healthy older adults would need only limited cognitive cues to support impaired frontal lobe functions whereas in AD, where key areas supporting memory function are damaged, strategies need to activate a larger network of areas in order to be effective. In addition, it has been suggested that in AD, effortful rather than passive processing is important for the efficacy of rehabilitation techniques (Clare & Wilson, 2004; Dunn & Clare, 2007; Thoene & Glisky, 1995). Thoene and Glisky taught face-name associations to people with memory impairments of varying origin, using mnemonics, vanishing cues, or watching a person on a video. The mnemonic strategy proved most effective for learning face-name associations. Clare and Wilson obtained similar results in a study that explored the efficacy of four different techniques for re-learning famous face-name associations in a single-case study of a person with early-stage AD. The three conditions requiring more effortful processing – mnemonic elaboration, spaced retrieval, and increased assistance – led to better recall than a vanishing cues condition regarded as requiring very little cognitive effort. In particular, mnemonic elaboration, in which the participant generated a verbal label for each picture using a facial feature and the first letter of the name, was found to be very effective during and directly following the training period. It was suggested that cognitively effortful strategies that capitalise on residual memory ability may be most effective in improving memory function. Imaging studies have shown that people with early-stage AD make use of similar neural circuits to healthy older adults when memory encoding is successful. Moreover, even

if an area known to underlie memory function shows hypoactivation, the region can still be functionally involved in the task. However, if very little or no paradigm-linked activity is observed in a certain region, this suggests the structure is no longer being recruited during memory processing. Sperling and colleagues (2003a) found very little activation in the hippocampus during encoding of face-name associations in their group of participants with mild AD. This has different implications for the focus of intervention strategies. If an area shows less activation, but this activation is still relevant and supportive to task performance, intervention may be aimed at making the most of the residual function, for example by focusing on semantic characteristics of a face and a name in order to establish an association between these items in the hippocampus.

Conversely, if there is little evidence of paradigm-linked response in an affected region, cognitive strategies may more usefully focus on networks that support functions that are largely intact in the initial stages of AD, such as semantic or implicit memory. It appears that in the initial stages of the disease, it would be most effective for cognitive rehabilitation strategies to target residual memory function and to do so through semantic associations for the information to be remembered, preferably using links that are generated by the patients themselves.

Implications for rehabilitation strategies

Apart from Logan et al. (2002) and Van der Veen et al. (2006), no study has hitherto compared the use of different strategies to tease out whether activation patterns in healthy older persons and people with AD could be reversed to resemble those observed in young participants. Other strategies known to aid memory performance in older people and people with AD, such as spaced retrieval (Camp, 1989; Camp & Stevens, 1990; McKitrick & Camp, 1993), have, as far as the author is aware, not been investigated with neuroimaging tools. At present, most imaging studies focus on alterations in activation between a patient group and a healthy control group during a given task. It is difficult to make use of these results when designing cognitive interventions because the findings inform us about how the ageing or AD brain responds to the task, but do not tell us under which circumstances task performance can be improved and activation differences minimised. Future research could compare brain activity during different encoding strategies to establish whether and to what extent people with AD can optimise memory performance, efficiency in

memory-supporting brain regions, and capacity in damaged areas. Imaging techniques such as fMRI offer useful methods of learning more about the efficacy and the nature of the success of certain techniques. Although there are studies showing positive effects of acetylcholinesterase inhibiting medication on cognition in AD (e.g. Shanks et al., 2007), no studies have looked at treatment outcome of cognitive rehabilitation intervention as yet. Moreover, fMRI can provide useful information about the functionality of brain structures vital to memory formation, and could potentially aid in assessing the feasibility of certain intervention methods and their individual tailoring.

CONCLUSION

The current review set out to link altered brain activity patterns in both healthy ageing and AD to findings from behavioural intervention studies. The aim was to understand the reasons why certain memory strategies are more successful than others, and to explore whether future interventions should focus on targeting 'compensatory' neural networks that have been reported in both healthy ageing and in AD. The key changes in brain activation during associative memory tasks lie in frontal areas in healthy ageing, and in hippocampal and parietal areas in AD. Activation differences compared to a control group are most pronounced during the encoding process in healthy ageing, whereas in AD difficulties occur at both encoding and retrieval. Although there are reports in the literature that activation differences in frontal areas may reflect recruitment of brain areas that help to compensate for impaired functioning in regions that directly subserve memory processes, it is argued that activation in posterior parietal areas reflects dysfunction and impaired communication between areas, and may be a marker of the degree of pathology. Rehabilitation techniques that induce semantic encoding are most likely to improve memory performance in both healthy older adults and people with early-stage AD. Rehabilitation strategies aimed at people in the early stages of AD should focus on the residual memory function and target the brain structures that typically support memory.

Chapter 3 – Can we change the brain with cognition-focused intervention in AD? The role of functional neuroimaging.

ABSTRACT

This review considers the application of functional magnetic resonance imaging (fMRI) to identify treatment effects and brain plasticity in cognition-focused interventions aimed at people with Alzheimer's disease (AD). At present there is little evidence available that bears directly on this question. Therefore, as the focus is on associative memory function, reviewed here are paradigms from the literature on face-name learning in fMRI in AD, mild cognitive impairment, and healthy ageing. Previous studies have generally selected participants with high levels of education, and have generally used challenging tasks, with considerable variations in task performance level across studies. In addition, studies are discussed that have used fMRI to measure treatment outcome of cognitive interventions in patient populations other than AD, such as people with acquired brain injury and schizophrenia. Based on the findings of the review, recommendations are made for a simple face-name learning paradigm that can be used with people with AD, and which can be applied either as a single assessment tool to compare various subject groups or as an outcome tool to assess functional changes following a cognitive intervention period.

Associative memory declines in healthy ageing, and shows a significant impairment in early-stage Alzheimer's disease (AD) (Fowler, Saling, Conway, Semple, & Louis, 2002; Grady & Craik, 2000). Many healthy older people as well as people with mild cognitive impairment (MCI) and people with AD complain of difficulties in associative memory, such as being unable to recall the names of people who are familiar to them. A number of studies have investigated changes in associative memory in healthy ageing, MCI, and AD, using a variety of stimulus sets such as word pairs, words and fonts, pictures and spatial positions, or words and background colour (Chalfonte & Johnson, 1996; Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2004). Although these paradigms are useful in establishing a decline or impairment in memory performance, it can be argued that they do not reflect those situations from everyday life in which associative memory is most often used, and therefore do not directly investigate problems that older adults experience in daily life situations. A task in which faces and names must be associated constitutes a more realistic and frequently-experienced activity. Thus, by studying associative memory with a face-name learning paradigm, it is possible to study an everyday memory-related activity in an experimental setting (Werheid & Clare, 2007). It may also usefully allow us to look at change over time, for example in identifying treatment effects.

Recent studies have used functional magnetic resonance imaging (fMRI) to examine age differences and changes related to AD during associative learning of faces and names. These methods are useful in determining changes in function of brain areas involved in associative memory, and can also identify involvement of additional, perhaps compensatory, brain regions in AD compared to healthy ageing. When it comes to assessing the outcome of cognitive interventions, functional imaging methods have rarely been applied to the field of ageing and dementia. This is remarkable given that numerous behavioural studies have been dedicated to identifying effective memory-enhancing strategies for both healthy older adults and people with AD, and a substantial number of imaging studies have compared brain activation in ageing and AD to characterise functional differences. Being able to identify biological markers of psychological intervention is important for a number of reasons.

Firstly, it would aid our understanding of neural mechanisms of treatment effects. It has been suggested that neural systems that are mildly damaged behave differently to systems that are severely damaged (Prvulovic et al., 2005). This

implies that the way in which a neural system responds to cognitive intervention may be different depending on the degree of neuronal loss. In a mildly damaged system, it may be possible to (partially) restore neural function. For example, it has been demonstrated that healthy older adults who learned word lists showed similar brain activation patterns to young adults if they were instructed to encode the words semantically (Logan et al., 2002). Alternatively, cognitive intervention might operate through promoting the use of additional, compensatory brain areas. In a recent review, Grady (2008) pointed out that altered patterns of activation in older participants may indicate that, to aid task performance, older adults recruit additional areas compared to younger adults. Some cross-sectional studies comparing memory-related brain activation in healthy older adults and people with AD have suggested that people with AD recruit additional brain regions compared to their healthy counterparts, and that these regions compensate for loss of function in typical memory areas (Grady et al., 2003; Pariente et al., 2005). A third mechanism through which cognition-based intervention may be effective is the reduction of aberrant brain activity. In healthy ageing, brain activation changes may reflect nonselective activation of areas in the older group that are not recruited by the younger group, and which play no significant role in task performance (Logan et al., 2002). In AD, it has been proposed that brain regions associated with a resting state network (Raichle et al., 2001) are disrupted, and that these may not be efficiently inhibited during engagement in a cognitive task (Buckner et al., 2005; Lustig et al., 2003).

Identifying biomarkers for effects of cognitive treatment can provide an additional outcome measure alongside task performance and measures of everyday functioning. In the field of pharmacological intervention aimed at improving cognitive function in people with MCI and AD, identification of neural mechanisms by which a drug operates is a key question, and there appears to be a rich tradition of assessing treatment effects using neuroimaging methods in such studies (Goekoop, Scheltens, Barkhof, & Rombouts, 2006; Kircher, Erb, Grodd, & Leube, 2005; Rombouts, Barkhof, Van Meel, & Scheltens, 2002; Saykin et al., 2004). There is no reason why evaluation of outcome in non-pharmacological cognitive intervention should not be based on an integration of neural and cognitive outcome measures.

Finally, if it were possible to identify brain activation patterns predictive of treatment success prior to the actual intervention, this knowledge could be used to decide on allocation to treatment group. In a recent review, Linden (2006) proposed a

model which classified recipients of cognitive behavioural therapy aimed at symptom reduction in psychiatric disorders (e.g. schizophrenia or obsessive compulsive disorder) as responders and non-responders, based on behavioural response. Linden advocated that in the future the biomarkers underlying reduction of symptoms could be identified using neuroimaging methods following the treatment period, and that this information could consequently be used to identify a priori which people might benefit from what sort of therapy. Given the time and effort that both the therapist and the recipient must often put into any non-pharmacological intervention, this method would be an effective step forward in order to maximise therapy outcome.

USING NEUROIMAGING TO ASSESS THE EFFICACY OF COGNITION-FOCUSED INTERVENTION

fMRI has been applied to demonstrate plasticity in a range of areas. For example, following an intensive remediation programme aimed at ameliorating reading performance, children with developmental dyslexia showed improved reading performance coupled with increased brain activity in areas that were associated with phonologic processing in control subjects (Aylward et al., 2003; Temple et al., 2003). In healthy young adults, working memory capacity, traditionally considered to be constant, was increased following a five-week training programme (Olesen, Westerberg, & Klingberg, 2004; Westerberg & Klingberg, 2007). Importantly, behavioural changes were associated with increased activation in frontal and parietal areas related to working memory function.

Two recent studies including healthy older adults have investigated the neural effects of differential instructions that may or may not induce semantic processing (Logan et al., 2002; Miotto et al., 2006). Although these studies demonstrate that it is possible for older adults to make use of a memory strategy and that brain activation patterns can become more similar to that in young adults with use of a semantic encoding strategy, strictly speaking they have compared brain activity under different learning methods but without providing a clinical intervention.

Given the minimal evidence on neural changes following cognitive intervention in ageing and AD, it is of interest to consider what information is available regarding the use of fMRI to evaluate outcomes of cognition-focused

interventions with clinical groups such as people with schizophrenia and people with traumatic brain injury (TBI). In an attempt to systematically study the neurobiological effects of cognitive rehabilitation of reading ability, two studies of people with acquired brain injury administered weekly 1-hour individual cognitive rehabilitation sessions over a period of 7 to 11 months (Laatsch & Krisky, 2006; Laatsch, Thulborn, Krisky, Shobat, & Sweeney, 2004). Participants were scanned prior to and following the intervention period while they engaged in a reading comprehension task that was similar to the exercises practised in the intervention. However, following the intervention, the participants each improved on different neuropsychological measures, and showed varying patterns of change in brain activity. Whereas some participants demonstrated overall increased brain activation, others showed a redistribution of activated areas, or an overall decrease in brain activity. Understandably, the participants varied in the location and extent of their lesions and in the length of time that had passed since the injury (between 2 and 29 months in Laatsch et al., 2004; between 3 and 22 years in Laatsch & Krisky, 2006). However, the great diversity in both neuropsychological and functional imaging findings in these studies casts doubt on the validity of the tasks used to assess treatment outcome, and the lack of homogeneity in brain activation patterns in participants following the treatment period also raises concerns regarding the reliability of the findings.

Wexler et al. (2000) trained participants with a diagnosis of schizophrenia on working memory tasks during four to five 30-40 minute training sessions per week for a period of 10 weeks. Prior to and following the intervention period, participants were scanned using a verbal working memory task they had practised on during the training period. After receiving the working memory training sessions, only participants who improved on the task showed higher activation in the left inferior frontal cortex. This area had been identified in a previous study by the same group as one that was activated in a verbal memory task in healthy subjects and showed reduced activation in people with schizophrenia (Stevens, Goldman-Rakic, Gore, Fulbright, & Wexler, 1998). However, behaviourally the overall task improvement at group level following the working memory training was non-significant, with only three participants showing a substantial increase in performance. The efficacy of the training can therefore be questioned. Moreover, no outcome measures to assess activities of daily living were reported, so that it is not possible to establish whether

effects of the training were transferable to daily life situations. In a second study aimed at improving working memory function in six people with schizophrenia through cognitive remediation therapy (CRT), information processing strategies were practised in 40 individual sessions spread over 12 weeks (Wykes et al., 2002). This study also included a control therapy group (n=6) and a group of healthy subjects (n=6). Although the study reported that half of the CRT group improved on neuropsychological measures tapping working memory, this improvement was based on a change in confidence intervals calculated for test scores pre and post treatment, and not in actual raw test scores. Neither the CRT group nor the control therapy group showed any improvement in performance on the working memory task used in the scanner. With regards to changes in brain activation prior to and following treatment, a repeated measures multivariate analysis of variance showed an interaction between group and time, but none of these effects was driven by a difference between the CRT group and the control therapy group. Despite the absence of substantial evidence for the success or efficacy of CRT in this study, the authors concluded that the participants for whom CRT had been successful showed increased brain activation in areas associated with verbal working memory and that this was clearly associated with the received cognitive intervention.

If anything, the studies discussed here show that results from intervention studies are inconsistent. To establish biomarkers for cognitive intervention, it is necessary to determine the reliability of particular findings following the use of a given paradigm. From a methodological perspective, studies are needed that re-test a paradigm once it appears to yield a specific pattern of brain activity in a large number of subjects. Additionally, the effects of simply re-testing participants who have not received cognitive treatment need to be examined to ensure that any activation differences do not merely reflect practice effects, or the result of testing at two different time points. In practice this may be difficult as interests of researchers and funding bodies alike are more likely to focus on the development of new ideas and paradigms rather than verifying the reliability of existing methods. Nevertheless, this type of research seems essential to meaningfully look at intervention effects. Alternatively, studies could make use of carefully designed control conditions, such as the inclusion of a placebo therapy group, to ensure specificity of the findings with regard to the efficacy of the experimental treatment. Next, studies examining neural mechanisms of treatment need to ensure the validity of their paradigm. Ideally, any

alterations on a neural level should be supported by a change in task performance on the paradigm. In addition, to avoid practice effects and present a strong argument in favour of therapy efficacy, researchers must choose a paradigm that addresses cognitive processes similar to those tackled in the intervention, while ensuring that the specific task used in the scanner has not previously been used as part of the treatment. As argued in an earlier section of this review, it is important that a paradigm bears resemblance to everyday situations in which the target client group experience difficulties. This allows for a demonstration of possible generalisability of the intervention effects to participants' daily life.

Can the above-mentioned studies aid us in developing a paradigm to assess memory-related neural changes following cognitive treatment in ageing and AD? Although they are informative to some respect, unfortunately they cannot. The designs utilised in these studies yield results that are as yet too inconsistent to serve as possible biomarkers of any particular type of intervention. Although the studies exploring activation changes following different instructions in healthy older adults have produced promising results and suggested that changes in brain activation patterns may occur following the use of a semantic encoding strategy, these studies did not employ a cognitive intervention and thus cannot demonstrate that healthy older adults show brain activation changes over time following a non-pharmacological intervention. The remaining studies did administer an intervention, yet differed greatly in terms of goals and approach from an intervention oriented at ameliorating episodic memory function. Finally, many of the studies discussed above have used the same paradigm in the scanner as that used during training, and thus it remains possible that they were to a certain extent evaluating automaticity of processing.

As the focus of the current review is specifically on identifying suitable paradigms to study associative memory in healthy ageing and AD in conjunction with cognitive intervention, the following section explores whether extant studies on face-name learning in healthy ageing, MCI and AD are useful when it comes to establishing an appropriate choice of paradigm for investigating this question.

USING NEUROIMAGING TO STUDY ASSOCIATIVE MEMORY IN HEALTHY AGEING AND AD

The use of fMRI in studying associative memory in healthy older adults and clinical populations brings into play a number of important methodological issues, for example task difficulty and the number of stimuli used. The paradigms that previous studies have employed, the groups that were compared, the success rate on the chosen task, and the findings in relation to their objectives will be considered. The main questions are:

1. Based on evidence from the included studies, what would be the optimal parameters of a face-name learning paradigm suitable for older people with MCI or AD?
2. What evidence is available about using such a paradigm to evaluate the effects of cognition-focused interventions?

Studies included in the review

A search of the PubMed and PsycInfo databases was conducted on 28 March 2008. The following search terms were combined: 'aging OR ageing', 'age difference*', 'Alzheimer*', 'mild cognitive impairment', 'associative OR relational learning', 'associative encoding', 'associative memory', 'associative retrieval', 'associative recognition', and 'fMRI OR imaging OR neuroimaging'. Studies were included if they used fMRI, if they included healthy older people, people with MCI, or people diagnosed with probable AD according to NINCDS-ADRDA criteria, or a combination of these groups, and if they focused on associative memory using a face-name learning paradigm. The search detected 46 published papers. Initial screening identified 14 apparently suitable papers. Upon further investigation, however, six papers had to be excluded from this selection. Reasons for exclusion were as follows. One of these was a behavioural study of associative memory in older people with cognitive decline and did not use fMRI (Collie, Myers, Schnirman, Wood, & Maruff, 2002). Diamond and colleagues (2007) used a face-name learning paradigm similar to Sperling et al. (2003a), but their aim was to study whether brain activation during encoding correlated with three neuropsychological measures in people with mild to moderate AD. Neither functional activation during the encoding process nor behavioural performance on the face-name task were discussed, which

resulted in this paper not meeting the inclusion criteria. Two other studies used picture-location pairs instead of face-name pairs to study functional activation related to associative memory in people with AD (Gould et al., 2006a; Gould et al., 2005), and another employed semantically related picture-word pairs (Hamalainen et al., 2007). Finally, a sixth study (Herholz et al., 2001) used positron emission tomography (PET), and included participants from a large age range, so that, given the rather small number of participants (n=11) in relation to the age span (26-72 years), it was difficult to draw any conclusions regarding possible effects of age on face-name learning. Consequently, eight studies remained that met the inclusion criteria. A description of these studies, including their objectives, participant samples, experimental tasks, success rates, and outcomes, is provided in Table 3.1.

Several methodological issues arise from these studies. In the next section matters relating to study design, experimental paradigm, and participant characteristics will be considered.

Using an event-related or a blocked design

The studies included in this review all used either a blocked or an event-related design. A blocked design offers the simplest way to compare the amount and the location of brain activity between, for example, a healthy control group and a patient sample in a given task. In an alternating blocked design, trials in a particular condition are grouped together and contrasted with a block of trials from another condition to identify brain regions specific to a particular task (Huettel, Song, & McCarthy, 2004). The majority of studies reviewed here used more or less the same alternating blocked design to study memory function in ageing and AD (Celone et al., 2006; Dickerson et al., 2005; Petrella et al., 2006; Petrella et al., 2007; Sandstrom et al., 2006; Sperling et al., 2003a), comparing brain activation during blocks of novel face-name pairs to that in blocks of familiar face-name pairs and blocks of fixation. The length of encoding blocks in these studies varied across studies, and lasted between 35 and 50 seconds. The blocked design in these studies is justified, as their main aim was to compare activation patterns between different groups.

Table 3.1 – Studies exploring face-name learning with fMRI in healthy older adults, and people with Alzheimer's disease and / or mild cognitive impairment

Study	*Objective*	*Participants*	*Paradigm*	*Success rate*	*Findings*
Celone et al., 2006	To investigate patterns of encoding-related brain activity across a continuum from healthy ageing to AD.	A total of 52 participants were included in the study: • 15 healthy older controls (mean age 75.5±6 years; 16.5±2.1 years of education; MMSE 29.5±0.5) • 15 people with MCI with a CDR sum-of-box score between 0.5 – 1.5 [low-SB group] (mean age 75.1±7.1 years; 17.1±2.6 years of education; MMSE 29.3±0.9) • 12 people with MCI with a CDR sum-of-box score between 2.0 – 3.5[high-SB group] (mean age 80±4.5 years; 15.3±3.7 years of education; MMSE 28.6±1.2) • 10 people with probable AD in accordance with NINCDS-ADRDA criteria (mean age 77.6±8 years; 12.5±2.8 years of education; MMSE 21.1±3.2) The AD group had a significantly lower education and MMSE score than the other three groups. The High-SB MCI group was significantly older than the other three groups.	The paradigm was very similar to that used by Sperling et al. in 2003 and also consisted of 84 novel and 2 repeated face-name pairs. There were there blocks of fixation between novel and repeated blocks, each lasting 25 seconds. Participants were instructed to try to remember the name associated with each face. For each face-name combination, they also were instructed to make a decision on whether the name 'fit' the face. Approximately 5 minutes after scanning participants performed two post-scan recognition tasks: a face recognition task and a forced choice associative recognition test. In the face recognition test, participants made 'old – new' judgments on 12 'old' faces, the two repeated faces, and eight novel faces. In the forced choice associative recoginition test (FCAR), another set of 12 'old' faces was shown, each paired with two names: the original name and another 'old' but incorrect name for that face. Subjects indicated the correct name by pointing to it on the computer monitor.	AD – face recognition 64.6%, FCAR 65.7% high-SB MCI – face recognition 75.3%, FCAR 87.0% low-SB MCI – face recognition 78.8%; FCAR 83.0% older controls – face recognition 74.8%; FCAR 87.7% On both tasks the AD group scored significantly lower than the other three groups.	A specific set of large-scale distributed brain networks is thought to mediate the process of associative encoding. There was a strong reciprocal relationship between the memory related activation in the hippocampus and deactivation of medial and lateral parietal regions. Also, the results provided support for a nonlinear trajectory of memory-related activation and deactivation over the course of prodromal AD. Subjects with very mild MCI demonstrated increased memory-related activation, as well as increased deactivation in a default network compared to older controls. Subjects with more impaired MCI showed decreased hippocampal activation compared to normal controls. These findings suggest that a widely distributed memory-network is altered in preclinical AD, and that there is an interaction between MTL and neocortical pathology.

Table 3.1, continued

Study	*Objective*	*Participants*	*Paradigm*	*Success rate*	*Findings*
Dickerson et al., 2005	To investigate whether hippocampal and entorhinal activation during learning is altered in the earliest phase of MCI, using fMRI	• 10 people with probable AD (NINCDS-ADRDA criteria); mean age 77.6±8.0 years; mean years of education 13.0±3.1; mean MMSE score 21.1±3.1; none were on cholinesterase inhibitors. • 9 people with MCI (CDR sum of boxes between 0.5 and 1.5); mean age 73.9±7.3; mean years of education 18.4±2.4; mean MMSE score 29.6±0.5. • 10 healthy older controls (OC); mean age 71.5±2.9 years; mean years of education 14.9±3.1; mean MMSE score 29.7±0.5. Educational level in the MCI group was significantly higher than in the other two groups. The MMSE score in the AD group was significantly lower than that of the MCI or the OC group.	Subjects viewed 84 novel face-name combinations and 2 repeated pairs, all presented for 5 seconds each, very similar to the earlier paradigm described in Sperling et al. (2003). The repeated pairs formed the control task. Subjects were instructed to try to remember which name was associated with which face for later testing. There is no mention of subjects practicing on the task prior to being scanned. There were six runs and each run lasted 4 min 15 sec, so that total scan time mounted to 25 min 30 sec. Approximately 5 minutes after the scanning session, subjects underwent a brief forced-choice recognition task for a subset of face-name pairs (14) presented in the scanner. Each face was shown with two names underneath: one that was previously paired with that face, and one that was previously paired with another face. Subjects indicated the correct name by pointing to it on the screen.	AD – 66.0% MCI – 85.0% OC – 87.0% There was no significant difference between the OC and the MCI groups, but both these groups performed significantly better on the task than the AD group.	Results show that MCI subjects with relatively mild cognitive difficulties show more hippocampal activation during a memory task compared to healthy older adults, but people with AD show less hippocampal activation compared to healthy ageing. The MCI group performed similarly to the OC group. The hyperactivation of the hippocampal formation in MCI could imply the recruitment of additional neural resources in response to AD pathology; a difference in processing strategy; a change in recruitment of other neocortical regions; or the increasing abnormality of mechanisms involved in plasticity. Even after correcting for volume, hippocampal activation was higher in MCI and diminished in AD, compared to the OC group. This finding is similar to results showing that individuals who are cognitively intact but are genetically at risk for AD show increased MTL activation. The results of the present study show that there is a phase of increased medial temporal activation early in the course of prodromal AD, prior to clinical dementia. This increase exists in the absence of MTL atrophy, suggesting that physiological changes may precede significant structural abnormalities in very early AD.

Table 3.1, continued

Study	*Objective*	*Participants*	*Paradigm*	*Success rate*	*Findings*
Pariente et al., 2005	To gain a better understanding of potentially compensatory networks during a memory task in AD compared to healthy older controls	• 12 people with probable AD (NINCDS-ADRDA criteria); mean age 70.9±6.4 years; mean years of education 12.9±2.3; mean MMSE score 25.1±1.8; none were on cholinesterase inhibitors. AD patients were selected by their ability to perform above chance on the paradigm. • 17 healthy older controls (OC); mean age 70.6±5.6 years; mean years of education 13.2±3.8; mean MMSE score 29.0±1.0. The AD group scored significantly lower on the MMSE than the OC group.	During event-related fMRI subjects studied a total of 48 face-name pairs. Images were acquired for both encoding and recognition. There were 12 face-name pairs in each study phase; each pair was presented for 6.4 seconds with an inter-trial interval of 0.1 second. Participants were instructed to associate the faces and names. Subjects were asked to press a key as soon as a new association appeared on the screen. Each study phase was followed by a test phase in which a face from the study phase was presented with four different names which had all been seen in the study phase. Subjects were asked to select the corresponding name using the keys on the response box. A distraction task was presented between study and retrieval phase to prevent rehearsal. The task was explained outside the scanner and there was a 20 minute practise session with different faces than those used in the actual task. There was another 10-minute practise session inside the scanner to ensure that all participants understood the task well. Task duration was 20 min 24 sec.	AD – 39.5%; range 15-22 out of 48 OC: 61.5%, range 18-38 out of 48 Although performance in the AD group was significantly lower than that of the OC group, patient accuracy was significantly above chance (25%).	The control group demonstrated activation in right hippocampus for correctly versus incorrectly encoded and recognised pairs. The right hippocampus was hypoactivated in the AD group for both encoding and recognition. The AD group, on the other hand, showed hyperactivation in parts of the parietal and frontal lobes. Even in young subjects, there is greater activation as the stimuli and the task become more complex. This effect has also been observed in subjects with neurodegenerative disease. It is believed that the hyperactivation in the AD group reflects successful compensation, and could indicate recruitment of additional cognitive resources or greater cognitive effort. However, the hyperactivation is thought not to be restricted to memory processes, but rather is linked with the involvement of a general attentional system.
Petrella et al., 2006	To assess abnormalities in brain activation patterns during encoding and retrieval in people with MCI, using 4 T fMRI	• 20 people with MCI; mean age 75.0±7.6 years; mean years of education 15.0±2.2; mean MMSE 26.7±1.5. • 20 healthy older controls (OC); mean age 71.2±4.5 years; mean years of education 15.9±2.9; mean MMSE 28.4±1.4. The MCI group scored significantly lower on the MMSE than the OC group.	The task was adapted from Sperling et al. (2003) and consisted of encoding and retrieval of 60 novel and two familiar face-name pairs, presented for 5 seconds each. Ten pairs were shown in each encoding block (four in one run: two novel, two familiar), followed immediately by a retrieval block (four in one run). In the retrieval block two faces were presented with one name beneath them. Subjects indicated via a button press which face the name belonged to. It is not mentioned whether the faces in the retrieval phase were novel or previously seen during the encoding phase. Each run (three in total) lasted 6.8 minutes, bringing the total scan time to 20 min 24 sec.	The MCI group scored significantly lower (60.0% correct) on the recognition task than the OC group (74.0% correct). There was no significant difference between the groups on the number of nonrecorded (missed) responses.	Results of this study show that both prefrontal and medial temporal lobe regions are activated by associative memory tasks in healthy older controls. The study also found activation in the parietal lobe and cerebellum, which is consistent with an earlier study involving memory in OC. The brain activation patterns during encoding and retrieval in this study were very similar, but there were slightly more extended areas in retrieval. Because both conditions required participants to make a button press, these extended activations cannot be attributed to response preparation.

Table 3.1, continued

Study	*Objective*	*Participants*	*Paradigm*	*Success rate*	*Findings*
Petrella et al., 2007	To identify brain regions in which memory-related changes in activation correlate with actual impairment in AD, MCI, and healthy older adults.	• 13 AD (6 females); mean age 71.2±6.8 years; mean education 12.7±2.3 years; mean MMSE 24.6±2.4. • 34 MCI (18 females); mean age 74.5±8.6 years; mean education 15.1±2.5 years; mean MMSE 26.7±1.9. • 28 older controls (14 females); mean age 72.0±5.0 years; mean education 16.3±2.8 years; mean MMSE 28.3±1.4. There were group differences in education and MMSE scores.	See Petrella et al. (2006).	Recognition scores for novel face-name pairs: AD: 46% correct MCI: 59% correct OC: 71% correct There was a significant difference in performance between the three groups.	fMRI signal decreased significantly across groups (OC > MCI > AD) in the left anterior cingulate and MTL regions. A significant increase across groups (OC < MCI < AD) occurred in posterior medial cortices as a result of progressive lack of deactivation in MCI and AD. Delayed recall scores obtained on a word learning list correlated positively with activity in left fusiform gyrus and negatively with activation in posterior medial cortices (PMCs). It is suggested that functional changes in PMCs may be a better marker for functional changes as a result of disease than MTL areas.
Rand-Giovannetti et al., 2006	To investigate the effects of repetition (a memory enhancing technique) during encoding on brain activation, especially hippocampal and neocortical regions, using event-related fMRI	12 healthy older adults; mean age 72.6 years (range 65-82); mean years of education unknown; mean MMSE score 29.5±0.7.	Subjects viewed a total of 40 face-name pairs, presented over 10 runs in a mixed event-related and blocked design. During encoding, each face-name pair was presented for 4.75 seconds and shown three times. All pairs were intermixed with a fixation cross. The presentation of the faces occurred in random order. Upon each presentation, the name was shown three times, to correspond with visual stimulus complexity during retrieval, where three names were presented. Subjects were instructed to view and remember the face name pairs. Recognition occurred immediately after presentation, and at a delay of 5 minutes. In the recognition blocks subjects were presented with a face paired with three names: the target name, a name previously paired with one of the other faces shown in that encoding block, and a distracter name not previously seen. The total scan time was 31 min 15 sec.	Immediate recognition – 94.3% Delayed recognition – 93.2% There was no significant loss of information over time.	The findings in this study suggest that the MTL memory system is largely preserved in healthy ageing. There was a striking difference in response between the hippocampus and neocortical areas to subsequent encoding trials. The neocortical regions were continually activated during repeated stimulus presentation, particularly in prefrontal and superior parietal cortices. Activation in these areas has previously been associated with maintaining complex attention. It was concluded that techniques that improve performance through repeated stimulus presentation may do so by modulating activation in neocortical attentional networks.

