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Research Report

Brain function during multi-trial learning in mild cognitive impairment: A PET activation study

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ABSTRACT

We explored functional brain changes with positron emission tomography (PET) in mild cognitive impairment (MCI) patients and elderly normal controls by employing an episodic memory task that included two successive encoding trials of semantically related word-pairs and final retrieval. Both groups demonstrated significant learning across the two trials. The control group showed predominantly left frontal activity during encoding, and right frontal plus left temporal activity during retrieval. However, the MCI patients recruited partly different brain regions. They failed to activate right frontal and left temporal areas during retrieval, and failed to show any different activation for encoding on the first and second trials, whereas the controls activated a region of posterior cingulate. There was indication of compensatory increases in rCBF of the occipital cortex during incremental learning and the left frontal lobe during retrieval in the patients. These results suggest different episodic memory processing in the MCI group, and a possible over-reliance on semantic processing. Subtle functional changes occur in the pre-Alzheimer brain before there are marked structural or behavioural abnormalities.

1. Introduction

The diagnosis of Mild Cognitive Impairment (MCI) is made for non-demented individuals with an objectively-assessed memory impairment (Petersen et al., 1999). Besides a subjective memory complaint, the diagnosis of MCI requires memory function that is below age and education norms, but without deficits in other cognitive domains and without an impact on activities of daily living (Petersen et al., 1999; Collie and Maruff, 2000). Petersen et al. (2001) found that people with MCI develop Alzheimer's disease (AD) at a rate of between 6% and 25% per year, suggesting that MCI can be conceptualised as incipient dementia. Unsurprisingly, research into neurodegeneration in AD has focussed on MCI to identify the pre-clinical behavioural and neurological markers of AD. In this paper we describe a functional imaging study that examined the brain–behaviour relationships in MCI with the aim of exploring the underlying neuropsychopathology of incipient AD and drawing together the memory and neurological literatures.

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Most studies that aim to elucidate the relationship between neuroanatomical and behavioural deficits in MCI and AD have used resting state metabolic or volumetric imaging studies. Arnaiz et al. (2001) studied glucose metabolism (as measured by PET) and cognitive functioning in a group of 20 MCI patients. They found that 9 of their patients developed AD, whereas 11 remained stable. Although there were no differences between these two sets of patients in demography and Mini-Mental State Examination (MMSE) test scores, glucose metabolism in the left temporoparietal area significantly discriminated those that developed dementia (showing lower glucose metabolism) from those that did not. In support, Convit et al. (2000) demonstrated, with a volumetric MRI, that atrophy in the medial occipito-temporal and the middle and inferior temporal gyri was associated with progression to AD from MCI, suggesting that atrophy in these areas could predict future AD among non-demented individuals. Similarly, pre-morbid MRI-based volume measurements of the hippocampus predict progression into AD (Jack et al., 1999; Visser et al., 2002).

While these studies indicate that MCI is associated with changes in brain physiology and structure, there has been less consideration of how these changes relate to brain function and behaviour. In the first fMRI study on MCI patients, Machulda et al. (2003) examined brain activation patterns during memory encoding of complex visual scenes in MCI and AD patients and controls. Their analysis was limited to medial temporal structures and found decreased BOLD responses in both patient groups when compared to the controls. In line with the reported structural changes cited above, their imaging results indicate a functional impairment in medial temporal regions and suggest that cognitive activation paradigms can yield important information on the brain–behaviour relationships in a pre-Alzheimer disease state. Two recent fMRI studies explored the neural correlates of verbal working memory (Saykin et al., 2004) and face–name associative learning (Dickerson et al., 2005) in MCI patients. The first study reported reduced frontoparietal activity in the MCI group, while the other one that focused at the medial temporal structures found more extensive hippocampal activation in MCI patients as compared to controls. Finally, Elgh et al. (2003) examined the fMRI activation in a group of six people with a high risk of developing AD, and six low risk controls during episodic memory tasks (face–name recognition), with the finding that prefrontal activation was reduced in a group of people at risk of AD. Surprisingly, this group also showed occipito-temporal activations during retrieval.

In this paper we used a PET activation method to continue this line of research by exploring the underlying brain activation patterns for a memory task that is sensitive to memory dysfunction in MCI, namely incremental learning of word pairs. A deficit in episodic memory is thought to be the most prominent feature of both AD and MCI. Amongst healthy participants, PET scanning during episodic memory tasks has repeatedly revealed that learning is associated with increased neural activity predominantly in the left frontal lobe, whereas retrieval from episodic memory tends to involve the right frontal areas (Nyberg et al., 1996). In general, left prefrontal cortex activation is found for encoding of information, although some authors have argued that this is related to the type of materials used, with activation increases related to encoding occurring in the hemisphere (either left or right) most specialised to those stimuli (Miller et al., 2002).

Current opinion (see Fletcher and Henson (2001) for a review) is that left frontal activation during encoding in predominantly dorsolateral and ventrolateral regions is associated with generation, maintenance, selection and organisation of semantic information that supports episodic learning. Fletcher et al. (1998) repeatedly presented participants with word pairs in an fMRI experiment. They found left frontal activation during initial learning of to-be-remembered stimuli. This activation diminished as the stimuli were repeated, presumably because the pairs were already well learnt. Most notably, they found that when well-known word pairs were re-arranged into novel to-be-learned pairs, the left frontal activation was greater than in the initial learning. Additionally, they found that the less closely semantically related the word pairs were, the higher the activation in the left frontal area. This suggests that increases in activation in the left frontal lobe are associated with more effortful encoding conditions.

The right frontal activation during retrieval is thought to reflect the setting up and maintenance of a retrieval mode in memory (Lepage et al., 2000) and post retrieval monitoring and evaluation (Nolde et al., 1998). Right frontal activation has been shown for retrieval using recall or recognition tasks and with a variety of materials. Fletcher and Henson (2001) suggest that episodic retrieval requires the specification of search parameters and the verification of output from search — operations that rely on ventrolateral and dorsolateral right frontal cortex, respectively. It is of note that, in broad terms, retrieval from episodic memory dissociates from retrieval from semantic memory, where tasks that involve semantic retrieval elicit relatively more activation in the left frontal lobe than the right (e.g. Wiggs et al., 1999; Hunkin et al., 2000). This generalisation of semantic retrieval relying on the left, and episodic retrieval relying on the right frontal lobe suggests that some of the left frontal activation during learning may in fact be due to semantic retrieval processes being used to support encoding. Thus, encoding and retrieval of material probably involves overlapping cognitive and neurological resources.

This overlap between encoding and retrieval is particularly important, considering that many memory tasks involve incremental learning. Kopelman et al. (1998) found that incremental (repeated) learning activated left medial temporal regions, whereas initial presentation produced more prominent left frontal activity. Their interpretation of this is that presentation of already learned material activates retrieval circuits during the re-rehearsal of that material. As with many other studies they also found left temporal activity during retrieval (as well as right frontal activity), and concluded that the same network used for 'binding' or 'consolidating' episodic memory was used during retrieval and incremental learning.

The study by Kopelman et al. on incremental learning is of particular relevance to the present study since in tests of incremental learning, MCI patients typically show a shallower learning curve than controls (Moulin et al., 2004). There is also evidence that incremental or multi-trial learning tasks are the most sensitive tests for detecting MCI or incipient AD (Chen et