Table 3.1, continued

Study	*Objective*	*Participants*	*Paradigm*	*Success rate*	*Findings*
Sandstrom et al., 2006	To assess whether hippocampal atrophy confounds measurements of hippocampal activation in MCI using fMRI during encoding and retrieval. Activations in template-based and manually drawn regions of interest (ROIs) were compared.	• 20 MCI (8 females); 75±7.6 yrs; 15±2.2 yrs of education; mean MMSE 26.7±1.5 • 20 older controls (11 females; 71.2±4.5 yrs; 15.9±2.9 yrs of education; mean MMSE 28.4±1.4	The task was adapted from Sperling et al. (2003) and consisted of encoding and retrieval of 60 novel and two familiar FN pairs. Each pair was presented for 5 seconds. Ten pairs were shown in one encoding block, followed immediately by a retrieval block. In the retrieval block two faces were presented with one name underneath them, and subjects indicated via a button press which face the name belonged to. However, it is not clear whether the faces in the retrieval phase were novel of previously seen during the encoding phase. There were four encoding blocks (two novel, two familiar) and four retrieval blocks in one run. There were three runs in total. Each run lasted 6.8 minutes, bringing the total scan time to 20 min 24 sec.	Not mentioned in this paper. Since it appears to use the same data set as Petrella et al. (2006), it can be assumed that success rates are identical to the rates reported in that paper.	In disagreement with previous studies, the authors argue that increased activation in the hippocampus in very mild MCI is considered likely to be confounded by activation in the surrounding tissue. It is suggested that template-based analyses are useful when comparing across subjects with MCI. However, when comparing MCI subjects with healthy controls, template-based analysis may lead to confounds in activation patterns because activity in tissue in the MTL but outside the hippocampus may be included in the template.
Sperling et al., 2003a	Using fMRI to compare activation patterns during associative encoding in normal ageing and mild AD	• 7 people with probable AD (NINCDS-ADRDA criteria); mean age 80.6±6.9 years; mean years of education unknown; mean MMSE score 22.6±2.2; none were on cholinesterase inhibitors • 10 healthy older controls; mean age 74.1±7.3 years; years of education unknown; mean MMSE score unknown • 10 young controls; mean age 24.9±3.5 years	A total of 84 novel face-name pairs was presented in blocks of 7 pairs. Two familiar items were repeatedly presented. All stimuli were shown for 5 seconds. There were two novel blocks per run, along with two repeated blocks and two fixation blocks. In total there were six runs. Post-scan memory testing took place immediately after scanning. Twelve faces were presented: six from the Novel block, four distracter faces, and the faces from the repeated block. Subjects indicated whether they had seen the face before with a yes/no answer. If yes, they were asked to recall the name associated with that face. Participants were explicitly instructed to learn the faces and names for a later memory test at the start of the experiment. Each run lasted 4 min 15 seconds, bringing the total time in the scanner to just over 25 minutes.	Novel face recognition: AD 60%, OC 78%, YC 94%; Name recall: AD 12%, OC 40%, YC 58%. Young adults performed better than the older adults apart from the name recall for the familiar faces. There was a significant difference in name recall but not face recognition between the AD group and the older adults.	The AD group showed greater activation in precuneus and posterior cingulate, compared to the OC group. These regions show disruptions in resting state metabolism in AD and may demonstrate exaggerated activation during encoding following substantial neuronal loss in the hippocampus. Similar activation patterns for all three groups were observed in striate and extrastriate cortices, suggesting that people with AD can mount to a significant BOLD signal. Age differences in memory performance may be related to changes in frontoparietal regions involved in complex attentional processes, whereas changes related to AD seem to reflect changes in hippocampus and medial temporal lobe.

CDR = Clinical Dementia Rating scale; FCAR = Forced choice associative recognition; MMSE = Mini Mental State Examination; NINCDS-ADRDA criteria = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorder Association; OC = healthy older control participants; YC = young control participants.

Although a blocked design allows for the detection of active voxels, it cannot give a good estimate of the time course or the shape of the BOLD signal because it groups together all trials from one condition. It is also not possible to separate brain activation during successful and unsuccessful trials.

Two studies opted for an mixed event-related design (Pariente et al., 2005; Rand-Giovannetti et al., 2006). In both cases, the design was a mix between a blocked and an event-related design because, as it was a memory experiment, it was necessary to group trials into encoding and recognition blocks. An event-related design allows for post-hoc trial sorting, and gives a good estimation of the time course of the hemodynamic response (Huettel, Song, & McCarthy, 2004). The disadvantage of this type of design is that it may offer reduced detection power if the hypothesised hemodynamic response differs from the observed response. Moreover, in the memory studies discussed here, very similar events (face-name pairs) are presented at a rate of between 4 and 7 seconds. This requires that the inter-trial intervals (ITI) are of different lengths and that these different ITIs are interspersed with the target trials in a random fashion (Dale & Buckner, 1997). Without this so-called 'jittering' the hemodynamic response will saturate, making the series of events look like one block of trials. In addition, to be effective the jitter must be of sufficient length in relation to the BOLD response. Rand-Giovannetti and colleagues (2006) aimed to compare functional brain activation in response to repeated presentation of the face-name pairs, and therefore needed to be able to distinguish which trials were first and which were repeated presentations. Their paradigm was based on an earlier study in which ITI varied between 0.25 and 10 seconds with a mean of 2.84 seconds (Sperling et al., 2003b). However, in this study no specific details were given as to interval length between trials. Pariente et al. (2005) opted for an event-related design because one of their aims was to compare correctly and incorrectly recognised trials. However, it can be questioned whether the design actually allowed for trial separation. Each stimulus was presented for 6.4 seconds with an inter-trial interval of 0.1 seconds. This is extremely short for an event-related design, nor does it meet the criteria of jittered ITIs (Dale & Buckner, 1997). Thus, it is unclear whether activation in each separate trial truly reflected activity for that trial, or whether there was added activation from the hemodynamic response during the previous trial.

Studying encoding, retrieval, or both?

Many imaging studies of memory have focused on the encoding process, as did four of the studies reviewed here (Celone et al., 2006; Dickerson et al., 2005; Petrella et al., 2007; Sperling et al., 2003a). However, the remaining four studies explored activation patterns during both encoding and recognition (Pariente et al., 2005; Petrella et al., 2006; Rand-Giovannetti et al., 2006; Sandstrom et al., 2006). A significant advantage of this approach is that information is obtained for both memory processes, which can be especially useful in the field of AD where it remains unclear whether the impairments are more encoding-related or more retrieval-related (e.g. Greene, Baddeley, & Hodges, 1996). In addition, the approach allows for a comparison of brain activation in AD and healthy older controls during encoding as well as retrieval. Studying recognition processes in an event-related paradigm may also add to the understanding of successful retrieval or recognition in comparison to failure to recognise a set of items. As will be discussed later in more detail, activation patterns may be quite similar between groups if comparisons are made using only successful trials (e.g. Daselaar et al., 2003a). Exploring both encoding and retrieval processes may, nonetheless, come at the cost of the number of trials, and may involve prolonged task duration and longer time spent in the scanner. However, Pariente and colleagues provide an example of a study that focused on both encoding and retrieval in AD using a notably reduced number of stimuli (48 face-name pairs – compared to 84 pairs in, e.g., Sperling et al., 2003a), whilst maintaining sufficient statistical power, and managing to keep time spent in the scanner to a minimum (approximately 20 minutes). To date there are only a few studies available on this topic, and more research into functional changes in AD during associative memory processes is clearly indicated. To advance knowledge in this area it seems desirable to explore both encoding and retrieval processes in AD.

Choosing an appropriate reference condition

In order to identify patterns of functional brain activation related to associative memory, an appropriate reference condition is needed to allow for a contrast with the experimental task. The reference condition must provide similar visual input to the experimental task, but must elicit no, or much less, memory processing. Following the procedures used by Sperling and colleagues (2003a), the studies in this review have all opted for a control task in which two familiar face-name associations are

shown repeatedly. The familiarity is achieved by showing these face-name pairs to participants several times before the start of the experiment, for example in a practice session. Only two studies reported actually having tested recall and recognition memory for the repeated face-name pairs (Petrella et al., 2007; Sperling et al., 2003a). Petrella and colleagues found ceiling effects for recognition of familiar face-name pairs in their groups of healthy older adults and people with MCI (96% and 91% correct, respectively). The AD group correctly recognised the familiar face-name pairs on 80% of trials. However, Sperling et al. obtained a different result. Two out of ten healthy older adults in that study were unable to recall one of the names of the two repeated face-name pairs, which were shown 49 times each over the course of the experiment. Two out of seven people with AD failed to recognise one of the repeated faces, and their recall of the names of the repeated pairs was significantly lower than that of the healthy older adults. Such poor recognition despite the extensive repetition raises doubts about the engagement of participants during this reference task. If participants are not engaged, then this type of reference task may not be optimal. A reference condition that may be more engaging for participants is proposed in a study that explored face-name learning across a large age range using PET (Herholz et al., 2001). In this case, the reference condition required identification of gender. Participants viewed unfamiliar male and female faces labelled either 'male' or 'female', and decided for each pair whether or not the label was valid. Because a decision needs to be made upon viewing each stimulus, this reference condition may ensure that participants are actively partaking in and directing their attention to the task, while also providing a valid contrast condition for the experimental task.

Testing memory for associations

A wide variety of retrieval tasks was used in the selected studies, ranging from free recall of names – in which people with AD only scored 12% correct (Sperling et al., 2003a) – to forced-choice of one out of a number of names to match a particular face (e.g. Celone et al., 2006; Pariente et al., 2005). The difficulty levels of these retrieval tasks vary considerably, and they tap into very different memory processes. It has been suggested that, when studying associative memory, care must be taken at the retrieval stage to ensure that recollection of the association and not of a single item is promoted (Naveh-Benjamin, 2000). For example, free recall of a name associated

with a particular face requires the initiation of an unstructured memory search, and while the face may serve as a cue, the memory tested in this case is arguably that for a single item. Naveh-Benjamin has proposed that to study associative retrieval, one must present participants with associations at encoding as well as retrieval. With respect to the studies included in this review, recognition paradigms have been used on a subset of the target stimuli (Celone et al., 2006; Dickerson et al., 2005; Sperling et al., 2003a) as well as on the full set of target items (Pariente et al., 2005; Petrella et al., 2006; Petrella et al., 2007; Rand-Giovannetti et al., 2006; Sandstrom et al., 2006). Thus, it is preferable if a *recognition* paradigm is used at the retrieval stage, either making use of a forced-choice paradigm with the target name in the presence of one or more distractor names, or presenting either intact or rearranged pairs that use items that have all been seen during encoding.

The role of instructions

All of the studies reviewed here have made use of intentional learning instructions which indicate that the associations are to be learned for a later memory test. Importantly, in most of the studies, participants were explicitly encouraged to study both the face and the name. The way in which participants are instructed to learn is known to affect their memory for the stimuli at the retrieval stage (Naveh-Benjamin, 2000; Troyer et al., 2006). In a study conducted with healthy older people, Troyer and colleagues (2006) showed that matching of faces and names was best when participants were aware that their memory for the faces and names would later be tested (intentional learning), compared to when participants were unaware of any later memory task (incidental learning). Besides intentional learning, recognition of the face-name combinations was best when participants had learned these through linking the semantic meaning of the name to a prominent feature in the face. For example, for a person named 'Ms. Rowe', the link might be 'This person's teeth are in a very straight row'. However, the advantage was only observed when the semantic association was generated by the participant, and not when it was provided by the experimenter. Naveh-Benjamin (2000) asked young and older participants to memorise either the font (perceptual), the meaning of the word (contextual), or both (associative), in a verbal learning task. Both groups performed better on a subsequent recognition test if they had been instructed during encoding to pay attention to the feature tested. Nevertheless, on the associative memory task young adults benefited

more than the older adults from the intentional instructions relative to incidental instructions. Whereas it seems quite clear that intentional learning instructions are beneficial to memory performance in healthy older adults, the same cannot be said for people with AD. In a study including people with AD, people with Parkinson's disease (PD), and healthy older adults, participants were expected to remember internally and externally generated words either with or without intent to remember these words for a later memory test (Barrett, Crucian, Schwartz, & Heilman, 2000). While the healthy older participants and those with PD recalled more words following intentional learning instructions, the opposite was true for people with AD. It must be added that the focus of this study was on memory for internally versus externally generated words and that the authors did not aim to test incidental versus intentional learning. On the contrary, another study specifically designed an *incidental* associative learning test (Visual Association Test) which successfully distinguished AD from other types of dementia with a high specificity (69%) (Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002). The findings indicate that incidental learning is impaired in AD at least as much as, and perhaps even more than, intentional learning. In addition, clinical studies aimed at improving memory performance in people with early-stage AD have yielded positive results using a variety of techniques under intentional learning conditions (Clare et al., 2000; Clare, Wilson, Carter, Roth, & Hodges, 2002). The above highlights the importance of giving intentional instructions at encoding.

Task difficulty

When comparing healthy and clinical participant groups, the question arises as to whether the experimental task needs to be adapted in order to achieve similar difficulty levels in each group. It has been suggested that in a memory task, brain activation differences in healthy older adults and people with AD may occur due to differences in task performance and effort (Gould et al., 2005). In an fMRI study of associative memory in which they adapted difficulty levels to individual participants' performance, Gould and colleagues found that during successful associative learning a network of frontal, parietal and occipital regions was activated in both healthy older controls and people with AD. They also reported group differences, but these were small and only detected at an uncorrected, liberal threshold. This approach seems very valuable in gaining a better understanding of brain activation patterns in

AD during a task that people with AD are able to perform with reasonable success. However, it does not tell us what neural processes account for difficulties that people with AD have with tasks that pose no problem for a healthy control group. The studies reviewed here have all opted for a design in which all participants engage in the same task. Clinical groups performed well above chance level in all studies that included a clinical sample (Celone et al., 2006; Dickerson et al., 2005; Pariente et al., 2005; Sperling et al., 2003a). Pariente and colleagues used an event-related design, which allowed them to compare performance for only the successfully encoded and retrieved items in the AD group and the healthy older control group. Given that all participants performed significantly better than chance, this method offers a good alternative to correcting for task difficulty. However, this method requires a sufficient number of successful trials, which may increase scan duration. In some studies a memory test was administered that included only a small subset of the learned associations (Celone et al., 2006; Dickerson et al., 2005; Sperling et al., 2003a). This makes it harder to draw inferences about how well participants performed on the task as a whole.

Number of stimuli

As noted earlier, some fMRI studies investigating face-name learning in AD have used relatively large stimuli sets of, for example, 60 (Petrella et al., 2006; Petrella et al., 2007; Sandstrom et al., 2006) or even 84 face-name associations (Celone et al., 2006; Dickerson et al., 2005; Sperling et al., 2003a). In contrast, neuropsychological tests aimed at assessing immediate recognition memory for faces have used smaller numbers of stimuli. The Faces subtest in the Wechsler Memory Scale (WMS-III; Wechsler, 1997) uses 24 stimuli to assess face recognition, while participants are required to study 50 faces in the Face recognition subtest of the Recognition Memory Test (Warrington, 1984). Although this latter number may seem similar to the 60 stimuli as described in some of the fMRI studies, note that the neuropsychological tests require people to encode single faces as opposed to face-name associations, which is an easier task to perform (Achim & Lepage, 2005; Naveh-Benjamin, 2000).

The striking differences in numbers of stimuli used raises the question as to what sort of task is feasible in an fMRI environment for people with AD. Surprisingly, participants in most of the included studies performed well above chance level in the case of associative recognition, even with the high number of

stimuli (Celone et al., 2006; Dickerson et al., 2005; Pariente et al., 2005; Petrella et al., 2006; Petrella et al., 2007; Rand-Giovannetti et al., 2006). One of the reasons for the overall high performance may be related to the generally high educational level of the participants in these studies. Mean number of years of education averaged across the included studies was 15.5 years for healthy older people, 16.0 years for people with MCI, and 12.8 years for people with AD (for details of the individual studies, see Table 3.1). This is somewhat higher than that of the average older population in the US and the UK. According to a survey assessing educational attainment in the United States, 73% of people aged 65 and over were high school graduates or equivalent (US Census Bureau, 2006), translating to 12 years of education. In England, a government survey showed that 64% of people aged 55-64 has had 12 years or less of formal education; more than half of this group obtained no qualifications and thus may have left school after 10 or even 8 years of education (Department for Children, Schools, and Families, 2007). In Wales, where the research described here was conducted, 79% of people aged 60-64 had 12 years or less of formal education, and half of this group obtained no qualifications (National Assembly for Wales, 2006). Besides issues relating to educational level, Pariente and colleagues explicitly indicated that they only included participants who were able to perform the task above chance level in a test session prior to scanning. While it can be desirable in terms of efficacy and costliness to include very able participants, it remains difficult to imagine that such challenging paradigms could be performed by the average older population or by the full range of people typically seen by clinicians in routine clinical practice.

DEVELOPING AN EVIDENCE-BASED FACE-NAME LEARNING PARADIGM FOR PEOPLE WITH AD

From previous studies that have used face-name learning in the scanner, it can be concluded that it is useful to study both encoding and retrieval processes. An engaging task should be used as a reference condition to ensure participants' interest in and attention to the task. Recognition rather than free recall should be tested to assess memory for associations so as to ensure recollection of the association instead of a single item. When participants are aware that their memory is being tested their performance tends to be better than when learning occurs incidentally; thus

instructions need to make clear that the information to be learned needs to be recalled later on. Task performance needs to be above chance level to ensure that participants understand the task and are engaging in memory processing. It has been pointed out earlier that stimulus sets in some fMRI studies are very large and that a small number of face-name pairs may be more feasible for people with AD. The existing paradigms to study associative memory in AD in an fMRI environment do not seem easily reconcilable with the cognitive abilities of the average population.

To overcome the above-mentioned issues, a face-name learning task was designed that could be used to evaluate treatment effects in groups that are representative of people with AD seen in routine clinical practice. First of all, it was established what number of stimuli can be presented to this group of people in order to yield a reasonable, above chance level, performance. A pilot task was carried out with 16 people with various types of dementia (AD, Vascular dementia, and mixed AD / vascular dementia) who were attending a Memory Clinic or a Day Hospital in a rural area of the UK. Characteristics and performance of this pilot sample are shown in Table 3.2.

Table 3.2 – Characteristics and success rates of the pilot sample (n = 16)

female / male	10 / 6
Mean age in years ± SD	76.9 ± 7.7
Mean education in years ± SD	9.8 ± 2.4
Mean MMSE score ± SD	23.9 ± 4.2
Mean success rate two-item version	.65 *
Mean success rate three-item version	.49
Mean success rate six-item version	.52

MMSE = Mini Mental State Examination (score out of a possible 30 points); SD = standard deviation; * = significantly different from the other conditions at $p < .05$

Initially, three versions of a face-name learning task were generated, each version varying with regard to the number of stimuli presented (two, three, or six face-name pairs). Participants were instructed to try to learn which name and face went together. They were aware that they would later be tested on what they had learned. Performance was best when two face-name pairs were presented. Consequently, the two-item face-name association task was adapted for use in an

fMRI environment. A description of the stimuli, procedure, and image acquisition of the proposed paradigm is presented below.

The face-name association paradigm

Stimuli: Figure 3.1 shows an example of the stimuli and presents a schematic overview of the different conditions. A total of 12 grey scale pictures of Caucasian faces (6 males, 6 females, aged between 20 and 70 years) was obtained from the AR Face Database (Martinez & Benavente, 1998). All were adjusted to match a size of 7*6 cm and were resized to 255*298 pixels at presentation. Each face was paired with a common two-syllable first name obtained from public lists on the internet of the most popular English names from each decade of the past century. Each face-name association was formed by a face centred on a black background with the first name printed in white below.

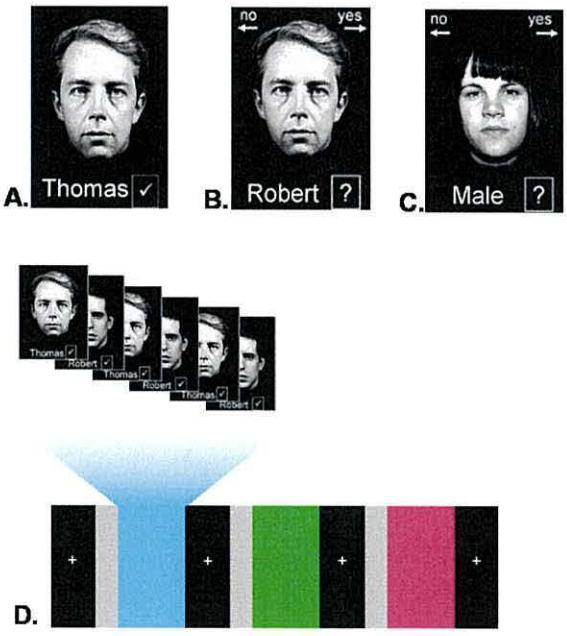

Figure 3.1 – Schematic representation of the face-name association task. Examples of the stimuli are shown in A. (encoding); B. (recognition); and C. (control task). D. represents one run which includes encoding (blue), recognition (green), and a gender control task (pink). The grey bars represent the instructions given prior to the start of each condition. The black bars represent the blocks in which a fixation cross was shown.

On each learning trial, the face-name association is accompanied by a box with a tick (✓) to stress that the face and name should be associated. All recognition trials are accompanied by a box with a question mark to elicit a response. The words 'yes' and 'no', together with an arrow pointing either to the left or right, are presented on the top right and left of the screen to aid participants in using the correct, previously identified button for responding. The paradigm will consist of six runs with three blocks each. Each block will start and end with a fixation dot in the centre of the screen. In each run, participants will be asked to perform three tasks: associating faces with names (Encoding), deciding whether a particular association is correct or not (Recognition), and making decisions on whether a face and a gender are correctly matched or not (Control). All faces together with either a name or a gender will be shown for 5800 ms with an inter-stimulus-interval of 200 ms. In the learning block, two face-name combinations will be presented three times in alternating order, bringing the total viewing time to 17400 ms per association. In the recognition block, six face-name combinations will be presented (three correct, three incorrect).

Procedure: A 10-minute training session will be conducted outside the scanner prior to the start of the experiment. During Encoding, an instruction will be given to try to learn which faces and names belonged together. In the Recognition phase, an instruction will be given to answer 'yes' if the face and name were paired during the encoding phase, and 'no' if they were not, via a button press. The associations will remain on the screen for the allocated time, regardless of whether a response is given. To avoid the introduction of novel stimuli, only the existing faces and names from the preceding learning block are used in a recognition block. The order of presentation is pseudo-randomised in that a face-name combination (either correct or incorrect) could never be directly followed by the same combination, and an equal number of correct and incorrect combinations will be presented. The control task block consists of one male and one female face with either 'male' or 'female' written below the picture (three correct and three incorrect combinations). Participants will be asked to indicate whether the combination of face and gender is correct by giving 'yes' and 'no' answers via a button press. The stimuli will be randomised as in the recall blocks. The control task will always be administered last in order to reduce task switching. Two different versions were created so that a different version can be used pre and post treatment. Functional images will be collected for six runs.

Following the functional image acquisition, once outside the scanner participants will be asked to view 48 pictures (12 from the FN task, 12 from the control task, and 24 novel pictures), and indicate by means of a button press on a laptop keyboard whether they have seen the face anywhere in the experiment or not. The order of presentation will be randomised.

CONCLUSION

As far as can be determined, fMRI has not been used as a tool to assess treatment outcome of cognition-focused intervention in healthy ageing, MCI, or AD. This is important because there is a need to understand more about neural mechanisms that underlie the potential success of cognitive interventions to understand what predicts a positive outcome of an intervention. This information may eventually be used to identify a priori which participants may benefit from a given cognitive intervention. The current evidence on the use of fMRI as a treatment outcome measure is as yet inconsistent and more attention should be directed at ensuring reliability and validity of a paradigm used to assess neural change over time. Careful scrutiny of cross-sectional studies employing face-name paradigms have revealed a number of important issues that such a paradigm might need to take into account. Based on this information, a simpler face-name association task has been presented, which yielded reasonable, above chance level performance in a pilot study with people with dementia. This suggests that the paradigm can be used both as a single measurement in time to compare different groups and as an evaluation of treatment effects.

Chapter 4 – Age differences in brain activation during a simple associative memory task

ABSTRACT

Associative memory function declines with age. Functional imaging can identify brain correlates of such cognitive decline, but may also detect changes in neural capacity before they manifest at the behavioural level. Using functional magnetic resonance imaging (fMRI), brain activation differences in healthy older and young adults were investigated while they studied and recognised face-name associations, and during a passive viewing task. Behavioural performance was comparable across the two groups. However, the older group showed higher activation in frontal and parietal areas and recruited a more widespread network of regions that was not activated in the young group. In addition, there was a qualitative difference in parietal and frontal midline areas with a trend to activation in the old and deactivation in the young group, which may indicate a different role of the default-mode network in the two groups. It is proposed that hyperactivation of cortical areas in the older group reflects the increased effort needed to attain similar task performance.

INTRODUCTION

Memory function, in particular episodic memory – the ability to recall events and newly learned information (Squire & Knowlton, 1995) – declines with increasing age (Gabrieli, 1996; Park et al., 2002; Schaie, 1994; Small, 2001). An important aspect of episodic memory, crucial to daily life situations, is the ability to link together two unrelated items of information, such as associating a name with a face. Older adults have disproportionate difficulty in recognition of face-name associations compared to recognising single faces and names, which is suggestive of a specific deficit in associative learning (Grady & Craik, 2000; Naveh-Benjamin et al., 2004). It has been suggested that age affects the capacity to recruit memory-related brain areas effectively (Logan et al., 2002) and that compared to their younger counterparts, older adults often show less asymmetric frontal lobe activation to support memory encoding (Cabeza, 2002). Functional magnetic resonance imaging (fMRI) presents a useful technique with which to study age differences in brain activity during encoding and recognition processes. Although behavioural evidence suggests that difficulties in memory performance are likely to originate in deficits at the encoding stage, few studies using neuroimaging techniques have directly compared encoding and recognition to determine whether age differences in brain activation are more pronounced during one or other of these processes. This has different implications for training strategies aimed at improving memory function in older adults. If age-related differences occur predominantly during encoding, older adults may benefit mostly from a strategy that capitalises on effectively memorising new information, for example by focusing on semantic aspects of that information. Conversely, if age differences are most pronounced during retrieval, then memory function in older adults may be improved by finding ways to offer more support when the information has to be retrieved from memory. Behavioural evidence suggests that retrieval is more impaired than encoding in older adults (e.g. Craik & Jennings, 1992). Despite this, functional imaging studies employing face-name paradigms to study age differences have focused largely on the encoding process (Ball et al., 2002; Miller et al., 2008; Sperling et al., 2003a).

In a study comparing healthy young and older adults to people with Alzheimer's disease during encoding of unfamiliar face-name associations, Sperling and colleagues (2003a) found that older adults showed greater activity in bilateral

superior and inferior parietal regions, but less activation in left superior prefrontal cortices in comparison to young adults, which may indicate age-related changes in a network involved in complex attention. Miller and colleagues (2008) focused on a network of regions that activated and deactivated during encoding of face-name associations in healthy young and older adults. They found that both groups recruited medial temporal lobe structures more or less to the same extent, but observed age differences in the amount of deactivation in parietal areas that are associated with a default-mode network of medial frontal and parietal midline regions that is more active during rest than during cognitive processes in young adults (Raichle et al., 2001). A third study examined the effects of repeated presentation (showing each face-name pair three times) on brain activation pattern during encoding in a group of older adults (Rand-Giovannetti et al., 2006). This study found an activation decrease after the first presentation of a face-name association only in the hippocampal formation, but not in frontal and parietal regions – these showed continued activation during further encoding trials. Again, it was suggested that age-related changes in brain activation affect attentional networks rather than classical medial temporal lobe memory areas.

As far as can be determined, no neuroimaging study has investigated age-related changes in brain activity during recall or recognition of face-name associations. Studies looking into age effects during retrieval of words found little difference in activation if young and older adults were compared on trials in which they had successfully retrieved a word (Daselaar et al., 2003a). Grady and colleagues (1995) also reported no age differences in brain activity during recognition of faces. Conversely, others have reported a more bilateral prefrontal pattern of activation in older adults compared to right-lateralised prefrontal activation during word retrieval in young adults (Cabeza, 2001; Cabeza et al., 1997).

In the current study, the aim was to explore age differences in memory performance using face-name associations. A face-name association task was chosen because a frequent problem reported by older people is forgetting people's names (Leirer, Morrow, Sheikh, & Pariante, 1990). Many studies investigating age differences in memory have used a task on which the young adults performed significantly better than the older adults. If task performance is not matched between groups, it becomes very hard to distinguish activation differences that are attributable to the factor of interest, age, from those associated with the performance difference,

such as failure to attend to or encode individual stimuli, frustration, or mind-wandering. Therefore, a relatively simple task design was chosen in order to match task performance in the older and young participants. Twelve young and twelve older adults were scanned while encoding and recognising face-name associations that were presented three times in total. It was expected that there would be less efficient memory processing in old compared to young controls, expressed in hyper-activation of frontal and parietal areas in older adults. Furthermore, the study investigated whether age differences would be more pronounced in encoding or recognition processes, and whether older adults would recruit additional brain areas compared to young adults when performance level was controlled between the groups.

METHODS

Participants

Twelve young adults (10 females) and 12 older adults (5 females) participated in the study. Participants were matched for educational level, so that there was no significant difference in years of education between the groups ($t(22) = 1.074$, $p = .294$, *n.s.*). Mean age and mean number of years of education are summarised in Table 4.1.

Table 4.1 - Group characteristics

	Older adults	**Young adults**
Demographic characteristics	**N=12**	**N=12**
Mean age in years (SD)	71.2 (9.23)*	25.7 (5.10)
Mean years of education (SD)	11.3 (2.81)	12.5 (2.50)

* significantly different from the young group at $p < .001$, SD = standard deviation

The young adults were recruited from among students at Bangor University, and through a community participation panel. The older adults were either recruited through the community participation panel, or were the partners of people with Alzheimer's disease who took part in a separate study. The older adults performed

within the normal range (mean 28.8±.9) on a screening tool for cognitive impairment (Mini Mental State Examination; Folstein, Folstein, & McHugh, 1975). All participants were paid for participation. All participants had normal or corrected to normal vision and were not dyslexic. Written informed consent was obtained from each participant. Experimental procedures were approved by the research ethics committee of the School of Psychology, Bangor University.

Cognitive activation tasks

Participants performed two different tasks in the fMRI scanner: a passive viewing task in which they were asked to look at pictures of faces and scenes, and an experimental paradigm that included encoding and recognition of face-name associations as well as a control task that was similar in visual presentation and action (a button press) and required a decision regarding the stimuli, but did not involve memory processes. The passive viewing task was included as an extra control measure to ensure that no age differences existed in basic processing of visual stimuli. Both tasks are described in detail below.

Passive viewing task: A set of 60 pictures (20 male faces, 20 female faces, 20 outdoor and indoor scenes) was used in a passive viewing task. Pictures were obtained from the AR Face Database (Martinez & Benavente, 1998). All pictures were sized 255*298 pixels and presented in black and white, centred on a white background. During the task, participants viewed three blocks of pictures (Fixation, Faces, Scenes) which were presented five times in alternating order during one run. A schematic overview of the task is presented in Figure 4.1 below.

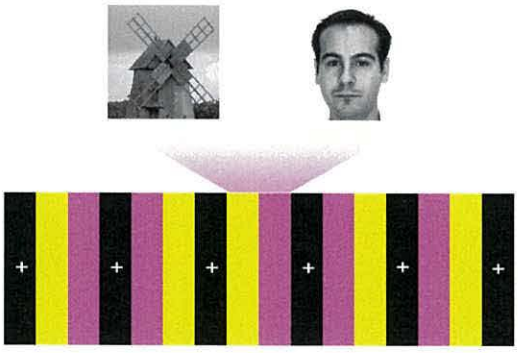

Figure 4.1 – Schematic representation of the passive viewing task. Each block represents a condition (fixation, faces, scenes) and had a duration of 16 seconds.

The Fixation block always preceded Faces and Scenes, while the order of the latter two was counterbalanced across the run. The Fixation block consisted of a fixation cross which appeared in the centre of the screen for 16 seconds. During the Faces and Scenes blocks, 32 pictures of either scenes or faces were shown in random order during 16000 ms (500 ms per picture).

Experimental paradigm: Twelve grey scale pictures of Caucasian faces (6 males, 6 females, aged between 20 and 70 years) were obtained from the AR Face Database (Martinez & Benavente, 1998). All were adjusted to match a size of 7*6 cm and were resized to 255*298 pixels at presentation. Common two-syllable first names were obtained from public lists on the internet of the most popular English names from each decade of the past century, and assigned to a face by the investigators. Each face-name association was formed by a face centred on a black background with the first name printed in white below. On each learning trial, the face-name association was accompanied by a box with a tick (✓) to stress that the face and name should be associated. All recall trials were accompanied by a box with a question mark to elicit a response. The words 'yes' and 'no', together with an arrow pointing either to the left or right, were presented on the top right and left of the screen to aid participants in using the correct, previously identified button for responding (for examples of the stimuli and a schematic representation, see Figure 4.2).

The experimental paradigm consisted of six runs with three blocks each. Each block started and ended with a fixation dot in the centre of the screen. In each run, participants performed three tasks: associating faces with names (Encoding), deciding whether a particular association was correct or not (Recognition), and making decisions on whether a face and a gender were correctly matched or not (Control). All faces together with either a name or a gender were shown for 5800 ms with an inter-stimulus-interval of 200 ms. In the learning block, two face-name (FN) combinations were presented three times in alternating order, bringing the total viewing time to 17400 ms per association. In the recognition block, six face-name combinations were presented (three correct, three incorrect).

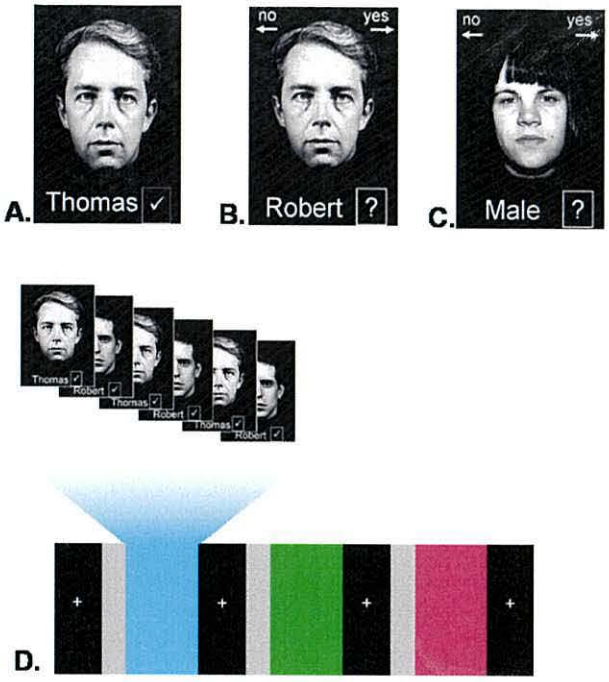

Figure 4.2 – Schematic representation of the face-name association task. Examples of stimuli used during Encoding (A.), Recognition (B.), and the Control task (C.). Figure 1D shows a schematic representation of one run with an Encoding block (blue), a Recognition block (green), and a Control task block (pink).

Procedure

The older adults received a 10-minute training task outside the scanner prior to the start of the experiment. Young adults received a short oral explanation of the task and were shown examples of the stimuli. During Encoding, participants were instructed to try and learn which faces and names belonged together. In the Recognition phase, participants were instructed to answer 'yes' if the face and name had been paired during the encoding phase, and 'no' if they had not, via a button press. The associations remained on the screen for the allocated time, regardless of whether a response was given. To avoid the introduction of novel stimuli, only the existing faces and names from the preceding learning block were used in a recognition block. The order of presentation was pseudo-randomised in that a face-name combination (either correct or incorrect) could never be directly followed by the same combination, and an equal number of correct and incorrect combinations were presented. The control task block consisted of one male and one female face with either 'male' or 'female' written below the picture (three correct and three

incorrect combinations). Participants were asked to indicate whether the combination of face and gender was correct by giving 'yes' and 'no' answers via a button press. The stimuli were randomised as in the recall blocks. The control task was always administered last in order to ensure the applicability of this paradigm in further planned studies including people with Alzheimer's disease (AD), as this sequencing would reduce confusion for memory-impaired participants. Two different versions were created, to which participants were randomly assigned. The order of the blocks and the hand with which participants were asked to answer 'yes' or 'no' were counterbalanced. After functional images had been collected for all six runs of the experimental paradigm, participants were scanned during one run of the passive viewing task. Following the functional image acquisition, once outside the scanner participants were asked to view 48 pictures (12 from the FN task, 12 from the control task, and 24 novel pictures), and indicate by means of a button press on a laptop keyboard whether they had seen the face anywhere in the experiment or not. The order of presentation was randomised. All stimuli were presented using NBS Presentation software for Windows XP on a Dell laptop. During functional image acquisition, stimuli were projected on a screen by an LCD projector connected to the laptop, and were viewed through a mirror attached to the head coil.

Image acquisition

All participants were scanned using a 1.5 T Philips scanner with a head coil for parallel imaging. Foam padding was used to reduce head motion. Functional images were obtained with a T2* weighted gradient echo sequence (TR = 2000 ms, TE = 40 ms, flip angle 90°, FOV = 192, 20 axial slices, 64 x 64 in-plane matrix, voxel dimensions 3 x 3 x 5 mm). A 3D anatomical T1 scan consisting of 150 slices (resolution 1 x 1 x 2 mm) was obtained for co-registration with functional data. The time per run was 3 min 46 sec for the experimental task (113 volumes) and 4 min 16 sec for the passive viewing task (128 volumes). Including the structural scan, the total time spent in the scanner was approximately 35 minutes.

Data analysis

Functional MRI data were pre-processed and analysed using BrainVoyager QX (Brain Innovation, Maastricht, The Netherlands). The first two volumes of each run were discarded to avoid differences in T1 saturation. All images were motion-

corrected and low frequency drifts were removed using a temporal high pass filter (0.0044 Hz). All data were spatially smoothed using a 4 mm FWHM Gaussian kernel. Temporal smoothing with a Gaussian kernel of 2.8 seconds FWHM was also applied to remove high frequency fluctuation. The functional data were manually co-registered with the three-dimensional anatomical scans and then resampled to isometric 3 x 3 x 3-mm voxels with trilinear interpolation. The 3D scans were transformed into Talairach space (Talairach & Tournoux, 1988). Subsequently, the co-ordinates of this transformation were applied to the co-registered functional data, which were resampled to 1 x 1 x 1 mm voxels.

For the passive viewing task, faces and scenes were contrasted to identify previously defined regions of interest in each individual. Face and scene predictors, obtained by convolving the respective blocks of the passive viewing paradigm with a two gamma hemodynamic reference function, were entered into a general linear model. Face- and scene-selective brain areas were identified by a *t*-test of this contrast. Based on previous literature (Epstein & Kanwisher, 1998; Kanwisher, McDermott, & Chun, 1997; Puce, Allison, Asgari, Gore, & McCarthy, 1996), regions of interest (ROIs) in the passive viewing task were defined as the right fusiform face area (FFA), the right occipital face area (OFA), and the left and right parahippocampal place area (PPA). The ROIs were defined by a set of contiguous significantly active voxels ($p < .0001$, uncorrected) within a 10 mm anterior / posterior, superior / inferior, and medial / lateral direction of the most significantly active voxel near the expected location in each individual.

All blocks in the experimental task were convolved with a standard two gamma model of the hemodynamic response function in order to obtain predictors for Encoding, Recognition, Control task and Reading Instruction. These were entered into a general linear model. For a between subjects analysis, whole brain, random effects group average activation maps were created and 2 x 3 analysis of variance with Age (Young, Old) as a between-subjects factor and Task (Encoding, Recognition, Control Task) as a within-subjects factor was carried out to examine possible interactions and main effects. Areas were considered significant at a level of at a threshold of $q < .005$ (FDR corrected for multiple comparisons) and with a minimum extent threshold of 100 contiguous active voxels.

Behavioural data were analysed using SPSS version 14.0 for Windows. Group differences in scores on the face-name task and the control task were explored using

a *t*-test. To analyse the post-scan recognition task data, a 2 x 3 mixed repeated measures ANOVA was used with Age (young, old) as a between-subject factor and Face type (studied faces, control task faces, novel faces) as a within-subject factor. Group differences were considered to be significant at $p < .05$.

RESULTS

Behavioural data

Experimental paradigm: Both the young and the older adults performed at ceiling level on the face-name association task and the control task. An independent samples *t*-test showed no significant difference in performance between the groups on either the face-name association task ($t(21)=1.723$, $p=.100$, *n.s.*) or the control task ($t(21)=.188$, $p=.852$, *n.s.*). Mean scores and standard deviations are presented in Table 4.2. Raw scores for each individual are provided in Appendix A.

Table 4.2 – Task performance on immediate and delayed recognition, and the control task.

	Older adults		**Young adults**	
	N=11[$]		**N=12**	
Task performance	**Mean correct score (± SD)**	**Mean raw score**	**Mean correct score (± SD)**	**Mean raw score**
Immediate recognition of face-name associations	.93 (±.09)	33 / 36	.98 (±.02)	35 / 36
Control task	.98 (±.03)	35 / 36	.97 (±.04)	35 / 36
	N=11[&]		**N=11[&]**	
Performance on post-scan recognition task	**Mean correct score (± SD)**	**Mean raw score**	**Mean correct score (± SD)**	**Mean raw score**
Face-name associations	.74 (±.16)	9 / 12	.83 (±.14)	10 / 12
Control task	.47 (±.18)	6 / 12	.59 (±.15)	7 / 12
Correct rejections	.78 (±.19)	19 / 24	.81 (±.12)	19 / 24
Total correct score on delayed recognition	.70 (±.09)	34 / 48	.76 (±.10)	36 / 48

SD = standard deviation; $ Responses for one older participant were not recorded due to technical failure of the button box used in the scanner; & Two participants (one young, one old) did not complete the post-scan recognition task because of time constraints.

Post-scan recognition task: The behavioural outcome on the post-scan recognition task was first explored by comparing scores for the three types of faces to be

recognised (faces from the face-name association task, faces from the control task, and novel faces) between the two age groups using a 2 x 3 mixed repeated measures ANOVA with 'Age' (old and young) as a between-subjects factor and 'Face type' (studied faces, control task faces, and novel faces) as a within-subjects factor. Recognition scores and standard deviations are presented in Table 4.2. Results showed a main effect of Face type ($F(2, 40) = 20.789$, $p < .001$). A paired samples *t*-test revealed that this effect was caused by a significantly lower recognition score for control task faces (mean .53 ±.17) compared to faces from the face-name learning task (mean .78 ±.15) ($t(21) = 7.771$, $p < .001$) and the correct rejection of novel faces (mean .79 ±.16) ($t(21) = 4.885$, $p < .001$). Notably, the recognition score for the control task faces did not differ significantly from chance (.5) ($t(21) = .828$, $p = .417$, *n.s.*), whereas the recognition score for faces from the experimental paradigm ($t(21)=8.801$, $p<.001$) and the score for novel faces ($t(21) = 8.760$, $p < .001$) were well above chance level. Subsequently, the recognition scores were collated into one total recognition score per age group. Although young adults achieved a slightly higher total recognition score than older adults, this difference did not reach significance ($t(20) = 1.591$, $p = .127$, *n.s.*). Both groups scored significantly above chance level (0.5; older group – $t(10) = 7.229$, $p < .001$; young group – $t(10) = 8.600$, $p < .001$).

Functional imaging data

Passive viewing task: Nine young adults and 11 older adults participated in this part of the study. To identify the ROIs in each individual subject, brain activation for faces was contrasted with that of scenes. The most significantly activated (peak) voxel near each previously described ROI was located. Subsequently, each individual's FFA, OFA, and PPA were defined by a set of contiguous significantly active voxels ($p < .0001$, uncorrected) within a 10 mm anterior / posterior, superior / inferior, and medial / lateral direction of the peak voxel. Beta values for faces and scenes for each participant were then extracted from these four ROIs. Talairach coordinates, cluster size, and statistical values for the peak voxels are presented in Table 4.3. Although significant voxels were present at the chosen threshold in the left and right PPA in all participants, no significant activation in the FFA in one older subject was detected, nor were significant voxels observed in the OFA in three older persons.

To explore whether there were any differences between the young and older adults in size of the ROIs (as defined by the number of significantly activated contiguous voxels around the peak voxel), the cluster sizes were entered into a 2 x 4 mixed repeated measures ANOVA with 'Age' as a between-subjects factor and 'Area' (right FFA, right OFA, right PPA, left PPA) as a within-subjects factor. There was a main effect of Area ($F(3, 42)=17.738$, <.001) and a significant Age by Area interaction ($F(3, 42)=5.314$, $p=.003$). Main effects of area are to be expected because PPA is commonly larger than FFA. A follow-up paired-samples *t*-test showed that the Age by Area interaction was caused by a cluster of significantly active voxels in the right FFA in the young adults that was nearly twice the size of that in the older group ($t(6)=4.075$, $p=.007$). Conversely, the cluster size in the right PPA was significantly larger in the older adults than in the young adults ($t(8)=4.620$, $p=.002$).

Table 4.3 – Overview of findings on the passive viewing task.

Region	Mean Talairach coordinates of most significant voxel			Mean number of active voxels in ROI	Mean T-value
	x	y	z		
Young group (n=9)					
Right FFA	40	-44	-15	611$^{\$}$	8.5893*
Right OFA	43	-70	-13	574	8.8564
Right PPA	25	-45	-9	582$^{\&}$	13.1568
Left PPA	-25	-49	-11	878	12.2888
Old group (n=11)					
Right FFA	38	-44	-18	346$^{\$}$	5.9890*
Right OFA	38	-66	-13	505	7.3666
Right PPA	23	-43	-10	811$^{\&}$	13.3123
Left PPA	-28	-46	-11	929	14.7987

*, $^{\$}$, $^{\&}$ groups significantly differ from each other at $p < .01$; FFA = fusiform face area; OFA = occipital face area; PPA = parahippocampal place area

Further analyses tested whether there were any group differences in activation patterns within the ROIs for faces or scenes. The beta-values extracted from individual subjects in each age group were compared using a 2 x 4 x 2 mixed repeated measures ANOVA with Age (young, old) as a between-subjects factor, and Area (right FFA, right OFA, right PPA, left PPA) and Stimulus (scenes, faces) as

within-subject factors. Significant main effects of Area ($F(3, 42) = 14.006, p < .001$) and of Stimulus ($F(1, 14) = 54.051, p < .001$) were found. As expected, there was also a significant Area by Stimulus interaction ($F(3, 42) = 771.371, p < .001$), as it is known that each ROI is more selective to one type of stimulus than the other. Although the activation in the young group (mean 1.16 ± 0.72) was slightly higher than that in the older group (mean 0.95±0.83), no significant main effect of Age was detected ($F(1, 14) = 1.286, p = .276$).

Experimental paradigm: The functional data were first entered into a 2 x 3 analysis of variance with Age (Young, Old) as a between-subjects factor and Task (Encoding, Recognition, Control Task) as a within-subjects factor. At the set threshold of $q < .005$ (FDR corrected for multiple comparisons) no areas were detected that showed a significant Age by Task interaction, or a main effect of Age. Eleven regions, mainly parietal and visual areas, showed a main effect of Task ($F(2, 44) = 11.19, p < .001$). Details of these structures are provided in Table 4.4. Follow-up paired *t*-tests showed that this effect was driven by the Control Task yielding the highest activation in most areas, followed by Encoding, and then Recognition. This was rather surprising as predictions were that the control task would be the easiest task, and behavioural results supported this idea.

Table 4.4 – Areas showing a main effect of Task (random effects analysis, $F(2, 44)=11.91, p < .001$, FDR corrected for multiple comparisons at $q < .005$)

Region	Hemi-sphere	BA	x	y	z	No. of voxels	T-value	p-value
Medial frontal gyrus	L	BA 10	-3	47	1	4665	26.909	$2.3266 \cdot 10^{-8}$
Superior temporal gyrus	L	BA 38	-42	17	-23	690	19.116	.000001
Insula	L	BA 13	-33	-10	16	916	21.171	$3.6229 \cdot 10^{-7}$
Hippocampus	L	-	-30	-25	-11	571	20.377	$5.4511 \cdot 10^{-7}$
Postcentral gyrus	R	BA 3 / 40	36	-25	46	531	24.093	$8.5789 \cdot 10^{-8}$
Inferior parietal lobule	R	BA 40	42	-34	43	735	18.250	.000002
Precuneus	L	BA 31	0	-73	28	1752	22.991	$1.4605 \cdot 10^{-7}$
Lingual gyrus	R	BA 18	3	-73	4	507	16.479	.000005
Lingual gyrus	L	-	-12	-73	-11	1241	19.035	.000001
Lingual gyrus	R	BA 17	18	-91	1	1602	19.312	$9.5392 \cdot 10^{-7}$
Lingual gyrus	L	BA 17	-15	-91	-2	4152	37.109	$3.6052 \cdot 10^{-10}$

BA = Brodmann Area; L = left; R = right

Despite the absence of an Age by Task interaction effect or a main effect of Age, regions within the brain that showed an age difference in encoding or retrieval were explored to investigate whether there was evidence for any age effects being more pronounced during encoding or recognition. Activation maps contrasting the two groups were created for each condition (Encoding, Recognition, Control task). For each contrast, areas were marked as ROIs if voxels were significantly activated at a threshold of $q < .005$ (FDR corrected for multiple comparisons) and if the minimum cluster size was 100 consecutive active voxels.

Encoding: Five small areas in which older adults showed higher activation than young adults were detected: right insular cortex, the left medial frontal gyrus, the left inferior parietal lobule, left thalamus, and right posterior cerebellum. Talairach coordinates, cluster sizes and statistical values of these areas are presented in Table 4.5. The older group appeared to involve these regions in task performance, while there seemed to be an absence of activation in the young group during encoding, as expressed by no significant difference from baseline (zero). Figure 4.3 presents anatomical locations and beta values during encoding for each group for each area. At the current threshold there were no regions in which the young adults showed higher brain activation than the older adults during encoding.

Table 4.5 – Between-group differences for encoding (random effects analysis, $t(46)=4.81$, $p < .001$, FDR corrected for multiple comparisons at $q < .005$). The one-sample t-test was carried out for each group separately.

Region	Side	BA	x	y	z	No. of voxels	T-value	One-sample *t*-test		
								t	df	*p*
Older adults > young adults										
Insula	R	BA 13	39	17	10	114	5.631	OC: 5.776 * YC: .563	11	OC: < .001 YC: .585
Medial frontal gyrus	L	BA 6	-6	-7	55	180	6.349	OC: 5.229 * YC: .888	11	OC: < .001 YC: .394
Thalamus	L	-	-3	-22	10	122	5.619	OC: 4.622 * YC: .783	11	OC: <.001 YC: .450
Inferior parietal lobule	L	BA 40	-42	-43	49	123	5.703	OC: 8.554 * YC: .666	11	OC: < .001 YC: .519
Pyramis	R	-	6	-73	-24	327	6.705	OC: 7.500 * YC: 3.283 *	11	OC: < .001 YC: .007
Young adults > older adults										
No significant differences at q <.005										

BA = Brodmann Area; L = left; R = right; OC = older adults; YC = young adults; * = significant at $p < .01$ (Bonferroni corrected for multiple comparisons)

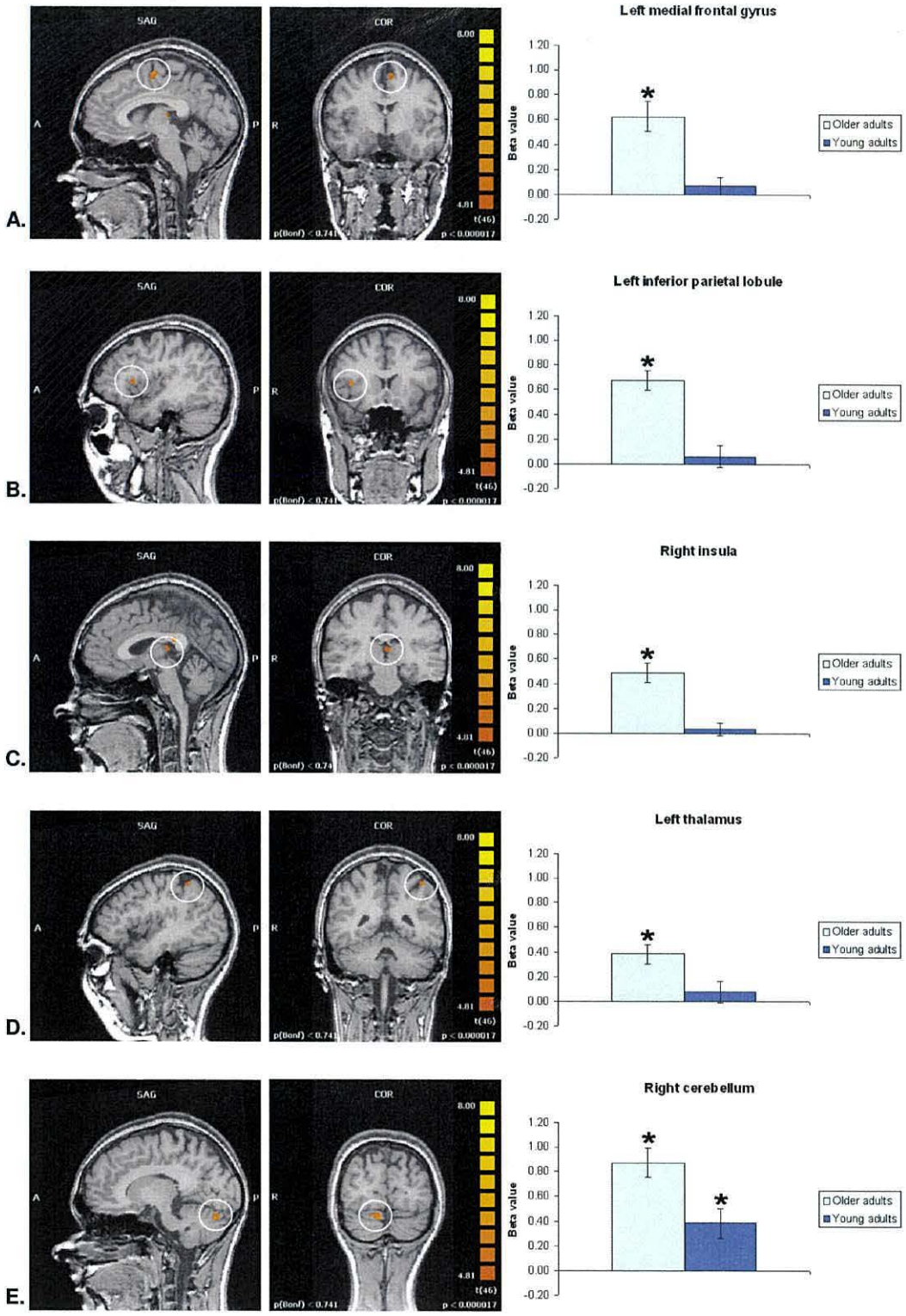

Figure 4.3 – Areas showing higher activation in the older group compared to the young group during encoding (A. left medial frontal gyrus; B. Right insula; C. Left thalamus; D. Left inferior parietal lobule; E. Right cerebellum). The asterisk marks beta values significantly different from baseline at $p < .01$ (Bonferroni corrected for multiple comparisons).

Recognition: The older adults showed higher activation than the young adults in a large number of predominantly left frontal and parietal areas. Location and size of the areas, as well as statistical values, are presented in Table 4.6. For each group separately, a one-sample *t*-test was carried out to examine whether brain activity in a particular region was significantly different from an artificial baseline (zero). Statistical values for this test are also shown in Table 4.6. Eight areas, including left middle and medial frontal gyri, and bilateral superior temporal gyri, were detected in which age differences were driven by a nonsignificant signal increase in the older group, coupled with a nonsignificant decrease in the young group. The left parahippocampal gyrus showed an increase for both young and older adults, but this increase did not reach statistical significance in either group. In the majority of brain areas showing higher activation during recognition for older than for young adults, the difference was caused by a significant signal increase in the older group coupled with an absence of significant signal change in the young group. The four most salient areas showing an age difference and the beta values for both groups during recognition (as identified by the highest T-values) are presented in Figure 4.4.

The young adults showed higher activation than the older adults in the left superior temporal gyrus and the right inferior parietal lobule. Talairach coordinates, cluster size and statistics are presented in Table 4.6. One-sample *t*-tests showed that differences in the left superior temporal gyrus were driven by an absence of significant brain activity in the young group coupled with a significant signal decrease in the older adults. On the contrary, activation differences in the right inferior parietal lobule were caused by a significant signal increase in the young adults and an absence of significant signal change in the older group. Details of the *t*-tests are also shown in Table 4.6.

Control task: No group differences were detected during the Control task.

WITHIN-GROUP ANALYSES

Within each group, a three-way analysis of variance was carried out to test for main effects of condition (encoding, recognition, control task). At the previously set threshold of $q < .005$ no significant clusters were detected in either group.

Table 4.6 – Between-group differences for recognition (random effects analysis, $t(46)=4.24$, $p < .001$, FDR corrected for multiple comparisons at $q < .005$). The one-sample t-test in the far right column was carried out for each group separately.

Region	Hemi-sphere	BA	x	y	z	No. of voxels	T-value	One-sample *t*-test		
								t	df	*p*
Older adults > young adults										
Inferior frontal gyrus	L	BA 45	-42	23	16	182	6.621	OC: 5.419* YC: 1.213	11	OC: < .001 YC: .251
Inferior frontal gyrus	L	BA 9	-42	5	34	237	5.660	OC: 7.460* YC: 5.308*	11	OC: < .001 YC: < .001
Middle frontal gyrus	L	BA 8	-24	20	37	140	6.085	OC: 4.118 YC: 2.635	11	OC: .002 YC: .023
Medial frontal gyrus	L	BA 6	-15	-13	49	1164	6.317	OC: 3.891* YC: 1.857	11	OC: < .001 YC: .002
Medial frontal gyrus	L	BA 6	0	-22	61	425	5.582	OC: 12.555 YC: 3.932	11	OC: .003 YC: .090
Cingulate cortex	L	BA 24	-6	8	37	224	5.281	OC: 5.693* YC: 3.359	11	OC: < .001 YC: .006
Cingulate cortex	L	BA 24 / 31	-6	-7	46	193	5.616	OC: 8.862* YC: 1.983	11	OC: < .001 YC: .073
Precentral gyrus	R	BA 4	18	-22	58	171	6.271	OC: 3.957 YC: .464	11	OC: .002 YC: .652
Precentral gyrus	R	BA 4	18	-28	55	237	5.117	OC: 2.996 YC: .994	11	OC: .012 YC: .342
Precentral gyrus	L	BA 4	-45	-16	37	124	6.130	OC: 5.503* YC: 2.505	11	OC: < .001 YC: .029
Precentral gyrus	L	BA 4	-27	-25	58	251	5.522	OC: 6.084* YC: .497	11	OC: < .001 YC: .629
Claustrum	L	-	-27	20	4	102	5.082	OC: 6.753* YC: 3.945	11	OC: <.001 YC: .002
Claustrum	L	-	-27	2	16	153	5.233	OC: 5.631* YC: 3.693	11	OC: < .001 YC: .004
Claustrum	R	-	27	-19	13	731	6.112	OC:12.231* YC: 2.815	11	OC: < .001 YC: .017
Thalamus	L	-	-18	-10	13	617	5.589	OC:16.302* YC: 7.738*	11	OC: < .001 YC: < .001
Superior temporal gyrus	R	BA 22	60	2	1	213	4.949	OC: 2.302 YC: 2.661	11	OC: .042 YC: .022
Superior temporal gyrus	L	BA 21	-63	-10	-2	308	5.399	OC: 2.531 YC: 1.974	11	OC: .028 YC: .074
Superior temporal gyrus	R	BA 22	45	-7	-2	614	6.060	OC: 2.986 YC: 2.572	11	OC: .012 YC: .026
Middle temporal gyrus	L	BA 21	-67	-16	-2	106	4.543	OC: 2.798 YC: .899	11	OC: .017 YC: .388
Postcentral gyrus	L	BA 43	-63	-7	19	788	7.182	OC: 6.775* YC: .904	11	OC: < .001 YC: .386
Postcentral gyrus	L	BA 43	-54	-16	16	191	5.226	OC: 7.439* YC: 2.524	11	OC: < .001 YC: .028
Postcentral gyrus	L	BA 3	-39	-22	49	377	5.676	OC: 8.559* YC: 1.958	11	OC: < .001 YC: .076
Postcentral gyrus	R	BA 3	36	-22	46	2475	7.621	OC:10.504* YC: 3.792	11	OC: < .001 YC: .003
Inferior parietal lobule	L	BA 40	-36	-34	49	136	5.525	OC: 6.489* YC: 2.944	11	OC: < .001 YC: .013
Paracentral lobule	R	BA 5	24	-37	46	783	7.978	OC: 5.887* YC: .028	11	OC: < .001 YC: .978
Parahippocampal gyrus	L	-	-24	-40	-14	111	5.133	OC: 3.480 YC: .246	11	OC: .005 YC: .810
Parahippocampal gyrus	R	-	24	-40	-5	246	6.093	OC: 6.642* YC: .125	11	OC: < .001 YC: .903
Young adults > older adults										
Superior temporal gyrus	L	BA 38	-36	15	-26	324	5.715	OC: 6.763* YC: .444	11	OC: < .001 YC: .665
Inferior parietal lobule	R	BA 40	54	-46	37	251	5.348	OC: 2.059 YC: 6.694*	11	OC: .064 YC: < .001

BA = Brodmann Area; L = left; R = right; OC = older adults; YC = young adults; * = significant at $p < .025$ (Bonferroni corrected for multiple comparisons)

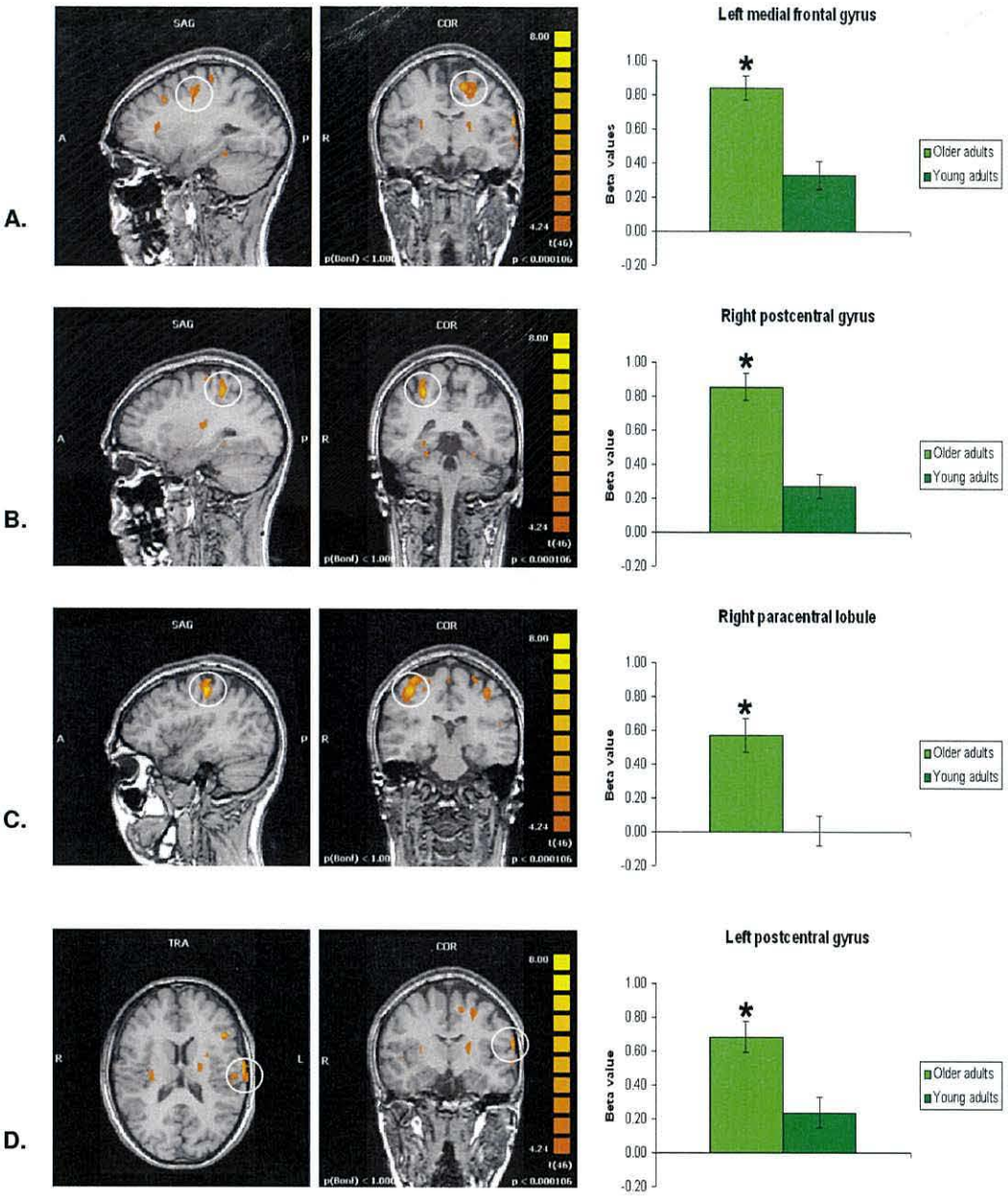

Figure 4.4 – Areas showing higher activation in the older group compared to the young group during recognition (A. Left medial frontal gyrus; B. Right postcentral gyrus; C. Right paracentral lobule; D. Left postcentral gyrus). The asterisk marks beta values significantly different from baseline at $p < .002$ (Bonferroni corrected for multiple comparisons).

DISCUSSION

The current study demonstrates greater brain activity in older than in young adults during a cognitively engaging task, but not during a passive viewing task. These effects were predominantly observed in frontal and parietal regions, and in parts of the fronto-striatal circuit. Age differences were most pronounced during recognition. No age-related differences were observed in the hippocampus. Behavioural performance was similar across the two age groups.

The finding of greater activation in predominantly inferior frontal and in parietal regions in older adults compared to young adults during an episodic memory task has been previously documented (Daselaar et al., 2003a; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Gutchess et al., 2005; Logan et al., 2002; Morcom et al., 2003; Sperling et al., 2003a), but the current findings of higher brain activation in the older group compared to the young group, coupled with the absence of any areas that are more activated for the young group compared to the older group, have not, as far as the author is aware, been reported before. Several explanations have been proposed to account for higher activation in older people. Although over-activation in older adults has been interpreted as being compensatory in nature (Cabeza, 2002), increased activation in older adults could also imply inefficient processing, dedifferentiation, or inability to inhibit task-irrelevant areas (Prvulovic et al., 2005; Reuter-Lorenz & Lustig, 2005). In addition, some of these studies have reported age differences in medial temporal lobe areas, which were less recruited by the older than the young adult group (Gutchess et al., 2005; Park et al., 2003; Sperling et al., 2003a). However, reduced memory performance related to alterations in brain activation in medial temporal areas has been linked to pathological ageing processes such as Alzheimer's disease, and is thought to be different to the main pattern of change in frontal and striatal areas commonly associated with memory difficulties in healthy ageing (Buckner, 2004; Hedden & Gabrieli, 2004). The age-related changes in a fronto-parietal network observed in the present study are broadly in line with previous literature (Gutchess et al., 2005; Logan et al., 2002) in which increased activation in the prefrontal cortex in the older group was also reported. Higher brain activation in parietal regions in the older adults compared to the young group was also observed by Sperling et al. (2003a), in a study that employed a similar, albeit more challenging, face-name learning

paradigm. Grady and colleagues (2006) reported a positive relationship between increasing age and higher brain activation in, among others, the left medial frontal gyrus and the left precuneus, two areas also showing higher brain activation for the older group in the present study.

Several possible explanations exist for the greater activation in older adults in this study. Firstly, a number of recent studies have suggested that older adults have difficulties in activating task-related areas appropriately, and in inhibiting areas that are irrelevant to the task (Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Grady et al., 2006). As such, higher activation in older adults may indicate failure to inhibit regions that are part of a 'default-mode' network that is active when the brain is not engaged in a goal-directed cognitive task (Raichle et al., 2001), and which consists of regions in the medial frontal cortex as well as lateral and medial parietal cortex (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Shulman et al., 1997). The current findings show that although there was no significant task-related signal deactivation in these areas in the young group, age differences did exist as a result of the older group showing a significant increase in activation. It has been suggested that older adults are less able to deactivate this 'default-mode' network during an active task with increasing age (Lustig et al., 2003). Inability of the older group to deactivate this network fully could explain part of the present findings. Areas of the default mode network are not normally recruited for processing of specific tasks (Raichle et al., 2001) and have been implicated in mind-wandering (Mason et al., 2007). They may thus represent the neural substrate of the cognitive reserve that is utilised for task processing in the older group.

Secondly, the right parahippocampal gyrus, specialised in the processing of scenes, showed higher activation in the older group compared to the young group during memory processing. However, no activation differences were found between young and older adults during passive viewing of faces and scenes in the areas specialised in the processing of these types of stimuli. Park and colleagues (2004) demonstrated decreased specialised neural response to images of faces and scenes during encoding in older adults in ventral visual areas (fusiform and parahippocampal gyrus) known to respond specifically to these particular stimulus categories in young adults. It has generally been argued that there is less neural specialisation (i.e. more dedifferentiation) with increasing age (Baltes & Lindenberger, 1997a). The present findings imply that the nature of the task

modulates activation in these visual areas. In the current study, the older group showed significant involvement of the right parahippocampal gyrus during encoding and recognition. The young group did not recruit this region at all for these tasks. If indeed neural specialisation differences between the age groups occur under high task demand, then the scene-specialised parahippocampal gyrus may respond to faces in the older but not the young group during cognitively demanding processes.

Finally, the findings of hyperactivation in frontal brain areas in older compared to young adults in the current study may indicate compensation for dysfunction in other regions. Gutchess and colleagues (2005) found increased activation for remembered compared to forgotten items in non-homologous prefrontal cortex in older adults compared to young adults, thus suggesting that this activation is indeed compensatory in nature. Interestingly, the increased prefrontal activity in older adults was negatively correlated with activation in the medial temporal lobe (MTL) in that same group, which would indicate that prefrontal areas may compensate for dysfunctional MTL activation. However, as Logan et al. (2002) point out, higher activation in prefrontal cortex may reflect nonselective recruitment of brain areas (activating areas not directly relevant to performance of the task), a process that occurs in older adults and cannot be reversed by varying the instructions so as to induce semantic encoding. Obviously, this does not rule out the possibility that the activation is compensatory, but it makes it likely that there may be other explanations for the increase. For example, Sperling and co-workers (2003a) concluded that there was an increase in activation in a fronto-parietal attentional network in older adults compared to young adults during the encoding of face-name associations. Support for this idea comes from a visual matching study with young adults, in which activation in mainly prefrontal regions increased as task difficulty was enhanced (Bokde et al., 2005; Grady, 1996). Thus, some of the age-related increases in frontal activation observed in the current study, in particular in those areas that are also involved in task performance in the young adults, could reflect more attention or effort employed by the older group during the experimental tasks to achieve a performance level similar to that of their young counterparts.

LIMITATIONS

One of the aims of the current study was to explore whether age differences might be more prominent during either encoding or recognition. Age differences in brain activation were minimal during encoding. The stimuli were repeated at encoding, and recognition instead of free recall was used to provide support for the older adults during both processes and minimise possible ageing effects due to enhanced controlled processing in the young group (e.g. Troyer et al., 2006). It has been suggested previously that ageing differences in memory performance stem from a failure in the older adults to efficiently recruit the appropriate brain regions during encoding without cognitive support (Daselaar et al., 2003a, 2003b; Logan et al., 2002). Thus, repeating the stimuli during encoding may have provided sufficient support for the older group to achieve similar levels of brain activation compared to the young adults. Daselaar and colleagues found no differences in brain activity between a young and an older adult group during recognition, so that the difference in performance between the groups was explained by differential strategy use during encoding. The current study found age-related hyperactivation and more widespread recruitment of areas in the older adult group, which suggests increased attention or effort put in by the older group to accomplish a performance level equivalent to that of the young group.

Both groups performed near ceiling level on the immediate recognition task in the present study. Excellent performance (> 90%) on a verbal recognition task in both a group of healthy young and older adults has been reported previously and was associated with very similar brain activation patterns between the two groups (Daselaar et al., 2003a). Nevertheless, it is possible that participants in the current study may have used a relatively small proportion of potential neural capacity during task performance, leaving more neural resources available for task-irrelevant cognitive processes such as mind-wandering. Neural capacity is generally assumed to be greater in young than in older adults (Hedden & Gabrieli, 2004), and as such there may have been more mind-wandering or other task-irrelevant brain activity in the young group. However, the present results do not support this idea. If more task-irrelevant processes occurred in the younger group, this would have been reflected in higher brain activity compared to the older group. The current findings show predominantly higher activation in the older adults compared to the young group.

The absence of any hippocampal activation in either group during encoding

and recognition of the face-name associations was unexpected. Hippocampal activation was anticipated as the hippocampus is thought to play a crucial role in associating unrelated items (Henke et al., 1997), and its involvement in face-name learning has been recorded previously (Sperling et al., 2001; Sperling et al., 2003b). However, in the current study the stimuli were presented repeatedly to assist the older group in encoding, which may have reduced hippocampal activation over the course of the six encoding trials. A recent study which also employed repetitive encoding in older adults demonstrated that hippocampal activation diminishes rapidly after the first stimulus presentation, while an attentional network consisting of inferior frontal and parietal areas continued to remain activated (Rand-Giovannetti et al., 2006). Thus, the repeated presentation time in combination with a blocked design makes it plausible that any hippocampal activation that occurred during initial presentation was levelled out with subsequent presentation of the same stimuli.

Conclusion

In conclusion, the current study demonstrates intact processing of visual stimuli during passive viewing, but hyperactivation in chiefly prefrontal and parietal areas in the older adult group compared to the young group when a cognitively effortful task was presented. Age effects were most pronounced during recognition. The hyperactivation in the older adults can be explained by several mechanisms that include failure to inhibit areas involved in a 'default-mode' network but are largely thought to reflect increased effort by the older group.

Chapter 5 – Functional activation changes in Alzheimer's disease may reflect a lack of efficient inhibition, not compensation.

ABSTRACT

Some neuroimaging studies suggest that during memory processing people with Alzheimer's disease (AD) show different patterns of brain activity compared to healthy older adults in order to compensate for AD pathology. In designing appropriate cognitive strategies to improve memory function in AD, it is important to understand if and how such compensatory activity might work. In the current study, 15 participants with early-stage AD and 12 healthy older controls (OC) were scanned during encoding and recognition of unfamiliar face-name associations, using functional magnetic resonance imaging. Participants also performed a control task that was similar in visual presentation and required motor output to the associative memory task, as well as a passive viewing task. Although the OC group scored significantly higher than the AD group on face-name recognition, all participants performed above chance level. Imaging results showed no group differences during the passive viewing task or the control task. During encoding of face-name associations the OC group showed higher activity in three small frontal areas. The largest group activation differences were observed during recognition. The OC group showed higher activation than the AD group in some frontal and insular regions, but the largest group differences were observed in posterior parietal areas in which the AD group showed higher activity than the OC group. These activations did not correlate with task performance and may therefore be a marker of a lack of efficient inhibition rather than compensating for loss of function in areas typically subserving memory function.

INTRODUCTION

The ability to link together two unrelated pieces of information, such as associating a name with a face, is an important function of episodic memory and is crucial in everyday situations. A decline in the ability to learn new associations is one of the earliest features of Alzheimer's disease (AD) (Fowler et al., 2002; Lindeboom et al., 2002). Functional magnetic resonance imaging (fMRI) data shows that compared to healthy older adults, people with AD demonstrate decreased activation in the hippocampus, a structure crucial to memory formation, during memory tasks (Dickerson et al., 2005; Machulda et al., 2003; Sperling et al., 2003a). It has been proposed that during memory processes compensational neural activity can occur in people with AD in response to neuronal loss in hippocampal regions (Buckner, 2004; Sperling, 2007). However, it is unclear exactly what constitutes a compensatory neural response in people with AD pathology. Some have argued that compensatory activity occurs in a more widespread network of regions in people with AD compared to controls, and may involve areas that do not normally play a key role in memory formation in healthy participants (e.g. Anderson et al., 2007; Becker et al., 1996; Grady et al., 2003; Pariente et al., 2005; Woodard et al., 1998). Specifically, the studies that reported recruitment of alternative brain areas in people with AD observed increased prefrontal activation, in some cases accompanied by an increase in activation in posterior parietal areas. Importantly, in their positron emission tomography (PET) study, Grady and colleagues were able to directly correlate activity in bilateral prefrontal and posterior parietal areas with better task performance, thus providing strong evidence that activity in the alternative areas supported memory processes. In contrast, other studies have found no support for the idea of a compensatory alternative network of brain areas, but have reported instead that people with AD show higher activation in the same areas as healthy older controls (Bäckman et al., 1999; Gould et al., 2006a; Gould et al., 2005). Of note, Gould and colleagues matched performance in the patient and the control group, and took into account only those trials in which successful memory formation occurred, to overcome effects of task difficulty. Taken together, these latter findings imply that neural plasticity in AD occurs through higher activation in a network of areas supporting memory function in healthy participants.

Understanding more about the way in which a compensatory mechanism might operate is of key importance in designing intervention strategies aimed at improving or maintaining memory function. If people with AD recruit an alternative set of brain areas to support memory function, then an intervention could focus on addressing this network. On the other hand, if people with AD make use of the same brain areas as healthy older adults, intervention could be targeted at making the most of residual function in the areas typically underlying memory processes.

In the current study fMRI was used to compare functional activation in people with AD and in a healthy age-matched control group during encoding and recognition of face-name associations. This type of task was chosen because, as noted above, associative memory is thought to be affected in the early stages of AD (e.g. Gallo, Sullivan, Daffner, Schacter, & Budson, 2004). Indeed, other imaging studies have administered similar tasks to a patient population (e.g. Pariente et al., 2005; Sperling et al., 2003a). However, these studies have used quite a challenging paradigm that included single viewings of 84 face-name combinations in which people with AD achieved a reasonable score for recognition of faces (around 60% correct) but a very poor score when asked to recall the name belonging to a face (12% correct)(e.g. Sperling et al., 2003a). Given the low success rate for the recall of face-name combinations, it can be questioned whether the activity observed in people with AD during learning reflects successful encoding. Moreover, recognising a face (as in Sperling et al., 2003a) does not indicate whether participants are able to recognise face-name associations. In the present study, we therefore opted for a blocked design in which the face-name associations are repeatedly presented to prolong study time. We also constructed a recognition task which challenged participants to recall the association. A behavioural pilot study, data from which are presented in Chapter 3, showed that this task was feasible for older adults with cognitive impairments.

Activation differences between people with AD and healthy older adults may be emphasised proportionately more during either encoding or retrieval processes. Behavioural evidence suggests that memory impairment in AD results mostly from deficits at encoding (e.g. Greene, Baddeley, & Hodges, 1996). In an fMRI study directly comparing brain activation during encoding and retrieval of face-name associations, Pariente and co-workers (2005) found the most prominent support for compensatory activation during encoding. In the present study, encoding as well as

recognition processes were explored to investigate possible recruitment of alternative brain areas in a group of people with early-stage AD compared to age-matched healthy control subjects.

Group differences were expected to be most pronounced during encoding. The expected outcome with respect to the existence of an alternative, compensatory network in the AD group may follow one of two possible patterns. If the AD group does indeed employ an alternative neural circuit compared to the control group, then we should see activation in the AD group in regions that are not recruited by the control group. On the contrary, if the AD group does not employ such a circuit, we expect to see activation in the same areas as the control group. If activation differences are compensatory in nature, then signal change in the AD group should ideally be positively correlated with behavioural performance. It is important to establish this link, because relating higher activation in alternative networks to improved performance provides support to the idea that the activation is helpful to the execution of the task. Alternatively, if the activation differences are not compensatory, then increased activation in the AD group might reflect failure of inhibition, perhaps as a result of the AD pathology. In this scenario, the activation observed in areas not recruited by the control group does not play a role in task performance and therefore it is unlikely that there is either a positive or negative correlation between this activation and task performance.

METHODS

Participants

Healthy older control group: Twelve healthy older adults (6 females) took part in the study. They were either the partners of the AD participants, or were recruited through a community participation panel. All participants in the Older Control (OC) group were paid for participation. The older controls scored within the normal range on a cognitive screening tool (range 27-30, mean score 28.8) (Mini Mental State Examination; Folstein, Folstein, & McHugh, 1975).

AD group: 15 people with AD (12 females) were involved in the study as part of their participation in an intervention trial, and were scanned during the initial (pre-intervention) assessment. Participants in the AD group were recruited through NHS memory clinics in North Wales. All participants in this group met NINCDS-ADRDA criteria for probable AD (McKhann et al., 1984). Patients were diagnosed by experienced psychiatrists who were not involved in the intervention programme. All participants in the AD group were on a stable dose of acetylcholinesterase (AChE) inhibiting medication for at least three months prior to participation. Inclusion criteria were the diagnosis of probable AD in the absence of any other neurological disease, a score of 18 or above on the Mini Mental State Examination (MMSE), on a stable dose of AChE inhibitors, and no current or past history of psychiatric illness or stroke.

Age, educational level, and MMSE scores for the two groups are summarised in Table 5.1. The two groups did not differ significantly in age or years of education. The older control group scored significantly higher on the MMSE than the AD group ($t(16.8) = 5.002$, $p < .001$). The degrees of freedom were corrected as Levine's Test showed that the assumption of equality of the variances was violated. All participants had normal or corrected to normal vision and were not dyslexic. Written informed consent was obtained from each participant. Experimental procedures were approved by the research ethics committees of the School of Psychology, Bangor University, and of the North West Wales NHS Trust.

Table 5.1 – Group characteristics

	OC group N=12	**AD group N=15**
Mean age in years (SD)	71.2 (9.2)	73.1 (8.3)
Mean years of education (SD)	11.3 (2.8)	10.0 (2.6)
Mean MMSE score (SD)	28.8 (0.9)	24.4 (3.3)*

* significantly different from OC at $p < .001$; SD = standard deviation; OC = older control; AD = Alzheimer's disease

Cognitive activation tasks

Passive viewing task: A set of 60 pictures (20 male faces, 20 female faces, 20 outdoor and indoor scenes) was used in a passive viewing task in which participants

viewed blocks of pictures (faces and scenes), interspersed with fixation blocks. This sequence was presented five times during one run. Details of the stimuli and the procedure are described in the previous chapter.

Experimental paradigm: A total of 12 grey scale pictures of Caucasian faces (6 males, 6 females) were shown in pairs of two over six runs. All faces were paired with a common Anglo-Saxon first name to form face-name associations. In each run, participants first associated each face with a name (Encoding), then decided whether a particular association was correct or not (Recognition), and finally made decisions on whether a face and a gender were correctly matched or not (Control task). The stimuli and procedure used in this task are described in detail in the previous chapter and will not be discussed further here.

Procedure

All participants received a 15-minute training outside the scanner prior to the start of the experiment. During Encoding, participants were instructed to try and learn which faces and names belonged together. In the Recognition phase, participants were instructed to answer 'yes' if the face and name had been paired during the encoding phase, and 'no' if they had not, via a button press. The control task block consisted of one male and one female face with either 'male' or 'female' written below the picture (three correct and three incorrect combinations). Participants were asked to indicate whether the combination of face and gender was correct by giving 'yes' and 'no' answers via a button press. The control task was always administered last to reduce task switching for the memory-impaired AD participants. After functional images had been collected for all six runs of the experimental paradigm, participants were scanned during one run of the passive viewing task. Following the functional image acquisition, once outside the scanner participants were asked to view 48 pictures (12 from the face-name association task, 12 from the control task, and 24 novel pictures), and indicate by means of a button press on a laptop keyboard whether they had seen the face anywhere in the experiment or not.

Image acquisition

All participants were scanned using a 1.5 T Philips scanner with a head coil for parallel imaging. Foam padding was used to reduce head motion. Functional images

were obtained with a T2* weighted gradient echo sequence (TR = 2000 ms, TE = 40 ms, flip angle 90°, FOV = 192, 20 axial slices, 64 x 64 in-plane matrix, voxel dimensions 3 x 3 x 5 mm). A 3D anatomical T1 scan consisting of 150 slices (resolution 1 x 1 x 2 mm) was obtained for co-registration with functional data. The time per run was 3 min 46 sec for the experimental task (113 volumes) and 4 min 16 sec for the passive viewing task (128 volumes). Including the structural scan, the total time spent in the scanner was approximately 35 minutes.

Data analysis

Functional MRI data were pre-processed and analysed using BrainVoyager QX (Brain Innovation, Maastricht, The Netherlands). The first two volumes of each run were discarded to avoid differences in T1 saturation. All images were motion-corrected and low frequency drifts were removed using a temporal high pass filter (0.0044 Hz). All data were spatially smoothed using a 4 mm FWHM Gaussian kernel. Temporal smoothing with a Gaussian kernel of 2.8 seconds FWHM was also applied to remove high frequency fluctuation. The functional data were manually co-registered with the three-dimensional anatomical scans and then resampled to isometric 3 x 3 x 3-mm voxels with trilinear interpolation. The 3D scans were transformed into Talairach space (Talairach & Tournoux, 1988). Subsequently, the co-ordinates of this transformation were applied to the co-registered functional data, which were resampled to 1 x 1 x 1 mm voxels.

For the passive viewing task, faces and scenes were contrasted to identify previously defined regions of interest in each individual. Face and scene predictors, obtained by convolving the respective blocks of the passive viewing paradigm with a two gamma hemodynamic reference function, were entered into a general linear model. Face- and scene-selective brain areas were identified by a *t*-test of this contrast. Based on previous literature (Epstein & Kanwisher, 1998; Kanwisher, McDermott, & Chun, 1997; Puce et al., 1996), regions of interest (ROIs) in the passive viewing task were defined as the right fusiform face area (FFA), the right occipital face area (OFA), and the left and right parahippocampal place area (PPA). The ROIs were defined by a set of contiguous significantly active voxels ($p < .001$, uncorrected) within a 10 mm anterior / posterior, superior / inferior, and medial / lateral direction of the most significantly active voxel near the expected location in each individual.

All blocks in the experimental task were convolved with a standard two gamma model of the hemodynamic response function in order to obtain predictors for Encoding, Recognition, and Control task. These were entered into a general linear model. For a between-subjects analysis, whole brain random effects group activation maps were created. Data were entered into a 2 by 3 analysis of variance with 'group' (OC, AD) as a between-subjects factor and 'task' (Encoding, Recognition, Control task) as a within-subjects factor, in order to detect any group by task interaction effects. We also compared activation in the two groups for encoding and for recognition to identify brain areas showing a difference specific to memory processes, using an independent samples *t*-test at a false discovery rate (FDR) corrected threshold of $q < .030$.

Behavioural data were analysed using SPSS version 15.0 for Windows. Group differences in scores on the face-name task and the control task were explored using an independent samples *t*-test. To analyse the post-scan recognition task data, a 2 x 3 mixed repeated measures ANOVA was used with 'group' (OC, AD) as a between-subjects factor and 'face type' (studied faces, control task faces, novel faces) as a within-subjects factor. Group differences were considered to be significant at $p < .05$.

RESULTS

Two AD participants only completed half of the experiment as they felt uncomfortable in the fMRI scanner. As they had only been presented with half of the stimuli, the post-scan recognition task was not administered to them. Two further AD participants did not answer any of the face-name recognition trials in one of the functional runs. These two runs were excluded from both behavioural and fMRI analyses as without the button press it is not possible to establish whether they were attending to the task. Recording of responses failed whilst scanning a healthy older participant. The functional data for this participant were included in the fMRI analyses because during the scanning procedure visual inspection by the experimenter verified that the participant was answering the questions.

Behavioural data

Experimental paradigm: Mean scores and standard deviations are presented in Table 5.2. Raw scores for each individual are shown in Appendix B. Performance scores for the face-name task (immediate recognition) and the control task for both groups were entered into a 2 x 2 repeated measures ANOVA with 'group' (OC, AD) as a between-subjects factor and 'performance' (recognition, control task) as a within-subjects factor. There was a significant group by performance interaction ($F(1, 24) = 11.489, p = .002$) and a main effect of performance ($F(1, 24) = 24.883, p < .001$) and group ($F(1, 24) = 21.597, p < .001$).

A follow-up paired samples *t*-test showed that the interaction was caused by the older control group scoring at ceiling level (> 90% correct) on both immediate recognition of face-name associations and the control task ($t(10) = 1.831, p = .097$, *n.s.*) while in the AD group performance on the control task was significantly higher than on the immediate recognition of faces and names ($t(14) = 5.297, p < .001$). An independent samples *t*-test showed that the older control group scored significantly better than the AD group on the face-name recognition task ($t(24) = 4.467, p < .001$) as well as the control task ($t(24) = 3.136, p = .004$).

A one-sample *t*-test carried out for each group separately showed that both groups performed significantly above chance level (.50) on immediate recognition of the face-name associations (OC: $t(10) = 12.783, p < .001$; AD: $t(14)= 1.947, p = .036$) and on the control task (OC: $t(10) = 36.922, p < .001$; AD: $t(14)= 14.512, p < .001$).

Post-scan recognition task: Recognition mean scores and standard deviations are presented in Table 5.2. An independent samples *t*-test revealed no significant difference between the groups in overall performance on the post-scan recognition task ($t(22) = 1.141, p = .266$, *n.s.*). Both groups scored significantly above chance level (.50) (OC group – $t(10) = 7.229, p < .001$; AD group – $t(12) = 5.882, p < .001$). We then explored responses to each type of face stimulus (studied faces, control task faces, novel faces) using a 2 x 3 mixed repeated measures ANOVA with 'group' (OC, AD) as a between-subjects factor and 'face type' (studied, control task, novel) as a within-subjects factor. Results showed a main effect of Face type ($F(2, 44) = 9.597, p < .001$). A paired samples *t*-test revealed that this effect was caused by a significantly lower overall recognition score for control task faces (mean .47 ±.25)

compared to faces from the face-name learning task (mean .67 ±.24) ($t(23) = 3.745$, $p < .001$) and the correct rejection of novel faces (mean .77 ±.19) ($t(23) = 3.766$, $p < .001$). Notably, a one-sample t-test revealed that the recognition score for the control task faces did not differ significantly from chance (.50) ($t(23) = .606$, $p = .551$, *n.s.*), whereas the recognition score for faces from the experimental paradigm ($t(23) = 3.508$, $p < .002$) and the score for novel faces ($t(23) = 6.794$, $p < .001$) were well above chance level.

Table 5.2 – Group performance

	OC group	**AD group**
Task performance (proportion of correct answers (± SD))	**N=11[$]**	**N=15**
Face-name associations	.92 (±.11)	.61 (±.21) *
Control task	.97 (±.04)	.87 (±.10) *
Performance on post-scan recognition task (Proportion of correct answers (± SD))	**N=11[&]**	**N=13[&]**
Faces previously associated with a name	.74 (±.16)	.61 (±.28)
Faces from the control task	.47 (±.18)	.47 (±.16)
Novel faces (correct rejections)	.78 (±.19)	.77 (±.20)
Total correct score	.70 (±.09)[@]	.65 (±.09)

SD = standard deviation; [$] Responses for one older participant were not recorded due to technical failure of the button box used in the scanner; * different from OC group at $p < .005$, [&] Three participants (one OC, two AD) did not complete the post-scan recognition task because of time constraints, and, in case of the two AD participants, because they only completed half of the functional runs; [@] OC performance on post-scan recognition task was different from OC performance on direct recognition of face-name associations at $p < .001$.

There was no significant difference between scores obtained on immediate (in the scanner) versus delayed (outside the scanner) recognition in the AD group ($t(12) = .394$, $p = .700$, *n.s.*), whereas the OC group showed a significant decrease in performance in delayed recognition compared to immediate recognition ($t(10) = 5.176$, $p < .001$).

During recognition, participants viewed a repetition of intact and rearranged items. Previous research has shown that recognition of rearranged items can lead to retroactive interference, i.e. the rearranged combination can be encoded as the correct association during recognition (Cleary, Curran, & Greene, 2001; Light, Patterson, Chung, & Healy, 2004; Perruchet, Rey, Hivert, & Pacton, 2006). To test whether lower performance on immediate recognition in the AD group was exacerbated by retroactive interference, mean scores from the first two recognition trials combined were compared to mean scores from the last four trials in a 2 x 2

repeated measures ANOVA with 'trial order' (first 2 trials, last 4 trials) as within-subjects factor and 'group' (OC, AD) as between subjects-factor. No Group by Order interaction ($F(1, 24) = .184$, $p = .672$, *n.s.*) or main effect of Order ($F(1, 24) = .001$, $p = .974$) was found. These findings suggest that retroactive interference is unlikely to have played a significant role during recognition in both the AD group and the OC group. See Appendix C and D for more detail on retroactive interference and a potential response bias in the AD group.

Functional data

BETWEEN-GROUP COMPARISON

Activation during passive viewing task: Nine people with AD and 11 older adults participated in this part of the study. To identify the ROIs in each individual subject, brain activation for faces was contrasted with that of scenes. The most significantly activated (peak) voxel near each previously described ROI was located. Subsequently, each individual's FFA, OFA, and PPA were defined by a set of contiguous significantly active voxels ($p < .001$, uncorrected) within a 10 mm anterior / posterior, superior / inferior, and medial / lateral direction of the peak voxel. Beta values for faces and scenes for each participant were then extracted from these four ROIs. Talairach coordinates, cluster size, and statistical values for the peak voxels are presented in Table 5.3.

Table 5.3 – Overview of findings on the passive viewing task.

Region	Mean Talairach coordinates of most significant voxel			Mean number of active voxels in ROI	Mean T-value	Beta value faces (mean ± SD)	Beta value scenes (mean ± SD)
	x	y	z				
AD group							
Right FFA	42	-47	-16	705	8.051	1.20 ± .68	.51 ± .62
Right OFA	42	-69	-9	839	7.543	1.48 ± .76	.97 ± .74
Right PPA	24	-49	-14	852	12.064	.52 ± .62	.51 ± .62
Left PPA	-26	-45	-14	579	11.064	.55 ± .43	1.18 ± .62
Older control group							
Right FFA	38	-44	-18	437	5.632	.78 ± .80	.35 ± .91
Right OFA	38	-66	-13	613	7.366	1.27 ± .30	.75 ± .35
Right PPA	23	-43	-10	891	13.033	.45 ± .37	1.14 ± .28
Left PPA	-28	-46	-11	948	14.022	.43 ± .29	1.15 ± .39

FFA = fusiform face area; OFA = occipital face area; PPA = parahippocampal place area; ROI = region of interest; SD = standard deviation; AD = Alzheimer's disease

The Talairach coordinates for the most significantly active voxels in the right FFA, right OFA, and bilateral PPA obtained in the present study are very similar to those reported in earlier studies (Peelen & Downing, 2005). Although significant voxels were present at the chosen threshold in the left and right PPA in all participants, no significant activation was observed in the FFA in one older subject, nor were significantly activated voxels detected in the OFA in three older controls and two people with AD.

It was investigated whether there were any group differences in activation patterns within the ROIs for faces or scenes. To this purpose, the beta-values extracted from individual subjects in each group were compared using a 2 x 4 x 2 mixed repeated measures ANOVA with 'group' (OC, AD) as a between-subjects factor, and 'area' (right FFA, right OFA, right PPA, left PPA) and 'stimulus' (scenes, faces) as within-subject factors. As can be expected, a significant area by stimulus interaction ($F(3, 39) = 92.134$, $p < .001$) was observed, as it is known that each ROI is more selective to one type of stimulus than the other. No other significant interactions or main effects were found (main effect of group: $F(1, 13) = 1.884$, $p = .193$, *n.s.*; main effect of area: $F(3, 39) = 1.902$, $p = .145$, *n.s.*; main effect of stimulus: $F(1, 13) = 3.199$, $p = .097$, *n.s.*; group by area interaction: $F(3, 39) = .564$, $p = .642$, *n.s.*; group by stimulus interaction: $F(1, 13) = 1.125$, $p = .308$, *n.s.*; area by stimulus by group interaction: $F(3, 39) = .923$, $p = .439$, *n.s.*).

Activation during experimental paradigm: The functional data were first entered into a 2 x 3 analysis of variance with 'group' (OC, AD) as a between-subjects factor and 'task' (Encoding, Recognition, Control Task) as a within-subjects factor. At the set threshold of $q < .030$ (FDR corrected for multiple comparisons) no areas were detected that showed a significant group by task interaction or a main effect of group. A large number of mainly medial frontal, posterior parietal, and occipital regions showed a main effect of task ($F(2, 50) = 8.04$, $p < .001$). Talairach coordinates, size and statistical values for areas showing a main task effect are presented in Table 5.4. Overall, this effect was caused by the encoding condition yielding significantly less activation than recognition ($t(26) = 3.801$, $p = .001$) and the control task ($t(26) = 3.652$, $p = .001$). There was no significant difference in activation between the recognition and the control task ($t(26) = .506$, $p = .617$, *n.s.*).

Table 5.4 – Areas showing a main effect of Task (random effects analysis; $q < .030$ (FDR corrected for multiple comparisons))

Region	Hemi-sphere	BA	x	y	z	No. of voxels	T-value	p-value
Middle frontal gyrus	R	BA 9	27	-4	49	1331	18.790	$8.2052 \cdot 10^{-7}$
Medial frontal gyrus	R	BA 10	10	47	-8	44	14.653	.000010
Medial frontal gyrus	L	BA 6	0	-1	58	52	10.244	.000187
Superior frontal gyrus	L	BA 6	0	11	46	628	15.100	.000007
Precentral gyrus	L	BA 6	-27	-10	49	110	10.619	.000143
Precentral gyrus	R	BA 6	30	-16	55	1879	16.497	.000003
Anterior cingulate	L	BA 32	0	44	1	318	11.029	.000108
Anterior cingulate	L	BA 24	-8	8	34	201	12.892	.000031
Paracentral lobule	L	BA 31	0	-16	49	2737	24.233	$4.3858 \cdot 10^{-8}$
Insula	R	BA 13	42	-4	10	177	11.499	.000078
Insula	L	BA 13	-36	-31	19	39	11.068	.000105
Insula	R	BA 41	39	-22	10	368	13.843	.000016
Putamen	R	-	24	-7	11	140	12.426	.000042
Thalamus	R	-	18	-10	16	40	9.913	.000237
Thalamus	L	-	-9	-19	13	1117	21.373	$1.9586 \cdot 10^{-7}$
Postcentral gyrus	R	BA 4	36	-22	46	1321	19.601	$5.1876 \cdot 10^{-7}$
Postcentral gyrus	L	BA 3	-36	-28	49	102	12.714	.000034
Postcentral gyrus	L	BA 2	-48	-28	37	540	16.156	.000004
Cingulate gyrus	L	BA 31	-12	-28	43	215	11.769	.000065
Posterior cingulate	L	BA 30	-6	-61	13	50	9.825	.000252
Superior temporal gyrus	L	BA 22	-55	2	-2	97	12.382	.000043
Middle temporal gyrus	R	BA 21	57	-31	-8	165	11.287	.000090
Middle temporal gyrus	L	BA 21	-66	-31	-11	121	11.492	.000078
Inferior parietal lobule	R	BA 40	51	-31	37	4023	29.267	$3.8461 \cdot 10^{-9}$
Inferior parietal lobule	L	BA 40	-36	-37	40	153	9.627	.000291
Inferior parietal lobule	R	BA 40	54	-43	28	667	19.033	$7.1440 \cdot 10^{-7}$
Inferior parietal lobule	L	BA 40	-39	-46	52	45	10.141	.000201
Supramarginal gyrus	L	BA 40	-39	-43	34	116	10.328	.000176
Fusiform gyrus	L	BA 37	-33	-37	-14	43	11.025	.000108
Fusiform gyrus	L	BA 37	-51	-58	-17	222	15.520	.000006
Precuneus	R	BA 7	24	-49	52	301	19.271	$6.2459 \cdot 10^{-7}$
Precuneus	L	BA 7	-3	-61	43	1296	21.362	$1.9702 \cdot 10^{-7}$
Superior parietal lobule	L	BA 7	-33	-67	50	33	11.092	.000103
Cuneus	L	BA 7	-3	-73	31	608	13.380	.000022
Cuneus	L	BA 18	-15	-73	16	210	15.540	.000006
Cuneus	R	BA 18/23	3	-73	13	1093	15.369	.000006
Middle occipital gyrus	R	BA 19	27	-79	19	113	10.397	.000168
Middle occipital gyrus	R	BA 18	21	-85	-5	910	13.102	.000027
Inferior occipital gyrus	L	BA 18	-30	-76	-5	70	12.432	.000041
Lingual gyrus	L	BA 17	-15	-91	-2	371	11.260	.000092

BA = Brodmann Area; L = left; R = right

Group differences

Subsequent analyses focused on regions within the brain that showed a group difference in the memory conditions. For both encoding and recognition, an activation map was created contrasting the two groups. For encoding, areas were marked as ROIs if activation exceeded a threshold of $q < .030$ (FDR corrected for multiple comparisons) and if the minimum cluster size was 30 consecutive active voxels. Activation patterns during encoding were very similar and only four small areas were found in which the OC group showed higher brain activity than the AD group. These were mainly located in left middle, medial and inferior frontal areas (for Talairach coordinates, statistical values, and size of the ROIs see Table 5.5; for anatomical position and graphical illustration of the data, see Figure 5.1). No areas were detected in which the AD group showed higher activation than the OC group.

Table 5.5 – Between-group differences during encoding (random effects analysis; $q < .030$ (FDR corrected for multiple comparisons))

Region	Hemi-sphere	BA	x	y	z	No. of voxels	T-value	p-value
ENCODING *OC > AD*								
Middle frontal gyrus	L	BA 6	-27	-10	40	254	4.934	.000009
Inferior frontal gyrus	L	BA 46	-36	35	7	208	5.159	.000004
Medial frontal gyrus	L	BA 6	-12	-22	46	182	4.685	.000021
Putamen	R	-	18	2	-2	637	5.699	$5.735 \cdot 10^{-7}$
ENCODING *AD > OC*								
No significant activation differences at the current threshold								

BA = Brodmann Area; L = left; R = right

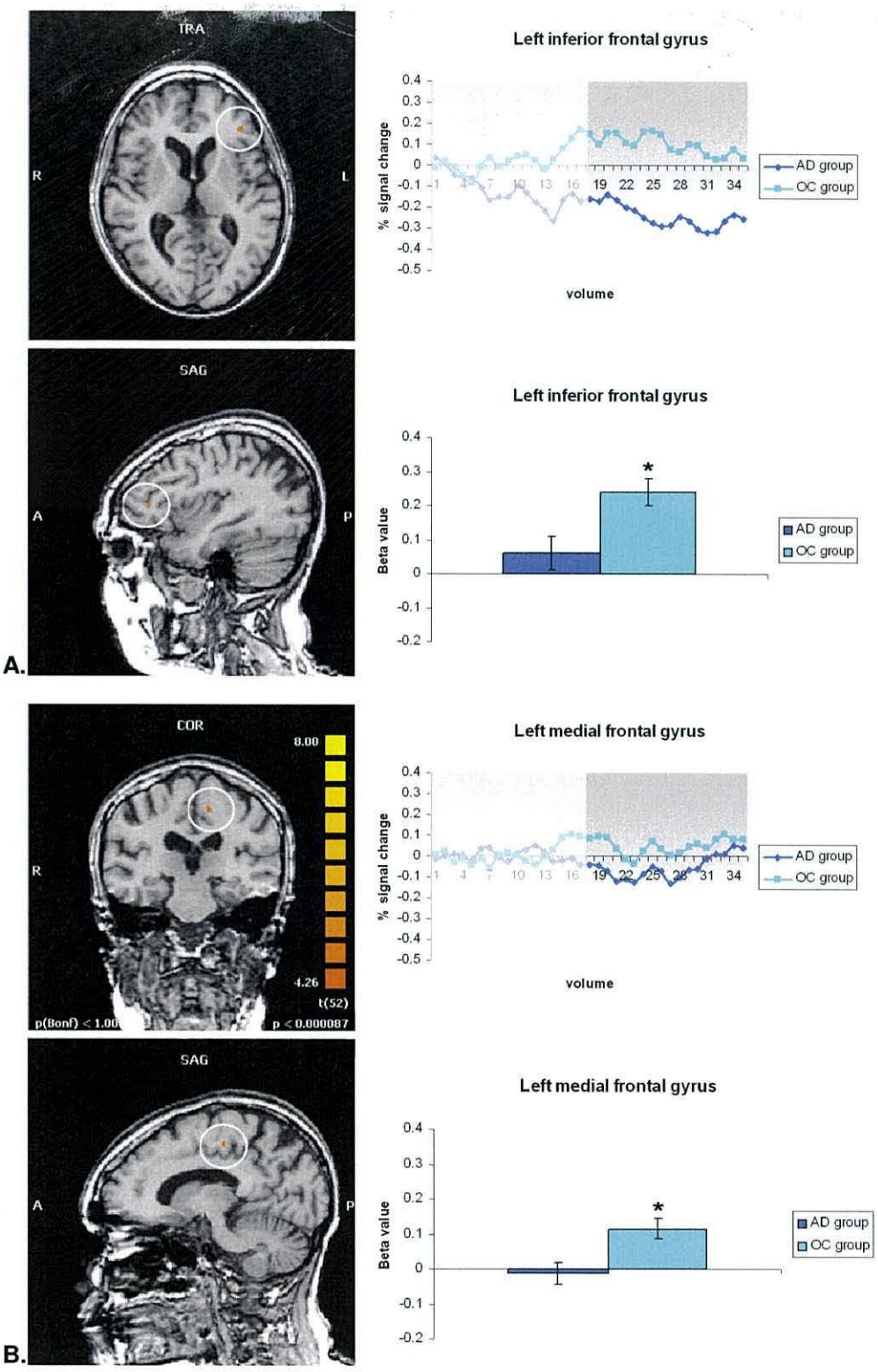

Figure 5.1 – Areas showing higher activation in the OC group than in the AD group during encoding (A. left inferior frontal gyrus; B. medial frontal gyrus; C. middle frontal gyrus; D. right putamen – C and D presented on the next page). Each anatomical area is presented in two views. The line graph demonstrates the signal change during encoding (volume 18-35) in that area. The bar graph represents the beta values for each group in that area. An asterisk indicates that beta values are significantly different from zero at $p < .05$. A = anterior side; P = posterior side; L = left side; R = right side; Sag = saggital view; Cor = coronal view; Tra = transversal view.

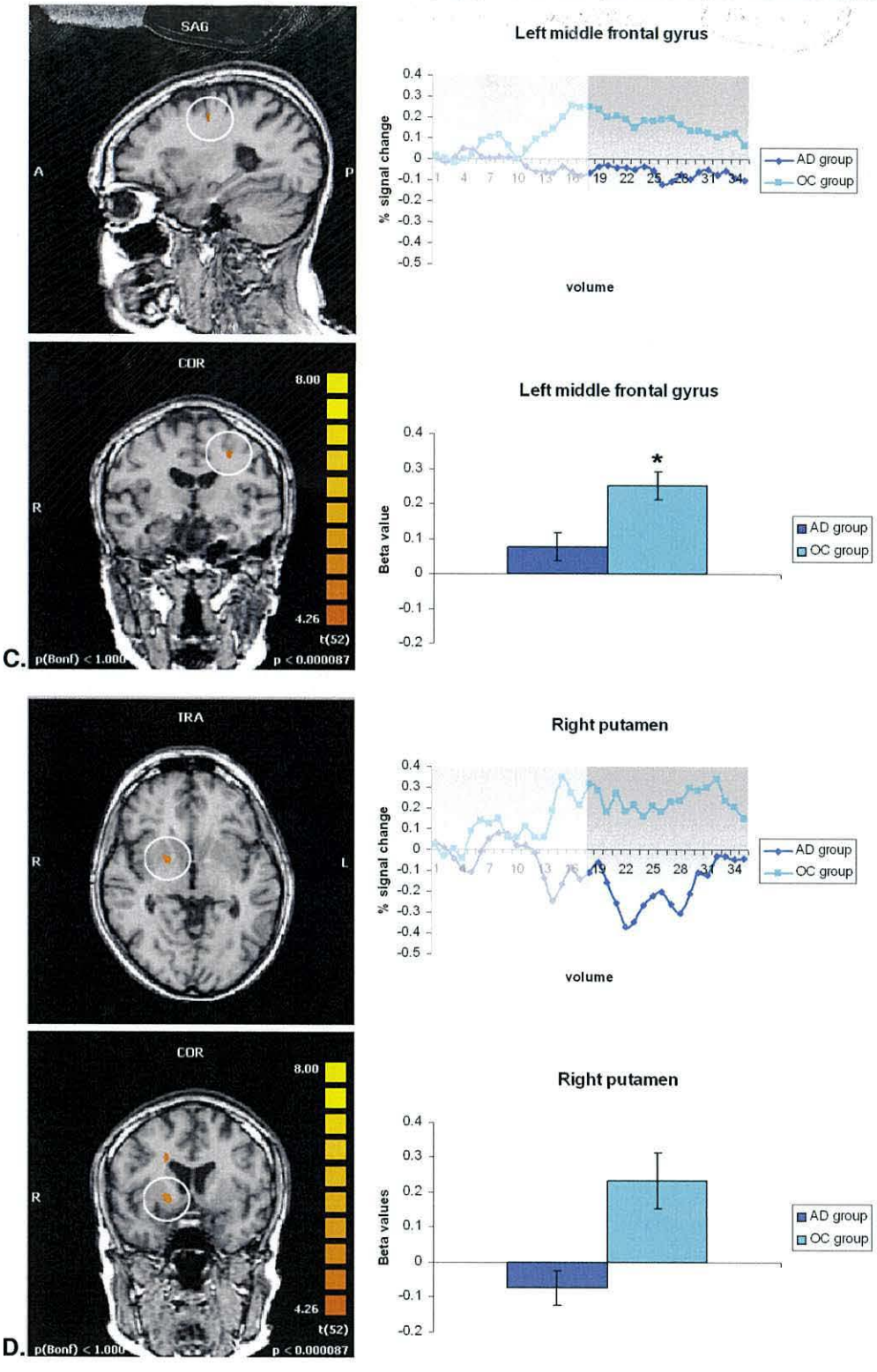

Figure 5.1 – continued

To explore the nature of the group differences during encoding, beta values for encoding from all participants were extracted from each ROI. A one-sample *t*-test was used for each group separately to establish whether activity patterns for the conditions significantly differed from baseline (zero). A Bonferroni correction was performed manually to correct for multiple comparisons (α =.0125). Although there is no true baseline in fMRI data, this procedure does give some information as to whether the group differences were caused by an increase or a decrease in signal change. During encoding, the older adult group showed a significant increase in the frontally located ROIs (left inferior frontal gyrus: $t(11) = 6.463$, p(Bonf.) < .001; left middle frontal gyrus: $t(11) = 6.623$, p(Bonf.) < .001; left medial frontal gyrus: $t(11) = 6.463$, p(Bonf.) = .001) but signal change in the right putamen was not significant ($t(11) = 2.774$, p(Bonf.) = .018, *n.s.*). The AD group showed no significant activations in any of the ROIs (left inferior frontal gyrus: $t(14) = 1.349$, p(Bonf.) = .199, *n.s.*; left middle frontal gyrus: $t(14) = 1.991$, p(Bonf.) = .066, *n.s.*; left medial frontal gyrus: $t(14) = .485$, p(Bonf.) = .635, *n.s.*; right putamen: ($t(11) = 2.774$, p(Bonf.) = .186, *n.s.*).

The recognition condition yielded more activation differences between the groups. Areas were again marked as ROIs if they exceeded a threshold of $q < .030$ (FDR corrected for multiple comparisons) and if clusters contained more than 30 consecutively active voxels. We detected 10 areas with higher activation for the OC group than the AD group. These included left inferior frontal gyrus (BA 46), bilateral insular cortex (BA 13), bilateral postcentral gyrus (BA 3/43), right posterior cingulate (BA 23), right fusiform gyrus (BA 37), and two clusters in the left culmen (Talairach coordinates, statistical values, and size of the ROIs are presented in Table 5.6. For anatomical position and graphical illustration of the data, see Figure 5.2). A considerably larger number of brain areas emerged in which the AD group showed higher activation than the OC group. These were largely located in inferior / posterior parietal regions bilaterally, and comprised bilateral inferior parietal lobule as well as the right supramarginal gyrus, cuneus, and precuneus. These areas, including coordinates, statistical values, and size of the ROIs, are also described in Table 5.6. For anatomical position and graphical illustration of the data, see Figure 5.3.

Table 5.6 – Between-group differences during recognition (random effects analysis; $q < .030$ (FDR corrected for multiple comparisons))

Region	Hemi-sphere	BA	x	y	z	No. of voxels	T-value	p-value
RECOGNITION *OC > AD*								
Inferior frontal gyrus	L	BA 46	-48	35	10	58	5.235	.000003
Cingulate	L	BA 24	-6	2	46	78	4.400	.000054
Insula	L	BA 13	-42	-19	4	63	5.096	.000005
Insula	R	BA 13	39	-19	13	44	4.267	.000084
Postcentral gyrus	L	BA 43	-54	-19	19	68	4.817	.000013
Postcentral gyrus	R	BA 3	36	-22	46	64	5.060	.000006
Posterior cingulate	R	BA 23	3	-31	22	30	4.421	.000050
Fusiform gyrus	R	BA 37	36	-43	-8	32	4.778	.000015
Culmen	L	-	-12	-31	-14	171	4.925	.000009
Culmen	L	-	-24	-34	-23	52	4.368	.000060
RECOGNITION *AD > OC*								
Middle frontal gyrus	L	BA 9	-30	29	34	39	4.539	.00034
Superior frontal gyrus	R	BA 8	18	17	46	601	5.307	
Prefrontal cortex	R	BA 44	48	5	10	518	5.376	.000002
Cingulate	L	BA 31	-6	-34	34	100	4.548	.000033
Claustrum	L	-	-30	-13	16	74	4.967	.000008
Caudate	R	-	18	-10	19	53	4.261	.000086
Caudate	R	-	36	-34	-2	88	4.547	.000033
Postcentral gyrus	R	BA 43	48	-10	22	77	4.244	.000091
Superior temporal gyrus	R	BA 41	36	-34	13	342	5.386	.000002
Paracentral lobule	R	BA 5	18	-37	52	34	4.374	.000059
Supramarginal gyrus	R	BA 40	54	-46	25	716	5.681	$6.113 \cdot 10^{-7}$
Inferior parietal lobule	R	BA 40	57	-34	31	375	5.583	$8.693 \cdot 10^{-7}$
Inferior parietal lobule	R	BA 40	48	-49	46	36	4.268	.000084
Inferior parietal lobule	L	BA 40	-39	-49	-56	108	4.879	.000010
Inferior parietal lobule	L	BA 39	-45	-64	37	315	5.009	.000007
Fusiform gyrus	L	BA 37	-48	-52	-20	223	4.939	.000009
Posterior cingulate	R	BA 29	3	-40	4	219	4.417	.000051
Posterior cingulate	L	BA 23	-3	-46	22	100	4.970	.000008
Posterior cingulate	L	BA 23	-3	-58	16	191	4.750	.000016
Superior parietal lobule	R	BA 7	12	-61	55	93	4.522	.000036
Cuneus	R	BA 7/19	6	-76	37	371	5.657	$6.668 \cdot 10^{-7}$
Precuneus	R	BA 31	9	-73	22	606	6.295	$6.560 \cdot 10^{-7}$
Lingual gyrus	R	BA 18	9	-70	4	149	5.053	.000006
Middle occipital gyrus	L	BA 19	-39	-67	7	399	4.963	.000008

BA = Brodmann Area; L = left; R = right

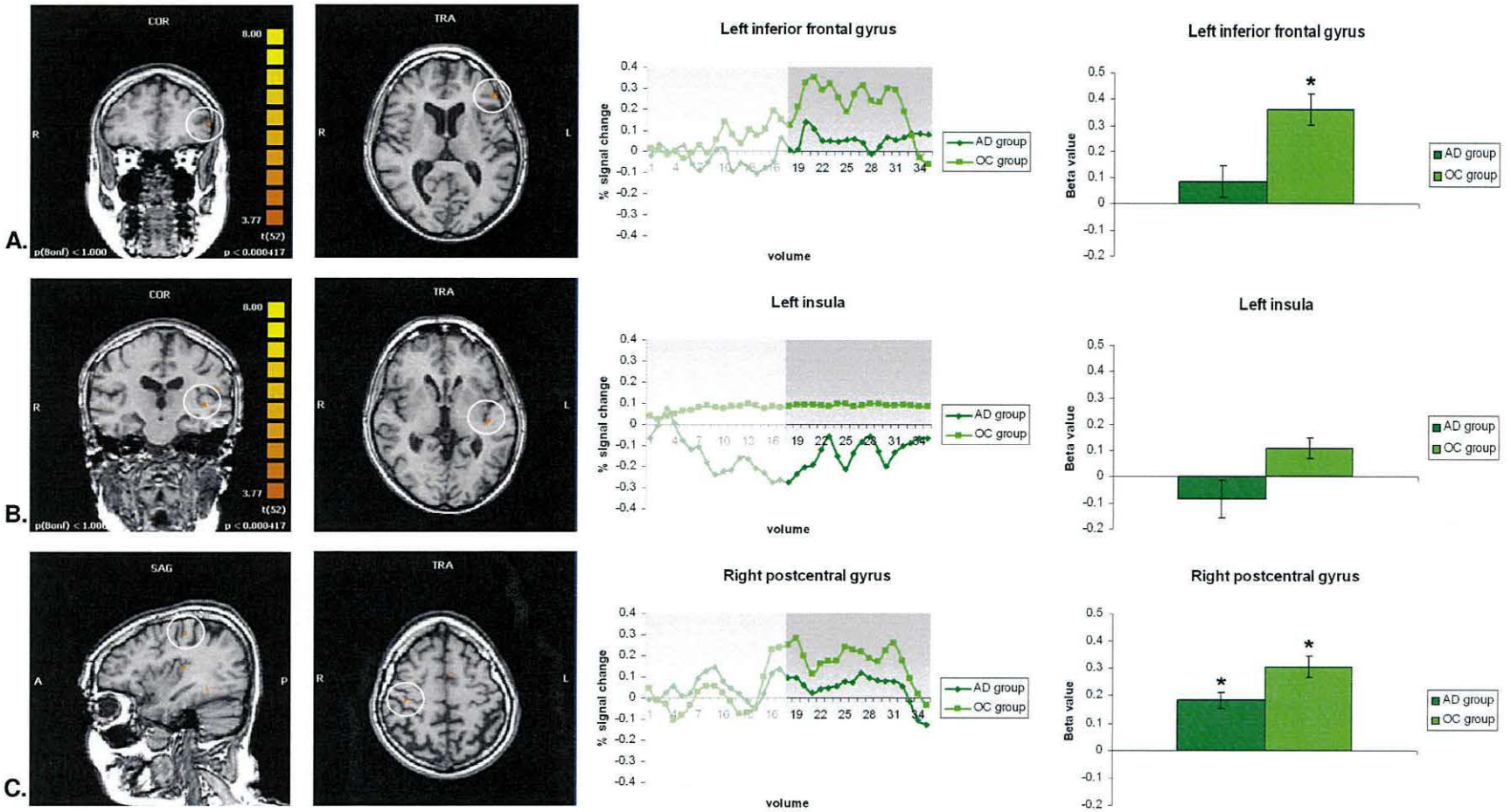

Figure 5.2 – Areas showing higher activation in the OC group than in the AD group during recognition (A. left inferior frontal gyrus; B. left insula; C. right postcentral gyrus). Each anatomical area is presented in two views. The line graph demonstrates the signal change during encoding (volume 18-35) in that area. The bar graph represents the beta value for each group in that area. An asterisk indicates that beta values are significantly different from zero at $p < .05$. A = anterior side; P = posterior side; L = left side; R = right side; Sag = saggital view; Cor = coronal view; Tra = transversal view.

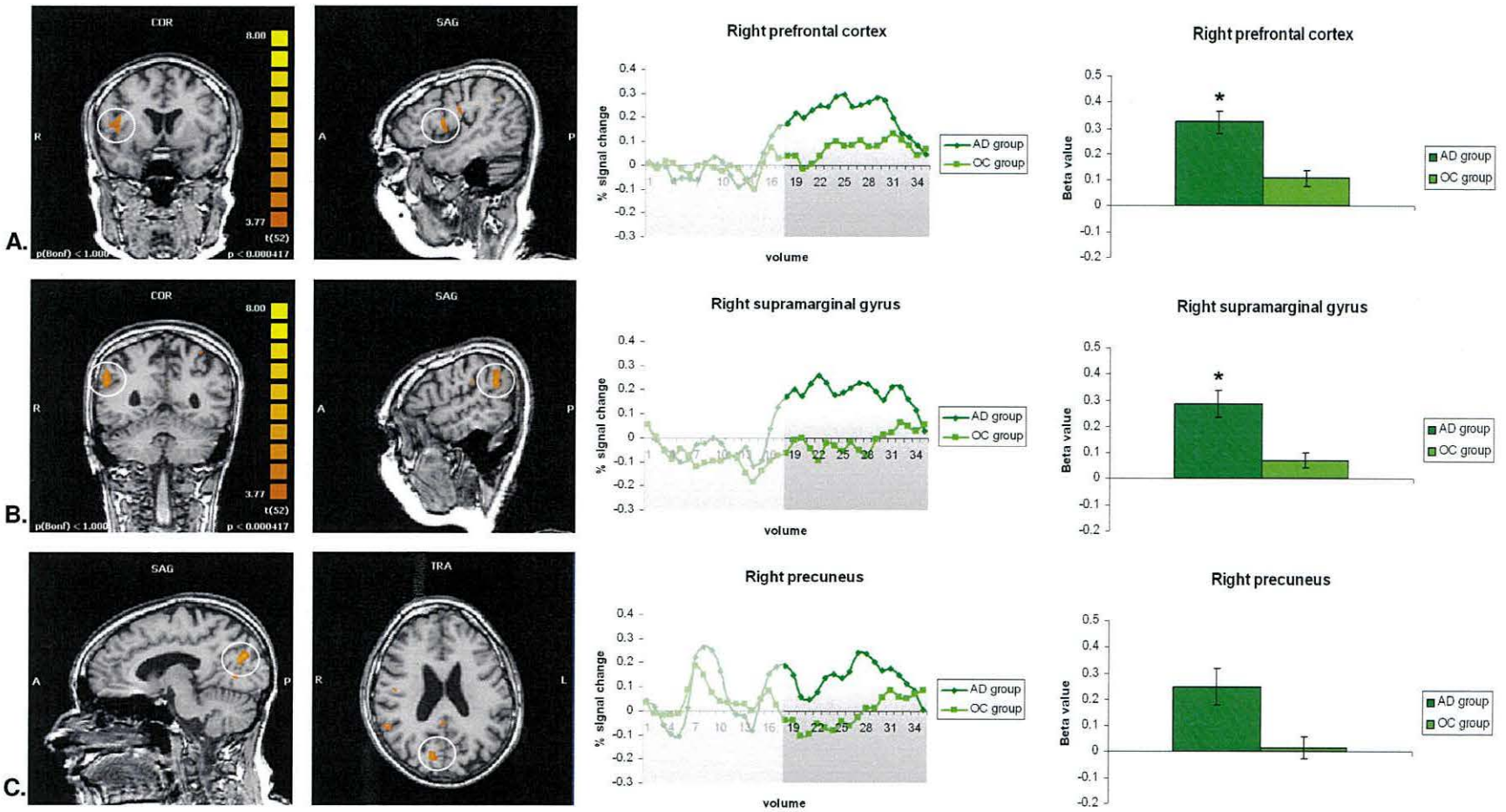

Figure 5.3 – Areas showing higher activation in the AD group than in the OC group during recognition (A. right prefrontal cortex; B. right supramarginal gyrus; C. right precuneus). Each anatomical area is presented in two views. The line graph demonstrates the signal change during encoding (volume 18-35) in that area. The bar graph represents the beta value for each group in that area. An asterisk indicates that beta values are significantly different from zero at $p < .05$. A = anterior side; P = posterior side; L = left side; R = right side; Sag = saggital view; Cor = coronal view; Tra = transversal view.

The vast majority of areas recruited by the AD group did not show involvement in the task in the healthy older adults. Other areas showed higher activation in the OC group compared to the AD group during recognition. Apart from a small region in the anterior temporal lobe, the healthy older group showed significant increase in these areas, which included a number of frontal regions, areas in primary sensory cortex, anterior and posterior cingulate, and the right fusiform gyrus. The only ROIs showing a significant, albeit significantly smaller, increase in the AD group were the areas within the primary sensory cortex. None of the other regions that healthy older adults recruited were significantly activated by the patient group.

No activation differences were detected between the groups on the control task.

Correlations of brain activation with task performance and cognitive status

One of the possible explanations for the group differences in brain activation may be that the AD group showed hyperactivation in certain regions compared to the OC group to compensate for neural loss and dysfunction in areas supporting memory performance in the OC group. To explore this idea, beta values obtained from brain areas in which the AD group showed higher brain activity than the OC group were correlated with behavioural performance on immediate and delayed recognition of the face-name associations, and with MMSE score. However, no significant correlations between brain activity and behavioural and cognitive measures were found.

WITHIN-GROUP ANALYSES

Within each group, a 3-way analysis of variance was performed to identify regions showing specific task effects (encoding, recognition, control task). The threshold was set at $q < .030$ and the analysis limited to clusters with more than 30 consecutively active voxels. The OC group did not show any significant activation clusters at this threshold. Conversely, in the AD group we found a main effect of task in the left medial frontal gyrus corresponding to BA 6 (Talairach coordinates 0 -16 49), the left paracentral lobule (BA 6; Talairach coordinates -12 -22 52), and the right inferior parietal lobule (BA 40; Talairach coordinates 51 -31 37). Follow-up paired

t-tests comparing beta values in each area for each condition revealed that in the left medial frontal gyrus, signal change for encoding was significantly lower than for recognition ($t(14) = 9.383$, $p < .001$) and the control task ($t(14) = 4.093$, $p = .001$). Although activation was higher during recognition than during the control task, this difference did not reach significance ($t(14) = 1.831$, $p = .089$, *n.s.*). In the left paracentral lobule, brain activity during encoding was also significantly lower than that during recognition ($t(14) = 8.590$, $p < .001$) and the control task ($t(14) = 8.245$, $p < .001$). Again, although recognition yielded higher activation than the control task, this difference was not significant ($t(14) = 1.086$, $p = .296$, *n.s.*). Similarly, in the right inferior parietal lobule the encoding condition also yielded lower activation than recognition ($t(14) = 8.768$, $p < .001$) and the control task ($t(14) = 6.769$, $p < .001$), but here, activation during recognition was significantly higher than during the control task ($t(14) = 2.883$, $p = .012$).

DISCUSSION

The current findings demonstrate differences in brain activity during memory processes but not during passive viewing in people with AD compared to healthy older adults. During the encoding procedure a small number of frontal regions were recruited by the healthy older controls but showed little or no activation change in the AD group. Likewise, the older control group showed activation in bilateral inferior frontal regions, bilateral anterior cingulate, and bilateral insular cortex during recognition of face-name associations. In contrast, the AD group activated a network of regions in predominantly posterior parietal cortex that was not employed by the control group during recognition. In particular, areas that are normally active when no cognitive task is performed and become deactivated during cognitive performance, such as posterior cingulate and posterior parietal regions, are not only insufficiently deactivated but indeed significantly activated by the AD group.

GROUP DIFFERENCES DURING ENCODING

The present findings show higher activity during encoding in the healthy older adults than in the AD group in a small number of frontal regions and the putamen. In the current study the AD group showed overall hypoactivation during the encoding of face-name associations in areas recruited by the healthy control group. Furthermore, the absence of areas in which the AD group shows higher activation than the OC group is somewhat different to earlier reports on activation changes in face-name learning in AD. Earlier studies reported higher activity in the AD group compared to the control group during encoding of faces and names in medial and middle frontal areas as well as the precuneus (e.g. Pariente et al., 2005; Sperling et al., 2003a). Our findings from the passive viewing task demonstrate that people with AD can mount to a meaningful blood-oxygen level dependent (BOLD) response which is very similar to that observed in our healthy controls. Furthermore, the behavioural results show that the AD group successfully encoded a substantial proportion of the trials and maintained this information over a delay. Thus, the hypoactivation observed in the AD group cannot merely be explained by patients not engaging in the task, or a difference in BOLD response in the AD group compared to the healthy older adults. A previous fMRI study comparing healthy older and young adults showed that the older group was unable to spontaneously engage in an effective encoding strategy (Logan et al., 2002). The use of this inefficient strategy was associated with decreased activation in a region in the prefrontal cortex in the older adults – a region that was linked to successful task performance in the young group. It may therefore be more likely that the overall hypoactivation in the AD group reflects the reduced ability to effectively encode new materials, perhaps as a result of inefficient strategy use in addition to ineffective neural processing due to AD pathology.

GROUP DIFFERENCES DURING RECOGNITION

Our findings demonstrate marked differences in brain activation during recognition between the AD group and the older controls. Healthy older adults recruited predominantly frontal areas including bilateral inferior frontal gyrus (BA 46), bilateral anterior cingulate, and bilateral insular cortex (BA 13). Involvement of these regions in retrieval processes has been reported previously (Krause et al., 1999; Stern et al., 2000) and is in line with other studies that have indicated that the right prefrontal cortex plays a key role in recognition in healthy individuals (McDermott,

Jones, Petersen, Lageman, & Roediger, 2000; Rugg et al., 1998). No hippocampal activation was observed during recognition in either group in the current study. A possible reason for this may be that rather than being involved in retrieval of memories, a key role of the hippocampus lies in binding novel stimuli, and in novelty detection. A study that directly compared recognition of associations to that of items in young adults showed involvement of left dorsolateral prefrontal cortex and bilateral superior parietal lobes in associative recognition (Achim & Lepage, 2005). The authors reported hippocampal activity only during recognition of single items. They argued that hippocampal activation was not related to the recognition process itself but to the detection of those items that had not been previously studied. Compared to the healthy older group, the AD group in our study recruited some clusters in the right prefrontal cortex during recognition but activation differences between groups were detected primarily in bilateral posterior parietal areas, including bilateral inferior parietal lobule (BA 40), bilateral posterior cingulate (BA 23/29), and right (pre)cuneus (BA 7/31). Group activation differences in prefrontal cortex and supramarginal gyrus during an episodic memory task were also reported by Grady and colleagues (Grady et al.), although the emphasis in their study was very much on prefrontal regions rather than on parietal areas as reported here. Pariente and colleagues observed that when activation for successfully recognised face-name associations was compared between healthy older adults and people with AD, the latter group showed higher activation in left inferior frontal gyrus and left inferior parietal lobule compared to healthy older controls. In a PET study, Bäckman et al. (Bäckman et al.) described increased activation in orbital prefrontal cortex, left cerebellum, right middle temporal gyrus, and right posterior cingulate, in AD patients compared to healthy controls during cued recall of words. Thus, the prominent group differences in posterior parietal areas in our data are slightly different to those reported in earlier studies.

Involvement of left posterior regions in successful retrieval of words was demonstrated in young adults (Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Wheeler & Buckner, 2004). Because we employed a blocked and not an event-related design it is impossible to distinguish trials involving successful remembering. The behavioural performance of the AD group does suggest that a majority of the trials reflects successful remembering. Nevertheless, the parietal regions recruited by the AD group did not show a significant signal change in the OC group. This makes

it unlikely that in healthy individuals these particular clusters play an active role in recognition memory in our paradigm. One explanation for the increased parietal activation in the AD group is that it implicates the recruitment of alternative areas to complete the task. If this hypothesis is true, then we would expect the amount of activation in these areas to correlate positively with the behavioural performance on the recognition task. However, none of the activations observed in the AD group correlated with immediate or delayed recognition memory performance, or MMSE scores. Thus, our data do not support a hypothesis of compensatory activation in areas that are not recruited by a healthy control group, and the role of the additional activation observed in the AD group remains unclear. Possibly, the activation simply reflects the inability to efficiently deactivate areas that are not directly involved in the task, although one might then expect a negative correlation between brain activity and performance.

Logan and colleagues (Logan et al.) described two types of activation differences comparing healthy young and older adults in a study on word encoding. When the older adults learned the words using their own strategy, they under-recruited the left prefrontal cortex compared to the younger group, and showed higher activation in the contralateral area that was not recruited by the young group. In a second experiment, all participants made semantic judgments about words, a process that is thought to induce semantic encoding. Under these conditions, the older adults recruited the left prefrontal cortex to the same extent as the young group and remembered more words in a subsequent memory test. However, the contralateral prefrontal cortex was still activated to a higher extent than in the young adults. This was interpreted as a possible breakdown in the mechanism of efficiently selecting regions appropriate to the task at hand, and inhibiting other areas. Although the study did not include participants with a neurodegenerative disease, it is plausible that similar processes occur in the AD brain, in which neurons in temporal and parietal areas are progressively damaged (Braak & Braak, 1991) and projections between in particular medial temporal regions, frontal and parietal cortex become increasingly disconnected (e.g. Arendt, 2001; Delbeuck, Van der Linden, & Collette, 2003).

INHIBITION OF RESTING STATE NETWORK AREAS

In a comprehensive review, Buckner (2004) noted that parietal areas involved in retrieval in young individuals are very similar to regions showing disruptions in resting state metabolism in people with AD. As such, an alternative interpretation of the hyperactivity in parietal regions observed in the present study is that it reflects dysfunction in areas that are part of a resting state network. This network of regions is thought to be more active when an individual is not engaged in a specific cognitive task than during cognitive processes. Areas associated with this network include the posterior cingulate and the precuneus (BA 7/31), left (BA 19/39/40) and right (BA 40) inferior parietal cortex, left frontal cortex (BA 8), left inferior frontal cortex (BA 10/47), a cluster of dorsal medial frontal regions (BA 8/9/10/32), left inferior temporal gyrus (BA 20), and the right amygdala (Mason et al., 2007; Raichle et al., 2001; Shulman et al., 1997). The resting state network described above largely overlaps with those areas showing greater activity during recognition in the AD than the OC group in our study. Several studies have found activation differences in default mode network areas in people with AD compared to healthy older adults (Celone et al., 2006; Greicius, Srivastava, Reiss, & Menon, 2004; Herholz et al., 2002; Lustig et al., 2003). Lustig and colleagues asked participants to make living / nonliving decisions about words and found that during this process people with AD showed a positive activation in the right medial parietal cortex (BA 31) while a group of young healthy adults showed decreased activation in the same area. It has been argued that the amount of deactivation in areas comprising the resting state network correlates with the amount of activation in hippocampal formation during a memory task (Della-Maggiore et al., 2000; Maguire & Mummery, 1999; Maguire, Mummery, & Buchel, 2000) and that the reciprocal connection between these regions is affected by the disease process at an early stage in AD (Buckner, 2004; Celone et al., 2006; Greicius et al., 2004). Our data support the idea of disrupted activation in areas associated with the default-mode network in AD.

BEHAVIOURAL FINDINGS

Although there were clear differences in performance between the groups in direct recognition (i.e. the recognition task performed inside the scanner), group differences disappeared on the post-scan recognition task. Moreover, performance of the AD

group was more or less comparable on these two tasks, whereas the OC group showed a significant decline in scores on the post-scan recognition task compared to the direct recognition task performed inside the scanner. The pattern observed in the AD group fits with earlier reports suggesting that once information is acquired there is no accelerated forgetting or impaired retrieval in AD (Greene, Baddeley, & Hodges, 1996). However, there is no straightforward explanation for the drop in performance in the older adults. It is clear from the behavioural data that the healthy older adults were very good at learning the original face-name associations. We speculate that perhaps one of the explanations for their performance decline is that the post-scan recognition task comprised faces only, without the names. It may be that the names served as cues to remember the faces. When the 'cues' were no longer there in the post-scan recognition task, it was perhaps harder for the OC group to remember the faces. The AD group, for whom it was – judging from their behavioural performance – more difficult to remember the face-name associations, may not have experienced the presence of the names as a help, and so their performance was not affected by the absence of the names.

Limitations of the current study

The older control group in the current study performed significantly better on immediate recognition of the face-name associations than the AD group. Previous studies have argued that when performance is not matched between groups, any observed differences in brain activation may reflect different cognitive operations such as increased effort rather than cognitive deficits (Gould et al., 2006a; Gould et al., 2005). In fact, when healthy older adults and people with AD perform a task that is comparable in difficulty level for each group, very similar brain activation patterns were found. The issue of difficulty level was illustrated in two studies where the same set of PET data comparing healthy older adults and people with AD on one-word repetition, three-word repetition, and eight-word free recall was analysed in two different ways (Becker et al., 1996; Herbster et al., 1996). In the first report, activation during the three-word repetition was contrasted with that for the eight-word free recall task for each group separately, and the results of these contrasts were then compared between the groups using a *t*-test (Becker et al., 1996). It was concluded that the AD group showed enhanced activation in areas that were also involved in the task in healthy older controls, but in addition, the AD group also

activated areas that were not activated in the control group, which was interpreted as compensatory re-allocation of brain resources. The second study, however, carried out a principle component analysis (Friston, Frith, Liddle, & Frackowiak, 1993) on the same data set, which enables identification of brain areas showing significant covarying activation levels (Herbster et al., 1996) even when the actual changes in brain activity itself are statistically not large. This analysis showed that a very similar network of brain areas was active in both groups during the free recall of eight words, despite the differences in task performance, and led the authors to propose that had the task been more difficult, the older control group would have shown similar changes in brain activity. Taken together, studies that have matched performance levels in both groups, or analysed their data in a way that overcomes the potential confounding factor of task difficulty level, have shown that in the early stage of AD, brain activation patterns are very similar to those of healthy older adults during memory processes. The findings of differences in brain activation levels during face-name pair recognition reported here may therefore be confounded by differences in performance level between the groups. However, it is important to mention here that by matching task performance, a different research question is addressed. If the focus of the research is in establishing whether people with AD are at all capable of recruiting a similar network of brain areas as healthy older adults during memory processing, then this question would have to be addressed with a paradigm that matches performance so that other differences such as increased effort or frustration are levelled out. On the other hand, if one is interested in why people with AD have difficulty with everyday tasks that they were previously very capable of carrying out, such as remembering the names of the people in their environment, the most informative way to investigate this is by presenting the same task to both the AD group and the control group in order to establish the underlying neural cause of these behavioural difficulties. The latter approach is commonly used in the literature to study changes in brain activation in AD (Celone et al., 2006; Dickerson et al., 2005; Pariente et al., 2005; Sperling et al., 2003a) and was also employed in the present study.

Secondly, participants were presented with a repetition of intact and rearranged items during recognition of the face-name associations. Recognition of rearranged items can trigger retroactive interference, in which a rearranged combination viewed during recognition can subsequently be remembered as the correct association

(Cleary, Curran, & Greene, 2001; Light et al., 2004; Perruchet et al., 2006). People with AD are thought to be more prone to retroactive interference than healthy older adults (Loewenstein et al., 2004). Hence, it is possible that lower recognition scores in the AD group as observed in the present study may have been caused by retroactive interference rather than difficulty in retrieving the association from memory. Scores from the first two recognition trials, which always included the two different faces presented during encoding but could either be intact or rearranged, were therefore compared to scores the last four trials. No difference in scores was found, suggesting that performance was comparable on the trials and that retroactive interference is unlikely to have had a detrimental effect on performance in the AD group in the present study.

Participants in the AD group in the current study were all taking acetylcholinesterase (AChE) inhibiting medication. It is known that such drugs may enhance brain activity during cognitive tasks (Rombouts et al., 2002). Thus, arguably the present findings of higher brain activation in the AD group compared to the OC group may have been caused by the former group taking cognition-enhancing medication. However, this explanation is unlikely for several reasons. Firstly, reports in the literature describe how a single dose of AChE inhibitors acts to reverse hypo-activation in people with AD to become more similar to that of healthy subjects both when participants are required to attend to visual stimuli (Bentley, Driver, & Dolan, 2008) and during encoding of novel faces (Kircher et al., 2005). Rather than leading to hyperactivation in AD compared to healthy participants, the drugs appear to operate mainly by counteracting hypoactivity and 'normalise' patterns of brain activation in AD during different cognitive processes. In addition, prolonged use of AChE inhibiting medication (5 days) led to hypoactivation in the parahippocampal gyrus but no activation changes in other brain regions during recognition of previously studied faces (Goekoop et al., 2006). Thus, previous studies investigating the effects of AChE inhibitors do not suggest that the use of this medication leads to hyperactivity in AD. Secondly, findings in the current study show group differences during encoding and recognition of face-name associations, but not during the cognitively less demanding control task or the passive viewing task. The AD group only showed hyperactivity compared to the OC group during recognition. Based on previous findings, it seems unlikely that the use of AChE inhibitors led to hyperactivity in the AD group compared to the OC group, and that this would be

observable only during recognition.

CONCLUSION

The present findings suggest that there are differences in brain activation in people with AD compared to healthy older adults, but only during an episodic memory task. In a passive viewing task we observed no marked differences between the groups, which suggests that people with AD can exhibit a meaningful neural response to stimuli as expressed by the BOLD response. During an associative learning task our AD group showed little activation during encoding compared to the healthy control group, which we attribute to a combination of failure to make use of an efficient encoding strategy and lack of efficient processing due to AD pathology. The most prominent group differences were found during the recognition process, in which the two groups employed largely different networks of brain regions. The AD group showed increased activation in mainly posterior parietal areas. Although a number of previous reports have speculated that this activation may be compensatory, only one study actually demonstrated a direct link between increased activation and improved task performance in people with AD. The term 'compensatory' implies that the activation 'corrects for (…) some undesired characteristic or effect' (Oxford English Dictionary, 1989). The question is very much whether that is indeed a correct interpretation of the activation pattern observed in AD. Although the present study cannot give a definitive answer to the question of whether the nature of activation changes in AD is compensatory, it seems unlikely that the observed group differences are 'helping' the AD group in their performance. Rather, it is possible that the differences may be a by-product of dysfunction and pathology in the AD brain, and reflect a lack of efficient inhibition. The current findings imply that cognitive intervention methods aimed at improving or maintaining memory function should seek to make the most of residual memory function in areas typically associated with such activity, rather than assuming the possibility of engaging alternative compensating networks.

Chapter 6 – Effects of cognitive rehabilitation on memory-related functional brain activation in people with early stage Alzheimer's disease.

ABSTRACT

Recent studies show that using learning strategies in combination with teaching personally relevant information can be effective in improving memory for that information in people with Alzheimer's disease (AD). Six people participating in an eight-week cognitive rehabilitation intervention programme were taught a mnemonic strategy to learn the names of unfamiliar people. Using functional magnetic resonance imaging (fMRI), possible changes in brain activation during face-name learning were examined pre and post treatment while participants learned and recognised unfamiliar face-name pairs, and engaged in a control task (making decisions about the gender of a face). Behaviourally, small improvements on immediate recognition of the face-name associations as well as on the control task were observed. On a neural level, brain activity was generally higher prior to than following the treatment during memory-related processing. During encoding, activation decreases following treatment occurred mainly in visual areas. The most prominent alterations were observed during recognition, where activation was lower following the intervention period in mainly parietal, occipital and temporal regions. Changes in brain activity during the control task were minimal. Although preliminary, the results were suggestive of more effective inhibition of regions comprising a default mode network. The approach adopted here to study the neural bases of cognitive rehabilitation has not been reported before, and the present findings indicate that this method can feasibly be employed with people with AD.

INTRODUCTION

As discussed earlier, Alzheimer's disease (AD) is clinically characterised in the early stages predominantly by progressive severe impairments in episodic memory (Förstl & Kurz, 1999; Fox, Warrington, Seiffer, Agnew, & Rossor, 1998; Greene, Baddeley, & Hodges, 1996), but also affects other cognitive domains such as attention and executive functioning (Greene, Baddeley, & Hodges, 1996; Perry, Watson, & Hodges, 2000), abstract reasoning (Caccappolo-Van Vliet et al., 2003), and language (Imamura et al., 1998).

BEHAVIOURAL EVIDENCE FOR IMPROVED MEMORY FUNCTION IN AD

Despite these frequently observed cognitive deficits, people with early-stage AD are capable of new learning when the appropriate cognitive support is given (Bäckman, 1992, 1996; Lipinska & Bäckman, 1997). Learning strategies such as mnemonic imagery (Bäckman, Josephsson, Herlitz, Stigsdotter, & Viitanen, 1991; Hill, Evankovich, Sheikh, & Yesavage, 1987), semantic elaboration (Bird & Luszcz, 1991, 1993; Dalla Barba & Goldblum, 1996), and spaced retrieval (Camp, 1989; Camp & Stevens, 1990) have enhanced memory performance in people with AD. Building on these findings, a series of studies provided individualised interventions for people with AD, using combinations of strategies to teach personally-relevant information or achieve changes in behaviour (Clare et al., 1999; Clare et al., 2000; Clare et al., 2003; Clare, Wilson, Carter, Hodges, & Adams, 2001; Clare et al., 2002). Although these studies all provided individualised treatment to people with AD, a frequent focus involved (re)learning names of familiar people. These tended to be people encountered in a social support group or in participants' direct environment. Strategies were based on errorless learning principles and included expanded rehearsal (Camp, 1989), and using a mnemonic (for example based on a prominent facial feature or a verbal elaboration of the name - Bäckman, Josephsson, Herlitz, Stigsdotter, & Viitanen, 1991; Hill, Evankovich, Sheikh, & Yesavage, 1987; Thoene & Glisky, 1995). Although no changes tended to be observed on neuropsychological measures following treatment, participants did improve on the task they had practised during the intervention and were in some cases able to transfer their memory improvements from the therapy sessions to the real-life setting in which they encountered the people whose names they had practised. One of the

explanations for the efficacy of these interventions may be that they targeted specific problem areas relevant to individual participants. Successful outcome of learning strategies is modified by motivation, which is higher when therapy goals are relevant to the patient's daily life (Bäckman, 1992; Clare & Woods, 2004). The findings from these studies have led to the development of a cognitive rehabilitation approach for people with early-stage AD (Clare, 2007). Cognitive rehabilitation (CR) is a form of cognition-focused intervention where people with cognitive impairments and their families work together with a therapist to tackle individually relevant goals (Wilson, 2002). Application of this approach for people with dementia includes interventions for a range of personalised goals, instruction and practice in the use of memory strategies, practice in attention and concentration, support for the implementation of practical strategies and memory aids, and practice in anxiety management (Clare, 2007).

What neural mechanisms underlie behavioural effects of cognitive rehabilitation in AD?

The evidence that people with dementia can learn or re-learn information or skills supports the possibility that neural plasticity can operate even in a degenerating brain. An important question is whether behavioural improvements are accompanied by changes at a neural level, and if so, which networks of brain regions are involved in or affected by such changes. These questions remain unanswered to date as the majority of cognitive intervention studies including people with AD have used only behavioural outcome measures to assess treatment effects. However, knowing more about the neural mechanisms relating to treatment effects would enable therapists to administer more focused treatments and would help to understand why some techniques work and others do not. By making use of neuroimaging methods such as functional magnetic resonance imaging (fMRI), we can investigate whether behavioural improvements in memory function following an intervention are supported by changes in functional brain activation, and if so, which areas in the brain are involved.

There are several possible ways in which mechanisms of cognitive plasticity in AD might operate, as indicated by results of studies comparing memory-related brain activity in people with AD with that of healthy older adults. As discussed in more detail in Chapter 5, some studies have proposed that people with AD recruited areas

that were not typically involved in the same task by healthy older adults and suggested that activity in these novel areas may compensate for loss of function in areas typically supporting memory function (Grady et al., 2003; Pariente et al., 2005; Sperling et al., 2003a). However, others found no evidence of the use of alternative brain areas and argued that when performance is matched between the AD group and healthy older controls, people with AD make use of very similar cortical networks during a memory task (Gould et al., 2006a; Gould et al., 2005). These two views have different implications for techniques aimed at improving memory function in people with AD. If people with AD use a network of atypical, 'compensatory' brain areas during a memory task that is not recruited by healthy older adults, then intervention strategies that aim to ameliorate memory function should target this network. On the other hand, if people with AD tend to recruit brain regions in a similar fashion to healthy older people, but are not able to recruit them as effectively (as indicated by decreased fMRI signal compared to healthy older adults), then techniques to improve memory function should aim to stimulate the existing memory circuits and make the most of residual memory function.

The current study focuses on possible changes in brain activation patterns following a cognitive rehabilitation intervention in people with AD. Six participants with early-stage AD received an 8-week individualised CR intervention. Using fMRI, subjects were scanned prior to and immediately following the treatment period while they engaged in task in which they associated an unfamiliar face and name. This chapter will address the following research questions:

1. Is there a change in memory-related brain activity in people with AD when activation is compared prior to and following a period of cognitive rehabilitation?
2. If there are activation changes, are these supported by a significant behavioural improvement in performance on a face-name association task?
3. If there are differences in brain activation patterns pre- and post-intervention, what is the nature of these changes? Is there a difference in activity in similar areas at both time points, which might indicate that an area has become more efficient, or has been stimulated by the intervention? Or are different areas involved in the task when brain activity is compared prior to and following the intervention, which would be suggestive of the recruitment of 'compensatory' brain areas to perform the task?

METHODS

Participants in the current study were among those recruited to a randomised controlled trial (RCT) investigating the effects of cognitive rehabilitation. Each participant in the RCT was invited to have an fMRI scan prior to and following the treatment period. Following their first scan (or following their last neuropsychological baseline assessment, if they could not be scanned), participants were randomly allocated to receive eight weeks of cognitive rehabilitation, relaxation therapy, or no intervention. Experimental procedures for the randomised controlled trial and for the fMRI part of the study were approved by the research ethics committees of the School of Psychology, Bangor University, and of the North West Wales NHS Trust. The fMRI data for those participants who received cognitive rehabilitation and were scanned both pre- and post-intervention are presented here.

Participants

Six participants who were subsequently randomised to receive cognitive rehabilitation consented to an fMRI scan and later received a second scan following the intervention. Participants were recruited through NHS memory clinics in North Wales and were diagnosed by experienced psychiatrists who were not involved in the intervention programme as meeting NINCDS-ADRDA criteria for early stage AD (McKhann et al., 1984). All participants were on a stable dose of acetylcholinesterase (AChE) inhibiting medication for at least three months prior to participation. Inclusion criteria for the randomised controlled trial were a diagnosis of probable AD or mixed dementia (vascular and AD) in the absence of any other neurological disease, a score of 18 or above on the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), and a stable dose of AChE inhibitors. Participants were excluded if there was evidence of current or past history of psychiatric illness, or a stroke. For the fMRI part of the study, further exclusion criteria comprised dyslexia, poor vision that could not be corrected to normal, and any other conditions generally known to be incompatible with fMRI, such as the presence of a pacemaker or shunt, or metal fragments in the eyes. Written informed consent to take part in the randomised controlled trial and in the fMRI part of that study was obtained separately from each participant. Demographic characteristics of the participants who received cognitive rehabilitation and took part in the fMRI study

are summarised in Table 6.1.

Table 6.1 – Participant characteristics (n = 6)

Demographic characteristics		
Mean age in years ± SD	71.2 ± 6.6	(range 64 – 80 years)
Mean years of education ± SD	9.0 ± 1.5	(range 8 – 12 years)
Mean MMSE score ± SD	25.7 ± 1.0	(range 25 – 27)
Gender distribution	3 males, 3 females	

SD = standard deviation

Procedure

All participants described in this chapter took part in a cognitive rehabilitation intervention programme. Prior to the start of the intervention participants were assessed by a researcher who was blind to allocation of treatment group, using a battery of neuropsychological tests. Up to four potential therapy goals were also identified. Participants were then invited to have two fMRI scans: one prior to the start of the intervention programme, and one immediately following the intervention. Following the pre-intervention scan, an occupational therapist carried out the intervention (8 weekly sessions of approximately 1.5 hours, conducted in the participant's own home and involving the primary family caregiver wherever possible). During the intervention participants worked on one or two therapy goals. In addition, all participants were introduced to the memory strategies of spaced retrieval, semantic elaboration and simple visual mnemonics, and practised face-name learning techniques using these strategies with a set of unfamiliar pictures and names. A detailed description of the intervention approach and the strategies used is provided in Clare (2007). More information on the cognitive rehabilitation intervention can be found in Appendix E.

fMRI paradigm

The fMRI scanning consisted of an experimental paradigm and a passive viewing task. The experimental task comprised encoding and retrieving unfamiliar face-name

associations, and indicating whether a printed gender and a face were correctly matched or not. The passive viewing task included viewing pictures of faces and scenes. Both paradigms are described briefly below and are illustrated in Figure 6.1. A detailed account of the tasks is provided in Chapters 3 and 4.

Passive viewing task

A set of 60 pictures (20 male faces, 20 female faces, 20 outdoor and indoor scenes) was used in a passive viewing task in which participants viewed blocks of pictures (faces and scenes), interspersed with fixation blocks. This sequence was presented five times during one run. Details of the stimuli and the procedure are described in Chapter 4.

Experimental paradigm

Twelve grey scale pictures of Caucasian faces (6 males, 6 females) were shown in pairs of two over six runs. All faces were paired with common Anglo-Saxon first names to form face-name associations. In each run, participants first associated each face with a name (Encoding), then decided whether a particular association was correct or not (Recognition), and finally made decisions on whether a face and a gender were correctly matched or not (Control task). The stimuli and procedure used in this task are described in detail in Chapters 3 and 4.

Scanning procedure

All participants received a 15-minute practice session outside the scanner prior to the start of the experiment. During encoding, participants were instructed to try to learn which faces and names belonged together. In the recognition phase, participants were instructed to answer 'yes' if the face and name had been paired during the encoding phase, and 'no' if they had not, via a button press. The control task block consisted of one male and one female face with either 'male' or 'female' written below the picture (three correct and three incorrect combinations). Participants were asked to indicate whether the combination of face and gender was correct by giving 'yes' and 'no' answers via a button press. The control task was always administered last to reduce task switching effects. After functional images had been collected for all six runs of the experimental paradigm, participants were scanned during one run of the passive viewing task. Following the functional image acquisition, once outside the

scanner, participants were asked to view 48 pictures (12 from the face-name association task, 12 from the control task, and 24 novel pictures), and indicate by means of a button press on a laptop keyboard whether they had seen the face anywhere in the experiment or not.

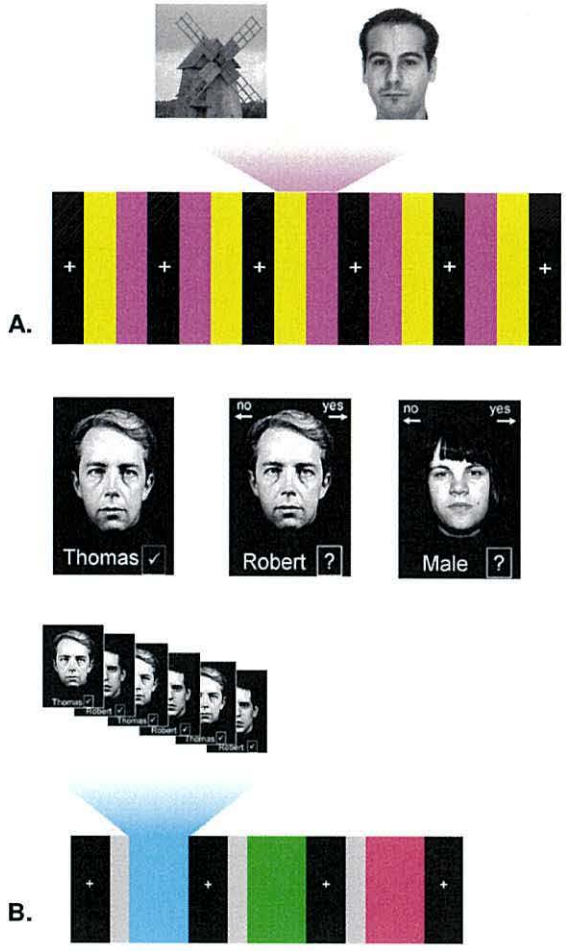

Figure 6.1 – Schematic overview of the passive viewing task (A.) and the face-name association task (B.).

Image acquisition

All participants were scanned using a 1.5 T Philips scanner with a head coil for parallel imaging. Foam padding was used to reduce head motion. Functional images were obtained with a T2* weighted gradient echo sequence (TR = 2000 ms, TE = 40 ms, flip angle 90°, FOV = 192, 20 axial slices, 64 x 64 in-plane matrix, voxel dimensions 3 x 3 x 5 mm). A 3D anatomical T1 scan consisting of 150 slices

(resolution 1 x 1 x 2 mm) was obtained for co-registration with functional data. The time per run was 3 min 46 sec for the experimental task (113 volumes) and 4 min 16 sec for the passive viewing task (128 volumes). Including the structural scan, the total time spent in the scanner was approximately 35 minutes.

Data analysis

Functional MRI data were pre-processed and analysed using BrainVoyager QX (Brain Innovation, Maastricht, The Netherlands). The first two volumes of each run were discarded to avoid differences in T1 saturation. All images were motion-corrected and low frequency drifts were removed using a temporal high pass filter (0.0044 Hz). All data were spatially smoothed using a 4 mm FWHM Gaussian kernel. Temporal smoothing with a Gaussian kernel of 2.8 seconds FWHM was also applied to remove high frequency fluctuation. The functional data were manually co-registered with the three-dimensional anatomical scans and then resampled to isometric 3 x 3 x 3-mm voxels with trilinear interpolation. The 3D scans were transformed into Talairach space (Talairach & Tournoux, 1988). Subsequently, the co-ordinates of this transformation were applied to the co-registered functional data, which were resampled to 1 x 1 x 1 mm voxels.

For the passive viewing task, faces and scenes were contrasted to identify previously defined regions of interest in each individual. Face and scene predictors, obtained by convolving the respective blocks of the passive viewing paradigm with a two gamma hemodynamic reference function, were entered into a general linear model. Face- and scene-selective brain areas were identified by a *t*-test of this contrast. Based on previous literature (Epstein & Kanwisher, 1998; Kanwisher, McDermott, & Chun, 1997; Puce et al., 1996), regions of interest (ROIs) in the passive viewing task were defined as the right fusiform face area (FFA), the right occipital face area (OFA), and the left and right parahippocampal place area (PPA). The ROIs were defined by a set of contiguous significantly active voxels ($p < .003$, uncorrected) within a 10 mm anterior / posterior, superior / inferior, and medial / lateral direction of the most significantly active voxel near the expected location in each individual.

All blocks in the experimental task were convolved with a standard two gamma model of the hemodynamic response function in order to obtain predictors for Encoding, Recognition, and Control task. Whole-brain group activation maps were

assessed using a random effects analysis. To examine whether there was an interaction between time of scan and condition, data were entered into a 2 x 3 repeated measures ANOVA with Time point (pre-intervention; post-intervention) and Condition (Encoding, Retrieval, Control task) as within-subject factors. Maps comparing each condition separately pre and post intervention using a *t*-test of that contrast were also created. Voxels that exceeded a threshold of $p < .001$ (uncorrected for multiple comparisons) and a cluster size of 50 consecutive active voxels were considered significant.

Behavioural data obtained from the experimental paradigm were analysed using SPSS version 15.0 for Windows. Differences in scores on the face-name task (immediate recognition), the control task, and the delayed recognition task prior to and following the intervention were explored using a Wilcoxon Signed Ranks test. Changes in scores were considered to be significant at $p < .05$.

RESULTS

Behavioural data

Individual raw scores, group mean scores and standard deviations for performance on the face-name association task, the control task, and the post-scan recognition task are presented in Table 6.2. Individual mean scores are shown in Figure 6.2. For the purpose of readability, in the following section data collection prior to the start of the cognitive rehabilitation intervention will be referred to as T1, whereas data collection following the intervention period will be referred to as T2.

For two participants (A and F), some behavioural and functional data were excluded. Participant A did not press any buttons during the recognition task in one run at T1 and one run at T2. Brain activity during these runs was different compared to the other runs where he did answer the questions. At T1, there was no activation in the left hippocampus during the run where no answers were given. At T2, there was no activation in the right precuneus in the excluded run compared to runs where participant A did answer the questions. On both occasions, this happened in the beginning of the experiment (i.e. on the first or second run), so it may be that participant A required some time to get used to performing the task inside the

scanner. Participant F either got every answer wrong, or failed to press the button to provide an answer, during the last three runs of his post-intervention scan. Possibly, fatigue may have played a role, although he did not report this when asked (after each run). As with participant A, the last three runs showed different patterns of brain activation compared to the first three runs. During the runs where no or wrong answers were given, there was an absence of activation in the left posterior hippocampus compared to the first three runs. Consequently, as it was not possible to know whether the two participants had actually engaged in the task during said runs, it was decided to exclude these runs from both behavioural and functional analyses.

Table 6.2 – Individual scores and group mean scores on the face-name association task (immediate and delayed recognition) and the control task.

Individual raw scores	**Pre-intervention**		**Post-intervention**	
	Immediate recognition	Control task	Immediate recognition	Control task
Participant A *	12 / 30	23 / 30	13 / 30	24 / 30
Participant B	26 / 36	36 / 36	35 / 36	36 / 36
Participant C	33 / 36	34 / 36	35 / 36	35 / 36
Participant D	26 / 36	28 / 36	29 / 36	34 / 36
Participant E	18 / 36	26 / 36	19 / 36	31 / 36
Participant F $	22 / 36	31 / 36	11 / 18	17 / 18

Task performance - proportion of correct answers (± SD)	**Pre-intervention**	**Post-intervention**
Immediate recognition	.65 (± .18)	.72 (± .23) &
Control task	.85 (± .11)	.92 (± .07) &

Performance on post-scan recognition task	**Pre-intervention**		**Post-intervention**	
	Proportion of correct answers (± SD)	**Mean raw score**	**Proportion of correct answers (± SD)**	**Mean raw score**
Faces from the face-name task	.63 (± .30)	8 / 12	.64 (± .18)	8 / 12
Faces from the control task	.50 (± .33)	6 / 12	.44 (± .26)	5 / 12
Correct rejections	.71 (± .33)	17 / 24	.73 (± .27)	18 / 24
Total correct score delayed recognition	.64 (± .14)	31 / 48	.64 (± .13)	31 / 48

SD = standard deviation; * = participant did not respond during one run prior to intervention and one run post intervention – these runs were excluded from both behavioural and fMRI analyses; $ = participant did not respond during the last three runs following the intervention period – these runs were excluded from both behavioural and fMRI analyses; & = significantly different from T1 at $p < .05$.

There were individual differences in task performance, with some participants scoring below or at chance level (.50) at both time points on the immediate recognition task (Participants A and E). The others scored above chance level both prior to and following the treatment period on this task. Participant B showed the greatest improvement on the recognition task, while Participant C obtained high scores both at T1 and at T2.

Although all participants scored above chance level at T1 on the control task, Participants B, C, and F obtained high scores (i.e. more than 80% correct). At T2, all participants obtained such high scores on the control task.

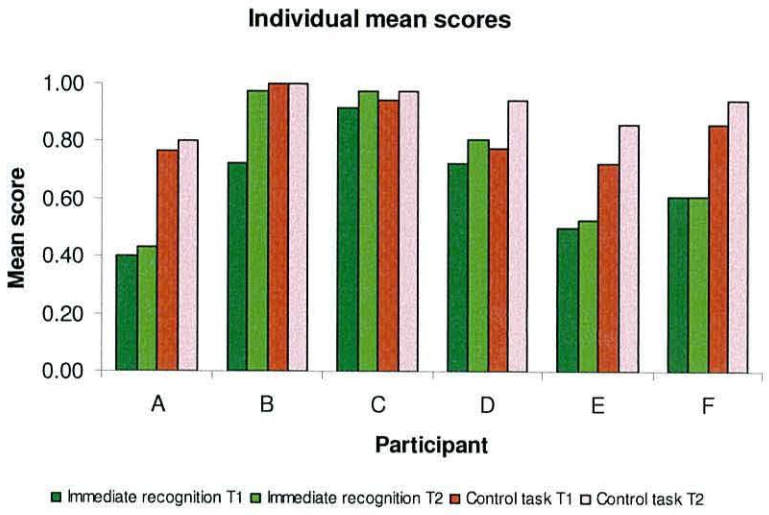

Figure 6.2 – Individual mean scores on the immediate recognition task and the control task.

A one sample *t*-test showed that the mean group score at T1 for immediate recognition was not significantly above chance level (.50), although there was a trend towards significance ($t(5) = 1.931$, $p = .056$, *n.s.*). At T2, the mean group score was indeed significantly above chance level ($t(5) = 2.339$, $p = .033$). This suggests that participants were able to perform the task to a reasonable extent without scoring at ceiling level. However, a one sample *t*-test also showed that group scores on the delayed recognition task carried out after the scanning procedure was completed were not significantly different from chance level (.50) either at T1 ($t(5) = 2.403$, $p = .061$) or at T2 ($t(5) = 1.890$, $p = .117$).

A one sample *t*-test also demonstrated that the mean group performance on the control task was well above chance level on both T1 ($t(5 = 7.796$, $p = .001$) and T2

($t(5) = 13.771$, $p = .001$), demonstrating that participants were able to concentrate in the scanner, understand the written instructions provided, and give 'yes' and 'no' answers using a button box.

To investigate whether there was an improvement in performance on the face-name association task following the intervention period, immediate recognition scores for the face-name association task and for the control task at both T1 and T2 were analysed using a Wilcoxon Signed Ranks test. Performance on immediate recognition was significantly better at T2 (*Median* = .71) compared to T1 (*Median* = .67), T = 0, $p < .05$, $r = -.59$. However, performance on the control task also improved significantly at T2 (*Median* = .82) compared to T1 (*Median* = .94), T = 0, $p < .05$, $r = -.59$.

On the delayed recognition task, a Wilcoxon Signed Ranks test showed that there was no significant difference in performance prior to (*Median* = .63) and following (*Median* = .64) the treatment, T = 7.50, $p = .528$, $r = -.18$.

fMRI data

Passive viewing task:

Talairach coordinates, cluster size, and statistical values for the peak voxels of the ROIs are presented in Table 6.3. To identify the ROIs in each individual subject, data from T1 and T2 were collated and brain activation for faces was contrasted with that of scenes. The most significantly activated (peak) voxel near each previously described ROI was located. Subsequently, each individual's FFA, OFA, and PPA were defined by a set of contiguous significantly active voxels ($p < .003$, uncorrected) within a 10 mm anterior / posterior, superior / inferior, and medial / lateral direction of the peak voxel.

Table 6.3 – Overview of findings from the passive viewing task.

Region	Talairach coordinates of most significant voxel			Mean number of active voxels in ROI	Mean T-value
	x	y	z		
Right FFA	40	-50	-15	412	7.607
Right OFA	46	-66	-5	511	7.572
Right PPA	27	-49	-12	922	15.407
Left PPA	-26	-48	-13	901	13.307

FFA = fusiform face area; OFA = occipital face area; PPA = parahippocampal place area

Beta values from both T1 and T2 for faces and scenes for each participant were then extracted from these four ROIs. To investigate whether there were any changes in neural response to viewing either faces or scenes, beta values from the condition a particular area was selective to were extracted from each ROI at T1 and T2, and compared using a paired samples *t*-test. No significant differences were found. For mean beta values and statistics, see Table 6.4.

Table 6.4 – Mean beta values and *t*-statistics obtained from the passive viewing task at T1 and T2.

Region of interest	Condition	Mean beta value at T1 (± SD)	Mean beta value at T2 (± SD)	T-value	p-value ($\alpha = .05$)	df
Right FFA	Faces	1.41 (±0.98)	1.51 (±1.15)	.223	.825	5
Right OFA	Faces	0.73 (±1.51)	0.68 (±0.88)	.093	.929	5
Right PPA	Scenes	1.09 (±1.21)	1.13 (±1.46)	.039	.970	5
Left PPA	Scenes	1.32 (±1.08)	1.87 (±1.53)	.796	.462	5

SD = standard deviation; FFA = fusiform face area; OFA = occipital face area; PPA = parahippocampal place area.

Experimental paradigm: The functional data from the experimental task were entered into a 2 x 3 repeated measures ANOVA with Time (T1, T2) and Condition (Encoding, Recognition, Control Task) as within-subjects factors to explore any changes in brain activation pattern pre and post intervention. No significantly activated voxels were detected at the set threshold of $p < .001$ (uncorrected for multiple comparisons). There were no areas showing a main effect of Time or Condition.

Changes in brain activity following the treatment period

To explore whether there were any changes at all in brain activation pattern following the treatment period, activation maps contrasting T1 and T2 using a *t*-test were created for each condition separately. These contrasts revealed that during encoding and recognition, there were indeed altered brain activity patterns at T2 compared to T1. For encoding, these alterations consisted of higher activity at T1 in mainly bilateral visual areas, including bilateral fusiform and lingual gyri. Statistics and Talairach coordinates of the most significantly active voxels are shown in Table 6.5. At the current threshold no areas were detected that were more activated at T2 than at T1. To examine the nature of the activation differences that occurred during

encoding, the beta values for each condition were tested against an artificial baseline (zero) using a one-sample *t*-test with a threshold of $p < .05$ (uncorrected for multiple comparisons). Areas showing a significant difference from baseline during encoding are indicated in Table 6.5.

Table 6.5 – Regions showing activation differences during the encoding condition following the treatment period in a whole-brain random effects analysis ($t(10) = 4.59$, $p < .001$, uncorrected for multiple comparisons).

Region	Hemi-sphere	BA	x	y	z	No. of voxels	T-value	p-value
T1 > T2								
Medial frontal gyrus	L	BA 10	0	50	4	54	6.456	.000073
Precuneus	L	BA 23	0	-61	22	145	7.099	.000033
Fusiform gyrus *&	R	-	30	-70	-14	100	6.199	.000102
Fusiform gyrus *	L	BA 19	-33	-76	-14	117	5.706	.000197
Lingual gyrus *	R	-	9	-79	4	153	6.094	.000117
Lingual gyrus *	R	BA 18	9	-82	-10	137	5.983	.000135
Inferior occipital gyrus *	L	BA 17	-12	-88	-5	153	7.024	.000036
T2 > T1								
No significant differences detected at the current threshold								

BA = Brodmann Area; L = left; R = right; * = beta values at T1 significantly higher than baseline at $p < .05$; & = beta values at T2 significantly higher than baseline at $p < .05$.

The most prominent activation changes occurred during recognition, in which brain activity was mainly higher at T1 than at T2 and occurred chiefly in left parietal and bilateral occipital areas. For statistics and Talairach coordinates, see Table 6.6. To examine the nature of the activation differences that occurred during recognition, the beta values for each condition were tested against an artificial baseline (zero) using a one-sample *t*-test with a threshold of $p < .05$ (uncorrected for multiple comparisons). Regions showing activation that was significantly different from baseline during recognition are indicated in Table 6.6.

During the control task, only two areas were found to show an activation difference: the left anterior cingulate cortex (BA 32; Talairach coordinates -6 11 40) and the left inferior occipital gyrus (BA 17; Talairach coordinates -12 -88 -5) showed higher activation at T1 than at T2. Areas showing the most significant changes in brain activation pre and post treatment (as defined by the most significant T-value) in the whole-brain analyses are presented in Figures 6.3 (encoding), as well

as in Figures 6.4 and 6.5 (recognition). Each individual's data are shown to demonstrate that participants showed more or less the same pattern of change in brain activity.

Table 6.6 – Regions showing activation differences during the recognition condition following the treatment period in a whole-brain random effects analysis ($t(10) = 4.59, p < .001$, uncorrected).

Region	Hemi-sphere	BA	x	y	z	No. of voxels	T-value	p-value
T1 > T2								
Superior frontal gyrus *	L	BA 8	-6	35	46	50	7.017	.000036
Anterior cingulate *&	L	BA 32	-6	11	40	55	5.808	.000171
Cingulate gyrus *	L	BA 31	-6	-25	40	60	9.145	.000004
Postcentral gyrus	L	BA 4	-51	-16	34	61	8.373	.000008
Postcentral gyrus *	L	BA 3	30	-31	61	87	7.450	.000022
Precuneus *&	L	BA 7	-3	-70	52	429	10.335	.000001
Posterior cingulate *&	R	BA 31	18	-52	13	111	5.886	.000154
Supramarginal gyrus *	L	BA 40	-51	-52	25	92	6.276	.000092
Superior temporal gyrus *	R	BA 39	42	-58	16	192	7.312	.000026
Superior temporal gyrus *	R	BA 22	39	-49	16	69	8.160	.000010
Fusiform gyrus *	R	BA 37	27	-40	-14	393	10.221	.000001
Fusiform gyrus *	L	BA 19	-21	-82	-2	226	7.427	.000022
Cuneus *&	L	BA 18	-21	-88	16	170	7.567	.000019
Lingual gyrus *	L	BA 18	-18	-70	-8	123	6.273	.000092
Lingual gyrus *	R	-	9	-79	4	214	8.876	.000005
Lingual gyrus *	L	BA 18	-21	-82	-2	103	6.308	.000088
Inferior occipital gyrus *&	L	BA 17	-12	-88	-5	149	6.643	.000058
Anterior cerebellum *	L	-	-15	-40	-17	121	6.601	.000061
T2 > T1								
Middle frontal gyrus &	R	BA 9	48	11	31	143	9.148	.000004
Precentral gyrus &	R	BA 44	51	11	7	84	5.335	.000331

BA = Brodmann Area; L = left; R = right; * = beta values at T1 significantly higher than baseline at $p < .05$; & = beta values at T2 significantly higher than baseline at $p < .05$.

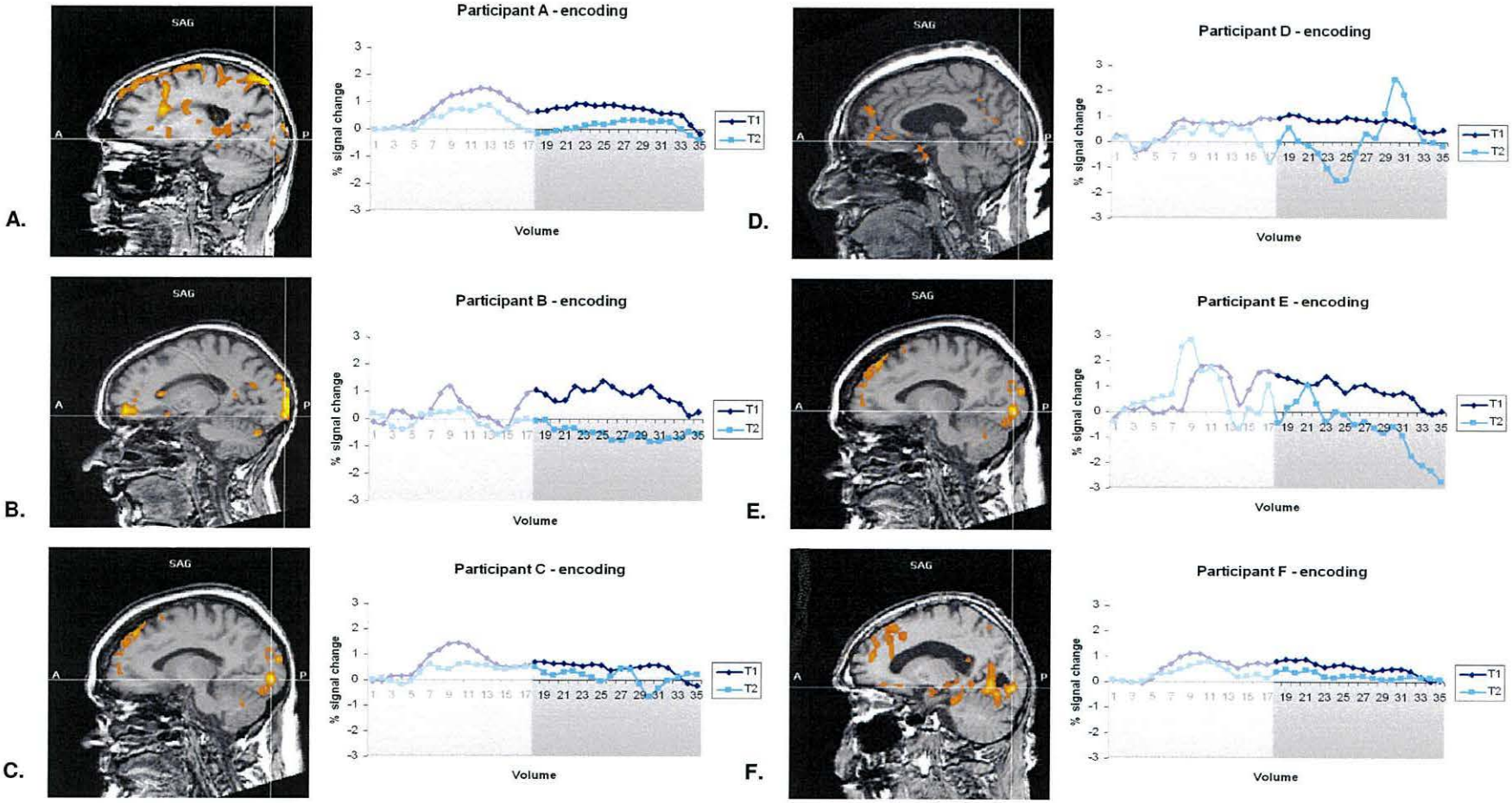

Figure 6.3 – The left inferior occipital gyrus showed higher activation during encoding at T1 than at T2 for each participant (A to F) at $p < .001$ (uncorrected). Each individual's anatomy is presented in saggital view along with the signal time course during encoding (volume 18 to 36). The letters A and P indicate the anterior and posterior side of the brain. Talairach coordinates for each participant's most significant voxel in the inferior occipital gyrus are indicated by a white cross (participant A; -20 -88 -5; participant B: -15 -97 -11; participant C: -12 -88 -5; participant D: -3 -91 -5; participant E: -12 -94 -8; participant F: -18 -88 -11).

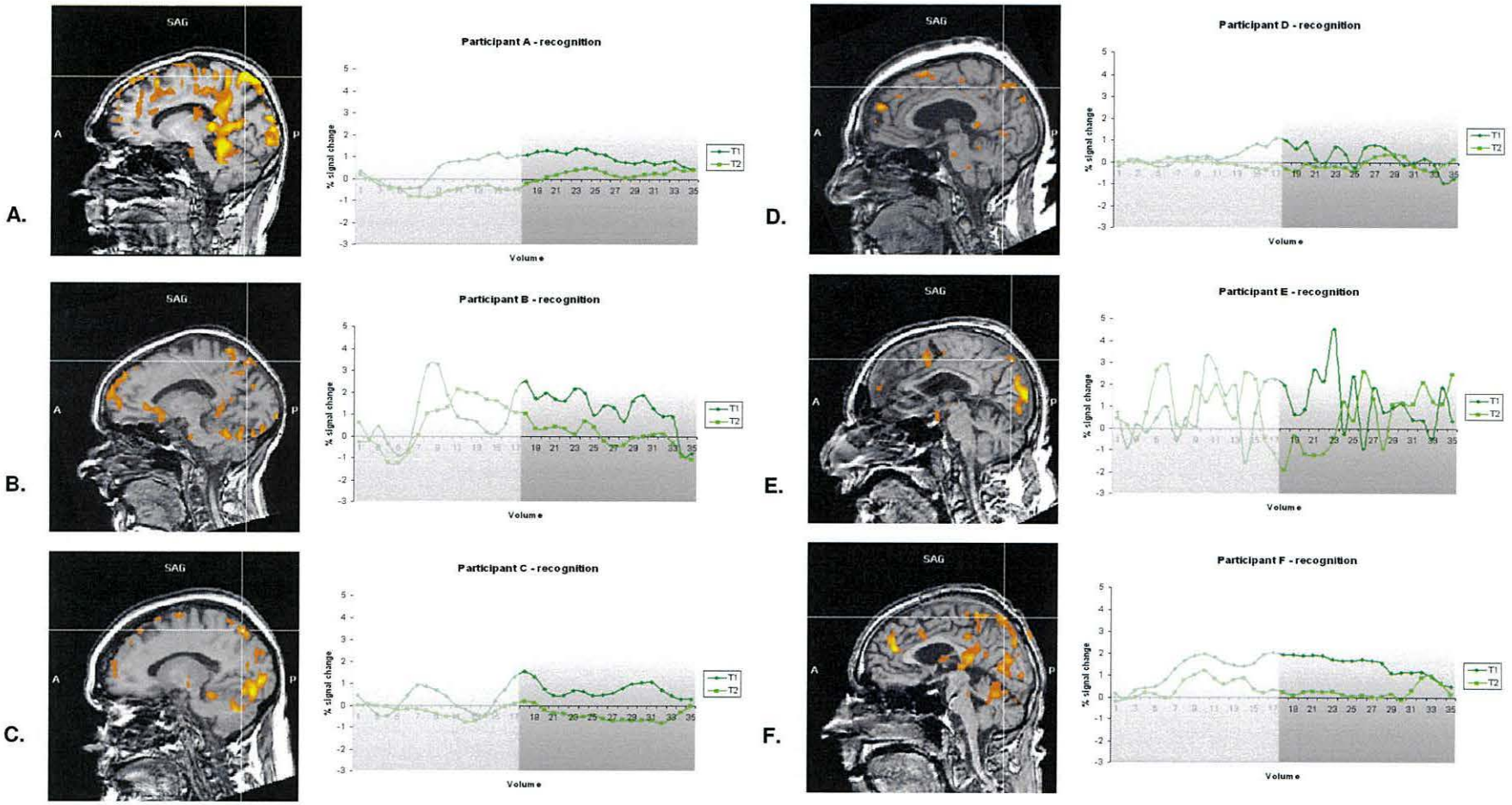

Figure 6.4 – The left precuneus showed higher activation during recognition at T1 than at T2 for each participant (A to F) at $p < .001$ (uncorrected). Each individual's anatomy is presented in saggital view along with the signal time course during recognition (volume 18 to 36). The letters A and P indicate the anterior and posterior side of the brain. Talairach coordinates for each participant's most significant voxel in the precuneus are indicated by a white cross (participant A; -15 -67 58; participant B: -12 -70 49; participant C: -14 -67 49; participant D: -3 -67 46; participant E: -3 -70 53; participant F: -3 -76 43).

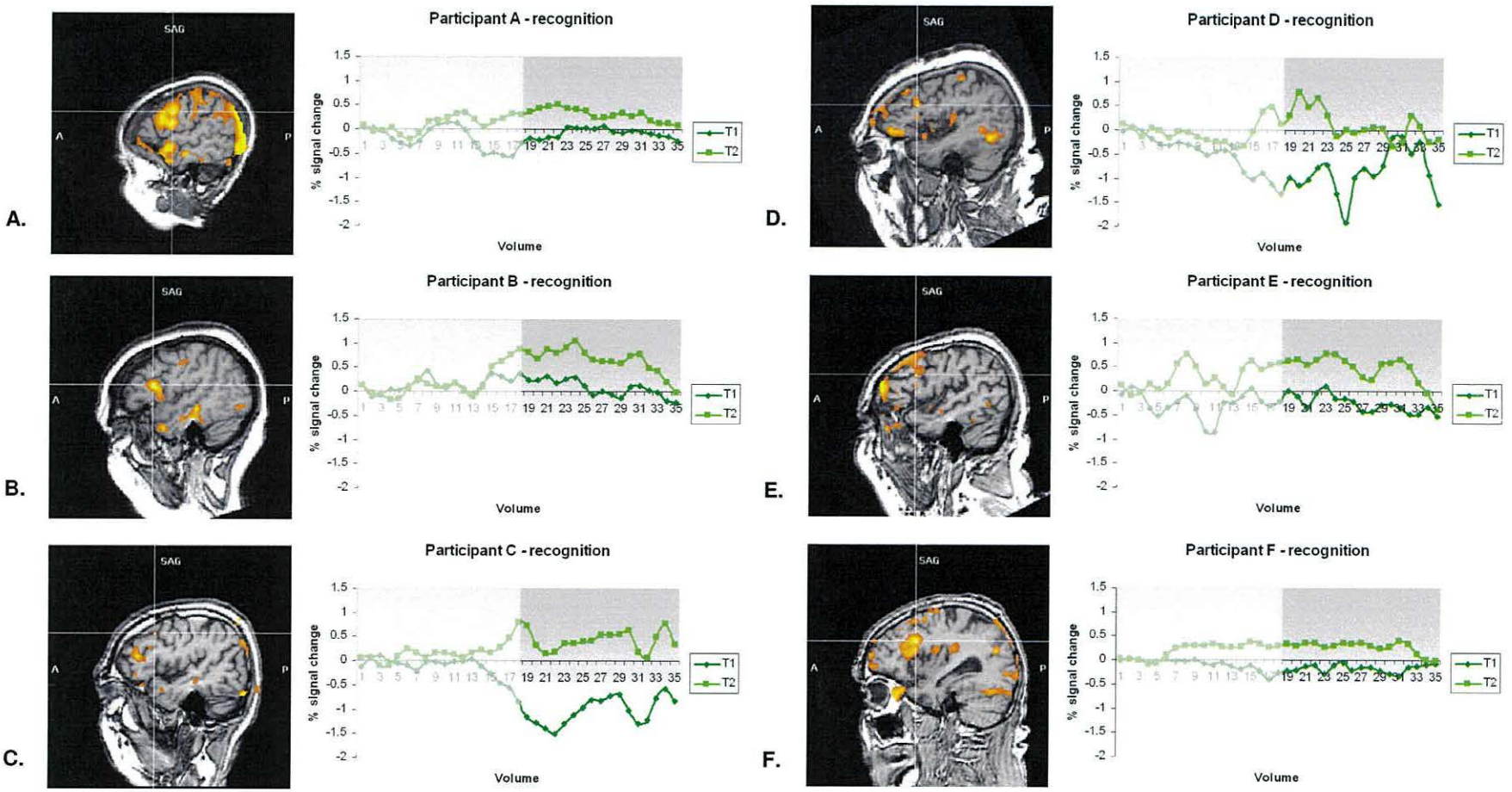

Figure 6.5 – The right middle frontal gyrus showed higher activation during recognition at T2 than at T1 for each participant (A to F) at $p < .001$ (uncorrected). Each individual's anatomy is presented in saggital view along with the signal time course during recognition (volume 18 to 36). The letters A and P indicate the anterior and posterior side of the brain. Talairach coordinates for each participant's most significant voxel in the middle frontal gyrus are indicated by a white cross (participant A; 45 17 37; participant B: 54 2 25; participant C: 45 20 16; participant D: 42 17 25; participant E: 48 17 25; participant F: 36 14 28).

DISCUSSION

The current study investigated whether any memory-related brain activation changes could be observed following an eight-week cognitive rehabilitation programme. During encoding of face-name associations, changes in brain activity were observed in mainly visual areas, where activity was greater prior to than following treatment. Results showed that, during recognition, activation differences occurred predominantly in parietal, temporal and occipital regions, where brain activity was higher before than after the treatment period. Two frontal regions showed greater activation during recognition after the treatment period than before. Activation differences in the control task that did not involve memory processing were minimal. Changes in functional activation were supported by small increases in performance on immediate recognition, although not every participant showed an improvement on the task. No differences were found in delayed memory scores obtained with the recognition task administered after each scan.

BRAIN ACTIVATION DIFFERENCES IN ENCODING FOLLOWING COGNITIVE REHABILITATION

Activation differences in a pre-post treatment comparison were found in the left medial frontal gyrus, the left precuneus, and several areas in the visual cortex, including the lingual gyrus. Brain activity in these regions was higher before than after the treatment period.

One possibility for this difference is that there was adaptation in neural activation simply because participants were more used to being in the fMRI environment, and they had performed the task on a previous occasion. However, this explanation is unlikely as activation changes in the lingual and fusiform gyri were not observed during the control task. Also, no activation differences were observed during the passive viewing task in temporo-occipital areas that specialised in viewing faces and scenes, thus suggesting that in principle the participants mounted to similar blood-oxygen level dependent responses on each occasion.

Alterations in occipito-parietal areas have been reported in previous studies that taught healthy participants to use a semantic (Miotto et al., 2006) or mnemonic memory strategy (Nyberg et al., 2003) to learn word lists, and scanned participants

prior to and after they had acquired the memory strategy. These regions have been associated with the use of mental imagery (e.g. Kosslyn, Ganis, & Thompson, 2001). However, both these studies reported a signal *increase* in parietal-occipital regions following the training. Consequently, Nyberg and colleagues interpreted their results as increased use of visual imagery following the use of a mnemonic strategy. It is unclear how their findings relate to the results of decreased parietal-occipital activity in the current study because the previous studies were carried out with healthy participants who were only trained on a single occasion in between scans. Participants in the present study received training over a period of eight weeks, and were obviously impaired in memory function due to Alzheimer's pathology. Also, the previous studies used words as stimuli whereas much richer visual stimuli (faces paired with names) were used in the current study. It may be that participants in the present study did use mental imagery during encoding, and that over the course of eight weeks they became more effective at performing the task and recruited less neural resources.

Cross-sectional studies comparing people with AD to healthy older adults during encoding of face-name associations have shown hyper-activation of a fronto-parietal network, including the middle / medial and inferior frontal gyri and superior parietal areas such as the precuneus, coupled with a decrease or absence of activation in the hippocampi (Pariente et al., 2005; Sperling et al., 2003a) Some have argued that hyper-activation in a fronto-parietal network correlates positively with, and thus aids, task performance (Grady et al., 2003). Although at a less stringent threshold some frontal regions did show higher activation at T2 compared to T1 in the current study, it was rather surprising to find little change in the frontal-parietal network described in previous studies as showing prominent alterations in AD and even being capable of a compensatory role. Obviously the present study differs in design from these previous reports in that it was longitudinal and did not compare brain activation with that of a healthy control group. Nevertheless, given the absence of any brain areas showing higher activation following the treatment period, the current findings do not support the idea of compensatory brain activity in AD, at least during the encoding process.

BRAIN ACTIVATION DIFFERENCES DURING RECOGNITION FOLLOWING COGNITIVE REHABILITATION

During retrieval of face-name associations, higher activation was found prior to than following treatment in some small left medial frontal clusters but predominantly occurred in left posterior parietal, right posterior temporal and bilateral occipital areas. The right middle frontal gyrus (corresponding to BA 9) and the right precentral gyrus (corresponding to BA 44) showed higher activation at T2 compared to T1.

The medial frontal, and parietal and occipital areas showing higher activation at T1 compared to T2 nearly all form part of a 'default mode' or 'resting state' network of regions that are more active when people are not engaged in any particular cognitive process than during the performance of a cognitive task (Mason et al., 2007). In a positron emission tomography study, Herholz and colleagues (2002) demonstrated reduced metabolism during rest in people with AD in posterior cingulate, temporo-parietal and frontal association cortices. In the previous chapter it was also noted that, compared to healthy older adults, people with AD appeared to show inefficient inhibition of parietal areas comprising the default mode network, resulting in increased task-related signal in these areas. The current findings suggest that prior to the treatment period participants were unable to inhibit brain regions associated with the resting state network. Consequently, the absence of task-related signal in these regions at T2 might denote that inhibition of default mode network areas has become more efficient, although not to the point of a significant signal decrease. As such, cognitive rehabilitation may lead to increased efficiency to inhibit task-irrelevant brain activity. However, it remains unclear why this effect is not observed during encoding.

The right middle frontal gyrus (BA 9) and the right inferior frontal gyrus (BA 44) showed activation increases at T2 compared to T1. The right dorsolateral prefrontal cortex (BA 9/46) has been linked to successful recognition of words (McDermott et al., 2000). The ventrolateral prefrontal cortex (BA 44 / 45/ 47) is thought to play a role in retrieval especially when external cues are provided, such as a category to which a previously studied word belonged (Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998). Miotto et al. (2006) reported use of these areas after healthy adults were taught a semantic strategy to encode verbal material, and suggested that these regions are involved in strategic memory processing. Although

their study focused on the encoding process, it may be that similar mechanisms occur during retrieval, for example when participants remember the mnemonic they used to encode the material earlier. Thus, one possibility is that increased prefrontal activation in the current study reflects the use of a memory strategy to recognise the correct name associated with a face. This idea would fit well with the use of a memory strategy being one of the key aspects in the cognitive rehabilitation programme besides working on individual goals. Moreover, this suggestion is supported by the modest increase in behavioural performance on the immediate recognition task.

LIMITATIONS OF THE CURRENT STUDY

The present study has some important limitations. Firstly, the group size (n = 6) is small and behavioural performance showed considerable individual differences, although the general pattern was one of very modest improvement. Participant C performed at ceiling level on the immediate recognition task at T1, meaning there was little room for improvement at T2. The neuropsychological test results (not presented here) for participant B called into question her diagnosis of AD and suggested her cognitive status may have been more properly classified as amnestic mild cognitive impairment. Participants A and F were not able to perform the immediate recognition task during all runs. Although at group level there is a small increase in performance, this must be interpreted with caution. The small group size and individual differences mean that any inferences made about possible biomarkers for cognitive rehabilitation are preliminary. Nevertheless, generally patterns of behavioural performance and brain activity were broadly similar.

A second limitation is that participants' behavioural performance improved significantly on the control task as well as on immediate recognition of face-name associations. Among others, the control task was designed as a simple paradigm that ensured participants were in principle able to carry out an undemanding task and press buttons in an fMRI environment. Participants already achieved a high level of performance on the control task at T1 (group average 85% correct) and scored even higher at T2 (group average 92% correct). It is difficult to interpret the implications of this improvement. One possible explanation may be that participants performed better in general because they were more familiar with the fMRI environment.

However, this does not explain the alterations in brain activation observed during recognition at T1 compared to T2 and the virtual absence of change in neural activity during the control task pre and post treatment. In addition, results from the passive viewing task carried out alongside the experimental task produced no significant changes in brain activity in any of the participants, indicating that merely having another fMRI scan does not lead to changes in brain activity. A second possible explanation for the improved scores on the control task is that the cognitive rehabilitation intervention was not specific in targeting associative memory function. As the present data do not include a control group, it is not possible to dismiss this possibility. However, the intervention focused on teaching strategies to memorise face-name associations along with targeting one or two individually set goals. There is no rationale to assume that any benefits from the cognitive rehabilitation intervention transfer to other tasks. As mentioned previously, the fMRI data suggest that any alterations in brain activity observed following the treatment period occur in the recognition task and not in the control task, supporting the idea that practising memory strategies to learn and remember face-name associations yields specific neural changes during recognition only. Thus, these findings provide some support for the alterations in brain activation patterns to be related to receiving eight weeks of cognitive rehabilitation therapy.

Conclusion

Following an eight-week cognitive rehabilitation programme, some small changes in memory-related brain activity were observed. These were most prominent during recognition, with findings suggesting more effective inhibition of brain regions comprising a default mode network following treatment, coupled with an increase in small right prefrontal areas that may reflect the use of a memory strategy. It is impossible to draw firm conclusions from these preliminary results, but there may be some pointers to suggest we can change brain activation patterns with cognitive rehabilitation. For example, although there were only modest changes in brain activity, these changes did occur during memory processes, which were targeted by the treatment, and there were modest improvements in immediate recognition of face-name associations. During the control task, which involved no memory processing, minor alterations in two small areas were observed, while no changes

occurred during the passive viewing task. These findings must be regarded as preliminary and the results remain inconclusive with regards to what mechanisms underlie any changes in brain activation following cognitive rehabilitation. Nevertheless, studying the neural mechanisms of cognitive rehabilitation in people with AD is innovative and has not been reported before. Despite the challenges and shortcomings of the present findings, the current study demonstrates that the adopted approach is feasible in people with AD and as such provides a starting point for future studies wishing to explore the neural bases of cognitive treatment aimed at improving memory function. Future studies including a larger number of participants and a control group receiving a placebo intervention are needed to ensure that any behavioural improvements are specific to receiving the treatment, and to enable generalisation of the findings and possible identification of biomarkers underlying cognitive rehabilitation.

Chapter 7 – Discussion

The aim of this thesis was to investigate changes in functional brain activation patterns in healthy ageing and Alzheimer's disease (AD) during an everyday associative memory task and link these alterations to what is known about effective memory-enhancing learning strategies. In addition, it was explored whether changes in brain activity in people with AD could be observed following an intervention programme of cognitive rehabilitation and whether it was possible to identify biomarkers of treatment success. The discussion chapter will first recapitulate the findings from each chapter and consider the implications, before going on to discuss limitations to the studies and providing an outlook for future research.

SUMMARY AND IMPLICATIONS OF THE MAIN FINDINGS

Brain activation during associative memory processing in ageing and Alzheimer's disease: implications for rehabilitation techniques

Chapter 2 reviewed extant studies on brain activation changes in healthy ageing and Alzheimer's disease, and aimed to link this knowledge to findings from behavioural intervention studies, in view of determining why certain strategies to improve memory function are effective and others are not.

Evidence from neuroimaging studies suggested that when older adults use semantic information to encode a stimulus, they can perform as well as young adults (Logan et al., 2002), but that it is seemingly difficult for older adults to engage in such an effective strategy spontaneously (Logan et al., 2002; Troyer et al., 2006). However, during successful encoding, healthy older adults us a very similar network of brain areas compared to young adults (e.g. Daselaar et al., 2003a).

Compared to healthy older adults, people with AD show disruptions in multiple areas underlying memory function, and typically under-activate hippocampal areas while hyper-activating superior parietal regions during episodic memory tasks (e.g. Pariente et al., 2005; Sperling et al., 2003a). These findings help to explain results from behavioural studies that have suggested people with AD need more cognitive support to achieve improvement in memory function, ideally both at encoding and retrieval. Furthermore, behavioural reports have shown enhanced memory performance when semantic information about an item is used during encoding (e.g. Bird & Luszcz, 1991, 1993; Lipinska & Bäckman, 1997). It may be that semantic encoding activates the hippocampus to some extent. One neuroimaging study demonstrated hippocampal activation in people with AD when participants

were given specific semantic instructions during encoding (i.e. making indoor / outdoor judgements on pictures of scenes) (Golby et al., 2005).

The chapter also discussed some of the interpretations of brain activation changes in healthy ageing and AD, as several reports in the literature have proposed that increased brain activity in areas not typically subserving memory function in healthy young adults may occur to compensate for neural loss in 'typical' memory regions in healthy ageing (e.g. Cabeza, 2002) and in AD (Grady et al., 2003; Pariente et al., 2005). However, others have argued that hyper-activation observed in healthy ageing may represent the inability to suppress task-irrelevant brain activity (Logan et al., 2002). In addition, some of the areas thought to comprise a 'compensatory' network in people with AD were identified as part of a default-mode network of regions that were more active during rest than during a cognitive task, and showed lack of effective inhibition during cognitive processes (Buckner, 2004; Lustig et al., 2003). Thus, rather than reflecting compensatory activity, hyper-activity may represent ineffective inhibition of brain regions in both healthy ageing and AD.

Both functional imaging and behavioural studies found that in healthy ageing, semantic processing of information plays a key role in enhancing memory function. Although older adults appear to find it difficult to engage in an effective encoding strategy spontaneously, they can do so when encouraged to use semantic characteristics of the information. In addition, the relevant neural circuits in frontal regions supporting such processes are intact in older adults.

Brain activation patterns during successful encoding in early-stage AD are similar to those observed in healthy older adults (Gould et al., 2006a; Gould et al., 2005). For people with AD, it was suggested that effortful cognitive strategies that make the most of residual memory ability may be most effective in improving or maintaining memory function.

The role of functional neuroimaging in cognition-focused intervention

In Chapter 3, the role of fMRI in assessing treatment outcome was considered and it was investigated whether knowledge about functional brain activation changes can be used to make recommendations for more effective cognitive strategies to ameliorate memory functioning in healthy ageing and AD. The identification of biological markers of treatment success is important in order to understand the neural underpinnings of treatment effects. It was established that, although fMRI has been

applied successfully to demonstrate plasticity in a range of areas, very little research has been carried out with respect to unravelling the neural mechanisms underlying cognitive intervention in the field of healthy ageing and AD. Defining biomarkers of a particular intervention is at present still very challenging as past results have shown inconsistent findings, and have often used the same paradigm to train participants in the intervention period and to assess functional changes, therefore rendering it possible that more automated processing of the task was studied rather than changes in cognition following treatment. Moreover, previous research has been carried out in areas other than memory, and is thus not very informative as to what sort of paradigm may be useful to study enhancement of episodic memory function in healthy ageing and AD. Associative memory decline is common in both cases (e.g. Lindeboom et al., 2002; Naveh-Benjamin, 2000). A paradigm tapping into associative memory processes, such as pairing a name with a face, was considered representative of an everyday associative memory task that healthy older adults and people with AD might have difficulty with.

After reviewing literature on fMRI paradigms of face-name learning used in healthy older adults, people with mild cognitive impairment (MCI), and people with AD, it was concluded that previous studies have used a large number of stimuli in conjunction with highly educated participants, and that such a task may not be feasible given the cognitive abilities of the average population. It was also argued that it is useful to study both encoding and retrieval processes, that it is preferable to test recognition rather than free recall of memory for associations, and that an engaging control task should be used. The need for a simpler face-name association task was expressed.

Finally, Chapter 3 described the development of a simple face-name paradigm that can either serve as a tool to evaluate treatment outcome in people with AD, but can also be used as a single measurement in cross-sectional studies comparing different populations.

Age differences in brain activation during a simple associative memory task

Chapter 4 addressed activation changes that characterise differences between healthy young and older people during associative memory processes. Brain activation patterns during face-name learning in a group of healthy young and older adults were studied using fMRI in conjunction with the paradigm described in Chapter 3, and

with a passive viewing task. The study focused on the nature of these activation differences and whether these signified neural compensation in the older group or were a sign of inability to suppress activation in areas irrelevant to the task.

Both groups scored at ceiling level on immediate recognition of face-name associations, hence there was no significant difference in performance between the groups. However, the older group showed significantly greater brain activity in mainly frontal and parietal regions during the episodic memory task. Age differences in brain activation were most pronounced during recognition. One possible explanation for these findings may be that the older group was unable to disinhibit areas that are not relevant to task performance. Lustig and colleagues (2003) proposed that with increasing age, older adults are less able to deactivate default-mode areas of the brain during a cognitive task. Secondly, the right parahippocampal gyrus, an area specialised in the processing of specific stimuli, showed an age difference in activation during encoding and recognition, but not during a passive viewing task. Decreased specialised neural response in this area has been reported before (Park et al., 2004) and is in line with the idea that there is less neural specialisation with increasing age (e.g. Baltes & Lindenberger, 1997b). The present findings further suggest that these effects are modulated by the type of task, and that these specialisation differences may occur only during cognitively demanding processes. The increased frontal activation in the older adults compared to the young adults is thought to reflect nonselective recruitment of task-irrelevant areas rather than compensatory activity, and, where it concerned areas also recruited by the young group, may also indicate increased effort or attention in the older group.

Functional activation changes in Alzheimer's disease

In Chapter 5, the face-name learning paradigm developed in Chapter 3 was applied to study changes in brain activation pattern between healthy older adults and people with AD, using fMRI. A passive viewing task was also administered to ensure that the groups were in principle able to mount to a similar BOLD response. An important question was whether any activation differences observed represented the use of additional brain areas to compensate for neural loss in the AD group, or alternatively, indicated dysfunction of a particular brain region.

Behaviourally, the older adults performed significantly better on the immediate recognition of face-name associations than the AD group, but no group differences in

were observed on the delayed recognition task. Brain activation differences did not occur during passive viewing or during the control task, but instead were only observed during the conditions requiring memory processing (encoding and recognition) characterised by hypoactivation in the AD group compared to the older control group during encoding in some left frontal areas (BA 6 / 46) and the right putamen. There were no areas in which the AD group showed higher activation than the OC group during encoding. During recognition, older adults also showed higher activation in some mainly frontal and parietal regions compared to the AD group. However, a large number of frontal, parietal and temporal areas showed higher activation for the AD group compared to the OC group during recognition. These latter differences were mainly caused by a significant signal increase in the AD group coupled with an absence of significant signal change in the OC group. Activation in the AD group did not correlate with immediate or delayed recognition performance, or with MMSE score, thus rendering it unlikely that these activations are compensatory and assist in task performance. It may be that these activations are an indicator of the inability in the AD group to inhibit areas that are not directly relevant to task performance. Indeed, it has been suggested previously that medial and parietal midline areas involved in a resting state network correlate negatively with hippocampal activation (Della-Maggiore et al., 2000; Maguire & Mummery, 1999) and these resting state network areas may be dysfunctional in AD (Buckner, 2004; Greicius et al., 2004; Lustig et al., 2003). Results from this study imply that intervention strategies aimed at enhancing memory function should be aimed at making the most of residual memory function in areas typically subserving memory, rather than focusing on an alternative, compensatory network of brain areas.

Effects of cognitive rehabilitation on memory-related functional brain activation in people with early stage Alzheimer's disease

Chapter 6 explored changes in memory-related brain activity in six people with early-stage AD who participated in an eight-week cognitive rehabilitation intervention programme. Participants were scanned prior to and following the treatment period while they engaged in the face-name association task described in Chapter 3. Participants also carried out a passive viewing task. Behaviourally, participants showed a modest improvement on immediate recognition of face-name associations, although individually not everyone showed enhanced performance, and

two participants performed at chance level both prior to and following the treatment period. No changes in performance were observed on a delayed recognition task. In terms of functional activation differences, no changes were observed during a passive viewing task, and alterations were minimal in a control task. However, during encoding of face-name associations participants showed greater brain activity prior to (T1) than following (T2) treatment, chiefly in visual areas. In addition, greater activation was observed in numerous regions in parietal, temporal and occipital cortices at T1 compared to T2. During recognition two areas exhibited greater activation at T2 compared to T1 in two right frontal regions (BA 9 / 44). Brain activity in visual areas during encoding has been associated with the use of mental imagery (e.g. Kosslyn, Ganis, & Thompson, 2001), although this study was cross-sectional and found a signal increase after instructing participants to use mental imagery. If the current findings of decreased brain activation following cognitive rehabilitation are indicative of the use of mental imagery, it may be that participants became more efficient at applying such strategies over the course of the intervention. Many of the brain regions showing a decrease in brain activity during recognition are thought to be part of a resting state network, and as such the decrease may be interpreted as more efficient inhibition of task-irrelevant brain areas following the treatment period. Although these results are preliminary and studies involving a greater number of participants and a control group receiving placebo intervention are needed, there are no previous reports studying neural changes following cognitive rehabilitation in people with early-stage AD. The present findings may serve as a starting point for future studies in this field.

LIMITATIONS OF THE STUDIES

Although the work presented here yielded some interesting findings, there are a number of limitations which need to be considered when interpreting the results. These will be addressed below.

Differences in task performance in people with Alzheimer's disease compared to healthy older adults

In Chapter 5, brain activity in a group of people with AD was compared to that of a group of healthy older adults during encoding and recognition of face-name

associations. The healthy older controls scored significantly higher than the AD group on immediate recognition of the face-name pairs. Previous studies have contended that when performance is not matched between groups, it cannot be ruled out that brain activation differences between groups reflect different cognitive operations such as increased effort rather than cognitive deficits (Gould et al., 2006a; Gould et al., 2005). These studies demonstrated that when task performance is matched, people with AD can make use of very similar networks of brain regions in comparison to healthy older adults. Hence, it can be argued that the current findings may simply represent, for example, increased effort in the AD group. However, if the goal is to study why people with AD have difficulty with an everyday task such as remembering a person's name, a cognitive process that they were able to do before the disease onset and that does not pose such a substantial problem to healthy older people, then studying encoding and retrieval with the same paradigm for both groups must be considered a valid approach to address brain activation differences in people with AD compared to healthy older adults.

Repeated trials of rearranged pairs during recognition

During recognition of the face-name pairs, participants were presented with a repetition of intact and rearranged items. Previous research has shown that recognition of rearranged items can lead to retroactive interference, meaning that the rearranged combination can be consolidated in memory as the correct association during recognition (Cleary, Curran, & Greene, 2001; Light et al., 2004; Perruchet et al., 2006). It has been proposed that retroactive interference is more pronounced in people with AD than in healthy older adults (Loewenstein et al., 2004). Therefore, it is possible that in the current study, lower scores on immediate recognition of face-name associations in the AD group compared to the older controls may have been aggravated by retroactive interference. If there was interference from the first two recognition trials on the later trials, then scores should be higher on the first two trials. However, as demonstrated in Chapter 5, there was no difference in recognition score between early and subsequent recognition trials. For that reason, it is unlikely that retroactive interference played a significant role in the recognition of face-name pairs in the current paradigm.

Using the control task as a reference condition

In Chapter 3, it was argued that a novel face-name learning paradigm was needed to study associative memory in people with AD. While the paradigm presented in this thesis was useful in that it was feasible to study associative memory in an fMRI environment in people with AD, it also presented some difficulties and issues. It was anticipated that the control task, in which participants made judgments on whether a printed gender matched a face, would be an automated process requiring no significant memory component. It was rather surprising that the control task yielded brain activation that was similar in signal strength and pattern to the recognition condition in both young and older adults, and people with AD. As such, the control task did not serve its purpose of an appropriate reference condition that can be used to identify brain areas specific to memory processes. There may be a number of underlying reasons for this observation. Because the task included matching a gender to a face, this may have unintentionally tapped into semantic memory processes. No such issues were mentioned in a PET study that also employed a gender decision task as a reference condition to face-name encoding (Herholz et al., 2001). The encoding task used by Herholz and colleagues was more challenging than the paradigm used in the present studies in that participants were required to learn a greater number of face-name associations (40 stimuli) which were presented only once. The combination of a more difficult task in combination with the gender decision control task may have been better able to tease out episodic memory processes. However, in the present study no main effects of task were observed in the AD group, who did perceive the face-name association paradigm as more challenging, as indicated by their behavioural performance. Behavioural results from the three fMRI studies presented here suggest that little or no memory processing was involved in performance of the control task. In Chapter 4, both the young and the older adults scored at or just above chance level for delayed recognition of faces seen in the control task but not the face-name association task. The same pattern was observed in Chapters 5 and 6. Furthermore, on the level of brain activation patterns, group comparisons in Chapters 4 and 5 and pre- and post-treatment contrasts in Chapter 6 showed no or few differences in brain activity during the control task, whereas during encoding and especially immediate recognition, changes in brain activity were substantial.

Absence of hippocampal activation during encoding and recognition within groups

The absence of hippocampal activation during encoding and recognition of face-name associations on a within-group level was unexpected. Hippocampal activation is thought to be crucial to the binding of unrelated items in memory (Henke et al., 1997; Henke et al., 1999; Stark, Bayley, & Squire, 2002), and hippocampal involvement in encoding face-name associations in healthy young and older adults has been reported previously (Pariente et al., 2005; Sperling et al., 2003a; Sperling et al., 2001; Sperling et al., 2003b). Others, however, reported no hippocampal activation during encoding of face-name associations (Herholz et al., 2001), encoding of face stimuli (Kuskowski & Pardo, 1999), or recognition of faces (Haxby et al., 1996). Haxby and colleagues argued that perhaps the hippocampus may play a role in consolidating recently formed memories rather than being involved in representation and retrieval of these memories, and that such consolidation processes are different to the process of retrieving a memory. It is also possible that differences in study design and in the ways the data were analysed account for the different findings. Firstly, those reports that did not observe hippocampal involvement used PET and not fMRI. Next, they used a blocked design and contrasted two conditions in a whole-brain analysis, similarly to what was done in Chapters 4-6. It is possible that in a simple contrast, potential differences in activation in the hippocampus are masked (Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996). In a further study that opted for a blocked design, Sperling et al. (2003a) conducted a region of interest analysis on the hippocampal formation alongside a whole-brain analysis to explore brain activation in the hippocampus. The studies conducted by Pariente et al. (2005) and Sperling et al. (2001; 2003b) were event-related fMRI studies that were able to distinguish between successfully and unsuccessfully encoded items. Hippocampal involvement during encoding was detected when contrasting those items that had been remembered successfully later on with those that had not been successfully retrieved.

Alternatively, rather than being related to methodological issues, the absence of hippocampal activation may have been a true representation of the structure's involvement in the paradigm employed in the current studies. In an event-related fMRI study, Rand-Giovannetti et al. (2006) presented face-name associations to healthy older adults three times to study the effects of repetition on brain activation pattern. They found signal increase in the hippocampus during the first presentation

of the face-name association, but hippocampal activation rapidly decreased on the second and third presentation, while activity in prefrontal and parietal regions maintained high throughout the three repeated presentations. The blocked design used in Chapters 4-6 did not allow for trial separation and could have levelled out any hippocampal activation that was present upon the first presentation of a face-name association.

Although the absence of hippocampal activation in Chapters 4-6 was unexpected, it was not viewed as problematic as the focus was on investigating group differences in a *network* of regions rather than any one specific brain structure. For documentation purposes, however, it would be interesting to separate out the signal time course for the first, second and third trial presentation to see whether hippocampal activation was indeed masked by the blocked design.

DIRECTIONS FOR FUTURE RESEARCH

Studying brain activation changes in healthy ageing

The nature of brain activation changes occurring in healthy ageing has been a matter of debate in the literature. While some have attributed these differences to compensatory reallocation of neural resources (Cabeza, 2002; Cabeza et al., 1997), others have suggested that brain activation in areas not supporting memory processes in young adults reflects a failure to inhibit these regions effectively (Logan et al., 2002). The present results presented some support for differential use of brain regions comprising a default mode network, but were also thought to reflect increased effort in the older group. Future research could place more emphasis on investigating the role of the default mode network in relation to task performance. One approach to investigate cognitive decline in ageing might be to compare brain activity during an associative memory paradigm in healthy young and older adults in conjunction with imaging data obtained during rest. It would be interesting to see whether those individuals with a more disrupted brain activation pattern during rest are also more likely to have decreased performance on an associative memory task.

Furthermore, recent studies have pointed out that damage to white matter, commonly caused by hypertension, is a major contributor to cognitive decline in healthy ageing (Pugh & Lipsitz, 2002). Future studies should consider medical comorbidities such as vascular compromise, as these may account in part for any

age-related brain activation differences.

Investigating brain activation changes in Alzheimer's disease

Alterations in brain activity pattern in AD compared to healthy ageing have been attributed by some to compensatory reallocation of neural resources (Becker et al., 1996; Grady et al., 2003; Pariente et al., 2005). Several studies have proposed that hyper-activation of parietal areas may indicate impaired inhibition of areas comprising a resting state network (Garrido et al., 2002; Remy et al., 2005). The present findings suggested that brain activation differences occur in regions related to a passive state (Raichle et al., 2001) and that rather than being compensatory, may reflect ineffective disinhibition of the default mode network. Several recent reports also proposed that the resting state network may be disrupted in early AD (Buckner & Vincent, 2007; Greicius et al., 2004; Lustig et al., 2003; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005). A future line of research might focus on developing methods to measure functional integrity of areas comprising the default mode network, in view of using this as a diagnostic tool to identify AD in the earliest possible stage.

On a different note, the current results reported brain activation differences in healthy ageing and AD in the presence of task performance differences. To justify this approach it was brought forward that the goal was to identify alterations in AD compared to healthy ageing. Nevertheless, it would be interesting to examine brain activation patterns both when performance is matched and when it is not matched. This would shed light on the question whether people with early-stage AD are in principle able to use similar neural circuitry compared to healthy older adults and secondly, it would then clarify how the use of this circuit changes when people with AD perform a task they perceive as more challenging. However, this would almost inevitably mean that participants will spend a longer time in the scanner, or would have to come back on a separate occasion. As experienced with the current studies, this may be a challenge in the case of the AD group.

Using fMRI as an outcome measure for cognitive intervention

The present work identified the importance of biomarkers for treatment efficacy. It is imperative for future studies developing cognitive intervention programmes to integrate behavioural as well as neural outcome measures so that the underlying

neural mechanisms of cognitive treatment success can be identified. In addition, Linden (2006) pointed out that information with regards to biomarkers of treatment success could then also be used to identify which people might benefit optimally from a given cognitive intervention. In this light, fMRI could be applied to study neural underpinnings of specific memory strategies without the need of an intervention. In healthy ageing, neuroimaging has been used to identify neural differences following the use of specific learning strategies such as semantic encoding (Logan et al., 2002; Miotto et al., 2006). The same principle could be extended to AD to explore differences in activation levels using different learning methods and varying levels of cognitive support.

In the work presented here, fMRI was applied to study neural changes following an eight-week cognitive rehabilitation intervention programme for people with AD. The current findings reported only data for those participants receiving cognitive rehabilitation, and pointed out the need for a control group to verify that changes in brain activation following the treatment period were specific to receiving cognitive rehabilitation. An obvious future line of enquiry would be to include a control group who received a placebo treatment.

Finally, real-time fMRI (rtfMRI) may be applied to teach people effective use of a memory-enhancing strategy. rtfMRI enables direct measurement of localised processes in the brain as they take place, and this information can consequently be used to train an individual to gain control over the specific neural mechanisms underlying these processes (Cox, Jesmanowicz, & Hyde, 1995). In a study investigating chronic pain management, participants were trained to actively control brain activity in the anterior cingulate cortex, a structure that mediates perception and regulation of pain (deCharms et al., 2005). The authors demonstrated that it was possible for people to gain active control over a brain region with the appropriate training. As this method has not been applied to the study of memory, it presently poses many hurdles, such as the identification of key brain structures that need to be targeted with a particular memory-enhancing strategy and trained during rtfMRI. Nevertheless, as our knowledge of brain activation changes in healthy ageing and AD, biological markers of treatment success, and neural mechanisms underlying specific learning strategies increases, it may in the future be possible to use rtfMRI in conjunction with rehabilitation techniques.

CONCLUSION

The following conclusions may be drawn from the present findings:

- Both behavioural and neuroimaging studies suggest that to optimise memory function, it is important that healthy older adults as well as people with AD make use of semantic information during encoding. Healthy older people show frontal brain activation patterns comparable to young adults during semantic encoding, and can achieve similar performance. In people with early-stage AD, semantic encoding may activate the hippocampus to some extent.
- fMRI is a useful tool to study neural mechanisms of treatment effects. More research is needed to identify biomarkers of treatment success. The current work presents a face-name learning paradigm with which neural effects of cognitive rehabilitation can be studied.
- When changes in brain activity in healthy ageing were studied with an associative memory paradigm, differences between the groups occurred mainly during recognition and were characterised by hyper-activation in the older group compared to the young group. Whereas increased frontal activation may indicate nonselective recruitment of task-irrelevant areas, hyper-activation in areas that were also activated by the young group may reflect increased effort in the older group to achieve similar behavioural performance compared to the young group.
- Changes in brain activation pattern in AD compared to healthy ageing were characterised by hypo-activation in the AD group during encoding, whereas during recognition the AD group showed hyper-activation in frontal, parietal and temporal brain areas. Since the hyper-activation in the AD group did not correlate with behavioural performance or with a cognitive screening score, it was interpreted as failure to inhibit task-irrelevant brain regions comprising a resting state network rather than compensating for neural loss in areas typically subserving memory function.
- A small group of people with early-stage AD showed modest behavioural improvements and changes in brain activity following an eight-week period of cognitive rehabilitation. Changes in brain activity were most prominent during recognition and were predominantly characterised by lower activation post- than pre-treatment in parietal, occipital, and temporal regions. Many of the brain areas

showing an activation decrease following treatment comprised a resting state network. Although the results are preliminary, they suggest that it is possible to observe neural changes following cognitive intervention, and that cognitive rehabilitation may help to reduce ineffective inhibition of brain areas.

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APPENDIX

Appendix A. – raw scores for older and younger participants

Subject ID	Immediate recognition	Control task	Delayed recognition
Older adults			
101	32 / 36	33 / 36	40 / 48
102	36 / 36	36 / 36	37 / 48
103	-	-	-
104	35 / 36	36 / 36	36 / 48
105	34 / 36	36 / 36	37 / 48
106	34 / 36	36 / 36	31 / 48
107	32 / 36	36 / 36	34 / 48
108	35 / 36	35 / 36	30 / 48
109	34 / 36	34 / 36	24 / 48
110	22 / 36	32 / 36	33 / 48
111	36 / 36	33 / 36	32 / 48
112	34 / 36	36 / 36	33 / 48
Young adults			
201	36 / 36	34 / 36	31 / 48
202	35 / 36	36 / 36	32 / 48
203	34 / 36	36 / 36	45 / 48
204	35 / 36	36 / 36	38 / 48
205	36 / 36	34 / 36	32 / 48
206	36 / 36	34 / 36	42 / 48
207	35 / 36	36 / 36	39 / 48
208	35 / 36	36 / 36	40 / 48
209	34 / 36	36 / 36	-
210	36 / 36	36 / 36	37 / 48
211	36 / 36	31 / 36	31 / 48
212	34 / 36	33 / 36	34 / 48

NB Responses for participant 103 were not recorded due to technical failure of the button box. Due to time constraints participants 103 and 209 also did not complete the delayed recognition task.

Appendix B. – raw scores for older adults and people with Alzheimer's disease

Subject ID	Immediate recognition	Control task	Delayed recognition
Older controls			
101	32 / 36	33 / 36	40 / 48
102	36 / 36	36 / 36	37 / 48
103	-	-	-
104	35 / 36	36 / 36	36 / 48
105	34 / 36	36 / 36	37 / 48
106	34 / 36	36 / 36	31 / 48
107	32 / 36	36 / 36	34 / 48
108	35 / 36	35 / 36	30 / 48
109	34 / 36	34 / 36	24 / 48
110	22 / 36	32 /36	33 / 48
111	36 / 36	33 / 36	32 / 48
112	34 / 36	36 / 36	33 / 48
People with AD			
1	11 / 30	20 / 30	25 / 48
3	12 / 30	28 / 30	33 / 48
5	10 / 18	12 / 18	-
7	17 / 36	30 / 36	29 / 48
10	22 / 36	36 / 36	28 / 48
22	6 / 18	16 / 18	-
26	33 / 36	34 / 36	38 / 48
31	17 / 36	31 / 36	29 / 48
36	34 / 36	36 / 36	34 / 48
39	26 / 36	33 / 36	23 / 48
45	32 / 36	32 / 36	34 / 48
47	23 / 36	29 / 36	29 / 48
48	12 / 36	31 / 36	35 / 48
53	27 / 36	30 / 36	34 / 48
55	25 / 36	33 / 36	36 / 48

NB as before, responses from participant 103 were not recorded due to technical failure. Due to time constraints this participant also did not complete the post-scan recognition task. Participants 5 and 22 only completed three runs in the scanner. Because they had not studied all the stimuli, the post-scan recognition task was not administered.

Appendix C. – correct answers during the first two and the last four trials

The first two trials of each run always showed the two different faces presented in the encoding phase, to reduce confusion and the possibility of retroactive interference. The first two trials could either be target trials, or distracters. The four remaining trials in the run were a mix of target and distracter trials, but each run always contained three target and three distracter trials. Also, in each run, each face was shown an equal number of times. The order in which the faces were shown was only controlled during the first two trials, to ensure that both faces were presented on trials 1 and 2. A possible order in which the trials could be presented is for example:

Trial	**Stimuli**	**Type**
1	Face A + Name A	Target
2	Face B + Name A	Distracter
3	Face B + Name B	Target
4	Face A + Name A	Target
5	Face A + Name B	Distracter
6	Face B + Name A	Distracter

Although it is not possible to completely rule out retroactive interference, scores during the last four trials can arguably expected to be significantly lower compared to scores obtained during the first two trials if repeatedly showing the same stimuli was a cause for retroactive interference. To test whether this was the case, the proportion correct scores during the first two trials were compared with those obtained during the last four trials for each participant, using a paired samples t-test. Results showed that the proportion correct answers was very similar across the trials (first two trials: mean score = .66, SD = .26; last four trials: mean score = .67, SD = .19) and that there was no significant difference between proportions of correct answers on the first two trials compared to those on the last four trials ($t(14) = .240$, $p = .814$).

Scores for each individual participant are presented below.

Subject ID	Proportion correct on first two trials	Proportion correct on last four trials
1	0.86	0.47
3	0.57	0.44
5	0.80	0.60
7	0.38	0.61
10	0.25	0.68
22	0.20	0.42
26	1.00	0.88
31	0.63	0.71
36	1.00	0.96
39	0.73	0.82
45	0.91	0.92
47	0.50	0.77
48	0.44	0.36
53	0.90	0.78
55	0.75	0.70

Appendix D. – response bias in the AD group

To test whether there was a response bias in the AD group, the proportion of hits in this group was compared to the proportion of correct rejections for both the experimental task and the control task with a paired samples t-test. If a response bias was indeed present, then it was expected that the proportion of hits and correct rejections would differ significantly from each other. For the experimental task, there was clearly no evidence of a response bias ($t(14) = .662$, $p = .519$), with very similar mean proportions for hits and correct rejections (hits: mean = .69, SD = .19; correct rejections: mean = .67, SD = .22).

Surprisingly, there was indeed a response bias in the control task, with participants showing a significant tendency to answer 'no' rather than 'yes' ($t(14) = .4.887$, $p < .001$; hits: mean = .84, SD = .12; correct rejections: mean = .92; SD = .07). It is not clear how this difference should be interpreted and why a response bias occurred during the control task. Some participants did report that they were not sure whether some of the faces shown were male or female. Potentially they answered 'no' in case of uncertainty. Since the purpose of the control task was to provide a task that did not involve memory processing and to ensure that the participants with AD were in principle able to carry out a task in an fMRI environment, the response bias was not considered relevant to the dataset.

Appendix E. – cognitive rehabilitation intervention

Clare (2007) has given a detailed description of the cognitive rehabilitation intervention and the techniques used. Below is an excerpt from her book in which she describes the intervention as it was carried out in the cognitive rehabilitation trial in which the participants in Chapter 6 took part.

"Both during and following assessment, individual goals are identified and a strategy for addressing these is devised [...]. This in turn is integrated within a comprehensive intervention plan that considers broader factors such as well-being and emotional responses. [...] Individualised cognitive rehabilitation trials aim to tackle directly those difficulties considered most relevant by the person with dementia and his or her family members or supporters. A key strength of the cognitive rehabilitation approach is that interventions are individually tailored and focus directly on real, everyday situations and difficulties. The starting point involves identifying desired outcomes in a collaborative manner. [...] The cognitive rehabilitation sessions take place for 1 hour a week over 8 weeks so that each participant receives eight sessions of therapy. Home practice is assigned between sessions. The aims of the intervention, for each participant, are as follows:

- To identify and work on one or two personal rehabilitation goals relevant to the person's everyday life, reflecting areas that aer currently causing difficulty or worry, or are felt to require improvement. Goals might include, for example, developing and using a strategy to help remember important events during the day or to keep track of important personal effects, learning to use a memory aid such as a calendar or memory board, or learning and retaining personally relevant information. Once goals have been identified, an individual approach to addressing these is designed. To assist in identifying personal rehabilitation goals and formulating a plan for addressing these, participants are asked to complete amemory diary during the 1-week interval between sessions 1 and 2. The diary consists of 25 statements relating to particular everyday memory problems that may occur (e.g. forgetting where you have put something). Participants are asked to indicate next to each statement how often the problem has happened each day for 7 days.
- To review the participant's use of memory aids and practical coping strategies, explore how it might be possible to build on these to make them more efficient, and consider the introduction of new aids or strategies where appropriate.
- To introduce techniques for learning new associations and information, provide practice in these, identify the person's preferred strategy, and encourage the wider application of this strategy in everyday life. The strategies used are simple verbal and visual mnemonics, semantic elaboration, vanishing cues and forward cueing, and expanding rehearsal. These are presented using face-name associations as an example of the kind of new learning or relearning that is relevant for everyday life. [...]

- To provide some practice in maintaining attention and concentration while processing information [...].
- To explore the person's current ways of coping with stress and anxiety, suggest some ways of building on these, and provide relevant practice using simple relaxation techniques [...].

The participant's spouse or other family member or carer is invited to join the last 15 minutes of each session. This part of the session is devoted to reviewing the content of the session, agreeing the home practice to be undertaken in preparation for the next session, and discussing ways of facilitating progress with the personal rehabilitation goals."

Excerpt from L. Clare, Neuropsychological Rehabilitation for People with Dementia (2008), pp. 113-126.

Appendix F. – letter of ethical approval for the Cognitive Rehabilitation intervention

Pwyllgor Moeseg Ymchwil Lleol Gogledd Orllewin Cymru
North West Wales Local Research Ethics Committee

North West Wales NHS Trust
Ysbyty Gwynedd
Directorate of Quality and Clinical Assurance
Bangor, Gwynedd
LL57 2PW

Telephone: 01248 - 384 877
Facsimile: 01248 - 365 318
Email: Rossela.Stoicescu@nww-tr.wales.nhs.uk

28 June 2005

Dr. Linda Clare
University of Wales Bangor
School of Psychology
Bangor
LL57 2AS

Dear Dr. Clare

Full title of study: **Functional and anatomical mechanisms underlying the effects of cognitive rehabilitation in early-stage Alzheimer's disease: implications for intervention**
REC reference number: **04/WNo01/73**

Thank you for your letter of 28 June 2005, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chairman.

Confirmation of ethical opinion

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

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		03 May 2005
Investigator CV		(None Specified)
Protocol	2	27 June 2005
Letter from Sponsor		09 March 2005
Statistician Comments		10 March 2005

Copy of Questionnaire		(None Specified)
Letters of Invitation to Participants	1	08 March 2005
GP/Consultant Information Sheets	1	08 March 2005
Participant Information Sheet	2	22 June 2005
Participant Information Sheet	v.2 stage 2	22 June 2005
Participant Consent Form	v.2 stage 2	22 June 2005
Participant Consent Form	2	22 June 2005
Research design overview		(None Specified)
Response to Request for Further Information	2	28 June 2005

Management approval

You should arrange for all relevant NHS care organisations to be notified that the research will be taking place, and provide a copy of the REC application, the protocol and this letter.

All researchers and research collaborators who will be participating in the research must obtain management approval from the relevant care organisation before commencing any research procedures. Where a substantive contract is not held with the care organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Notification of other bodies

The Committee Administrator will notify the research sponsor and the R&D Department for NHS care organisation that the study has a favourable ethical opinion.

Statement of compliance

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

04/WNo01/73	**Please quote this number on all correspondence**

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

Yours sincerely

MC Jack

Dr. M.C. Jackson
Chairman

Enclosures:

Standard approval conditions

SF1 list of approved sites

Appendix G. – information sheet and consent form used in Study 1 and 2

School of Psychology: University of Wales, Bangor
Information Sheet for Participating in a Research Project

Title of the study: "Effects of age on functional brain activation during memorization of face-name associations."

Purpose: You have been asked to participate in a research study using functional magnetic resonance imaging (fMRI) to investigate the brain mechanisms involved in encoding and retrieval of associations between unfamiliar names and faces. This study uses fMRI, a variant of the standard clinical MRI scan, to measure changes in brain activity in response to visual images of different kinds.

Procedures: The study involves lying still in the scanner while images are obtained for about 60 minutes. The MRI scanner uses a magnetic field – no radiation is involved and no dye needs to be injected. The scan is not in any way painful, but the scanner makes a loud noise. Because a magnetic field is involved, you cannot be scanned if you have a pacemaker, or metal, in your body. Because the scanner is configured as a narrow tube, some individuals with claustrophobia may find the procedure uncomfortable or intolerable. So, you cannot be scanned if you have a history of claustrophobia. You will be able to see outside the scanner – through mirrors – during the scan and will be able to communicate with the radiographer. If you find the scan to be uncomfortable in any way, the radiographer will immediately stop the scan.

Risks: These tests are neither painful nor dangerous in any way. They do **not** involve any drugs, surgery or experimental treatment. They will in no way interfere with any medication or other therapy. The MRI scanner at the hospital will be operated by an NHS radiographer to ensure the safety of the test.

Benefits: There are no direct benefits to you for participation in this part of the study. Occasionally, when scanning healthy individuals, some unexpected abnormality may be found incidentally. If this should occur, someone will talk to you about providing this information to your personal physician.

Confidentiality: The scientific information obtained from these experiments may be published in scientific papers, but your name will not appear in any public document, nor will the results be published in a form which would make it possible for you to be identified.

Compensation: If you should decide to participate, you will receive £20 per hour.

Right to refuse or withdraw: you may refuse to participate without any penalty. You may change your mind about being in the study and quit after the study has started, and if you feel, for any reason, uncomfortable, the study will be discontinued.

Questions: We welcome the opportunity to answer any question you may have about any aspect of this study or your participation in it. You can contact Dr. Linden at 01248 382564.

Complaints: In the case of any complaints concerning the conduct of research, these should be addressed to Professor R.P. Hastings, Acting Head of School, School of Psychology, University of Wales, Bangor, Gwynedd, LL57 2AS.

Thank you for your consideration.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Title of the study: "Effects of age on functional brain activation during memorization of face-name associations."

Investigator's name: Dr. Linda Clare; Dr. David Linden; Jorien van Paasschen

Please circle as appropriate:

Have you read the patient information sheet?	YES / NO
Have you had the opportunity to ask questions and discuss this study?	YES / NO
Have you received enough information about this study?	YES / NO
Do you understand that you are free to withdraw from the study - at any time - without giving a reason - and without affecting future medical care?	YES / NO
Do you agree to take part in this study?	YES / NO

_____ _____

Date signature of participant

_____

Name in block letters

_____ _____

Date signature of investigator

_____

Name in block letters

Appendix H. – information sheet and consent form used in Study 2 and 3

School of Psychology: University of Wales, Bangor
Information Sheet for Participating in a Research Project

Title of the study: "Functional and anatomical mechanisms underlying the effects of cognitive rehabilitation in early-stage Alzheimer's disease: implications for intervention."

Purpose: You have been asked to participate in a research study using functional magnetic resonance imaging (fMRI) to investigate the brain mechanisms involved in encoding and retrieval of associations between unfamiliar names and faces. This study uses fMRI, a variant of the standard clinical MRI scan, to measure changes in brain activity in response to visual images of different kinds.

Procedures: The study involves lying still in the scanner while images are obtained for about 60 minutes. The MRI scanner uses a magnetic field – no radiation is involved and no dye needs to be injected. The scan is not in any way painful, but the scanner makes a loud noise. Because a magnetic field is involved, you cannot be scanned if you have a pacemaker, or metal, in your body. Because the scanner is configured as a narrow tube, some individuals with claustrophobia may find the procedure uncomfortable or intolerable. So, you cannot be scanned if you have a history of claustrophobia. You will be able to see outside the scanner – through mirrors – during the scan and will be able to communicate with the radiographer. If you find the scan to be uncomfortable in any way, the radiographer will immediately stop the scan.

Risks: These tests are neither painful nor dangerous in any way. They do **not** involve any drugs, surgery or experimental treatment. They will in no way interfere with any medication or other therapy. The MRI scanner at the hospital will be operated by an NHS radiographer to ensure the safety of the test.

Benefits: There are no direct benefits to you for participation in this part of the study. Occasionally, when scanning healthy individuals, some unexpected abnormality may be found incidentally. If this should occur, someone will talk to you about providing this information to your personal physician.

Confidentiality: The scientific information obtained from these experiments may be published in scientific papers, but your name will not appear in any public document, nor will the results be published in a form which would make it possible for you to be identified.

Compensation: you will not receive any compensation for taking part; however, your travel cost will be compensated.

Right to refuse or withdraw: you may refuse to participate without any penalty. You may change your mind about being in the study and quit after the study has started, and if you feel, for any reason, uncomfortable, the study will be discontinued.

Questions: We welcome the opportunity to answer any question you may have about any aspect of this study or your participation in it. You can contact Dr. Linden at 01248 382564.

Complaints: In the case of any complaints concerning the conduct of research, these should be addressed to Dr. Oliver Turnbull, Head of School, School of Psychology, Bangor University, Gwynedd, LL57 2AS.

Thank you for your consideration.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Title of the study: "Functional and anatomical mechanisms underlying the effects of cognitive rehabilitation in early-stage Alzheimer's disease: implications for intervention."

Investigators' name: Dr. Linda Clare; Dr. David Linden; Jorien van Paasschen

Please circle as appropriate:

Have you read the patient information sheet?	YES / NO
Have you had the opportunity to ask questions and discuss this study?	YES / NO
Have you received enough information about this study?	YES / NO
Do you understand that you are free to withdraw from the study - at any time - without giving a reason - and without affecting future medical care?	YES / NO
Do you agree to take part in this study?	YES / NO

_____ _____

Date signature of participant

_____

Name in block letters

_____ _____

Date signature of investigator

_____

Name in block letters