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Research report

Functional neuroanatomy of the encoding and retrieval processes of verbal episodic memory in MCI

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ABSTRACT

Introduction: The goal of this study was to explore the association between disease severity and performance on brain activation associated with episodic memory encoding and retrieval in persons with mild cognitive impairment (MCI).
Method: This was achieved by scanning 12 MCI persons and 10 age- and education-matched healthy controls while encoding words and while retrieving them in a recognition test.
Results: Behaviorally, there was no significant group difference on recognition performance. However, MCI and healthy controls showed different patterns of cerebral activation during encoding. While most of these differences demonstrated reduced activation in the MCI group, there were areas of increased activation in the left ventrolateral prefrontal cortex. Reduced activation was found in brain areas known to be either structurally compromised or hypometabolic in Alzheimer's disease (AD). In contrast, very few group differences were associated with retrieval. Correlation analyses indicated that increased disease severity, as measured with the Mattis Dementia Rating Scale, was associated with smaller activation of the right middle and superior temporal gyri. In contrast, recognition success in MCI persons was associated with larger activation of the left ventrolateral prefrontal cortex during the encoding phase.
Conclusion: Overall, our results indicate that most of the memory-related cerebral network changes in MCI persons occur during the encoding phase. They also suggest that a prefrontal compensatory mechanism could occur in parallel with the disease-associated reduction of cerebral activation in temporal areas.

1. Introduction

People with mild cognitive impairment (MCI) experience more marked memory deficits than what would be expected based on their age and education, yet fail to reach criteria for dementia (Petersen et al., 2001; Gauthier et al., 2006). They are, however, at risk of developing AD and voxel-based morphometry and Magnetic Resonance Imaging (MRI) volumetry studies of MCI show that this condition is associated with marked reduction in hippocampal and entorhinal cortex volumes (Whitwell et al., 2007; Xu et al., 2000; Pennanen et al., 2005, 2004). Moreover, the atypical atrophy in MCI persons is

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positively correlated with conversion to AD (Erten-Lyons et al., 2006; Korf et al., 2004; Jack et al., 1999). The aforementioned regions are typically involved in episodic memory and a certain number of studies have investigated whether those structural changes in MCI are associated with effects on brain activation while completing episodic memory tasks. Understanding how MCI modifies the brain's physiological response to cognitive events is critical because such functional changes may represent early indicators of neurodegenerative diseases. In addition, activation studies may provide crucial information about how brain networks support memory performance in persons with MCI and whether these brain networks differ qualitatively or quantitatively from those supporting memory in healthy older adults.

A number of studies have documented the alterations of the medial temporal lobe in MCI individuals and in early AD (Mitchell et al., 2002; Markesbery et al., 2006). In addition, there is also some recent evidence that the basal forebrain cholinergic system, which provide cholinergic innervations to all cortical areas, appears to show some of the earliest AD neuropathology (Auld et al., 2002; Mesulam et al., 2004). This may explain the fact that functional brain imaging studies have observed brain dysfunctions that extend beyond the medial temporal lobe area and alter the functioning of large neural networks involved in memory (e.g., Johnson et al., 2006; Petrella et al., 2007; Ries et al., 2005; Kircher et al., 2007; Heun et al., 2007). However, whether those alterations result in hyper or hypoactivation is unclear as well as the more specific localization of those impaired networks, particularly along the anterior/posterior axis. While a number of studies of memory encoding have found decreased activation in the medial temporal lobe (Johnson et al., 2006; Machulda et al., 2003; Trivedi et al., 2006) and in the prefrontal cortex of persons with MCI (Dannhauser et al., 2008; Mandzia et al., 2002, 2009), some studies have reported that MCI persons or persons at risk for AD have more activation than healthy older adults in the medial temporal lobe (Bookheimer et al., 2000; Kircher et al., 2007; Dickerson et al., 2005; Hamalainen et al., 2007), in the prefrontal cortex (Bookheimer et al., 2000; Bondi et al., 2005; Han et al., 2006), and in posteromedial cortices (Petrella et al., 2007). Studies of the retrieval phase of episodic memory have also reported conflicting results, with some of them reporting decreased activations in the prefrontal cortex (Mandzia et al., 2002, 2009) and in posteromedial cortices (Ries et al., 2005), while another study reports increased activations of the prefrontal cortex (Heun et al., 2007).

Our literature review suggests that across studies, persons with MCI and healthy controls show more areas of reliable brain activation differences during the encoding phase when compared with the retrieval phase. This may suggest that encoding is particularly vulnerable to the early stage of AD. However, in most studies, participants were scanned either while learning the list (for encoding studies) or while recognizing items (for retrieval studies) and differences in patient sample and design complicates direct comparison of their results. Investigating both the encoding and retrieval phases in the same set of participants facilitates comparison of the activation associated with the two phases and can thus provide data regarding their differential sensitivity to the disease. It can also help us to understand whether both phases would be associated with similar localization and pattern of brain changes.

The inconsistent findings in the literature can also arise from the fact that MCI criteria are extremely variable and different studies include MCI participants that may diverge in terms of their clinical characteristics. Group differences in levels of severity are an important issue to this regard. Studies that have assessed the natural history of cognitive deficits in MCI have reported that those persons experience a gradual increase in their symptom severity, due to accumulation of AD pathology (Bennett et al., 2002). Differences in severity may reveal themselves to be a determining factor in accounting for differences in the patterns of brain activation in neurodegenerative diseases (Prvulovic et al., 2005; Celone et al., 2006). Within this perspective, a recent model has proposed that milder brain neuropathologies in early AD might lead to a mild decrease in processing efficiency accompanied by a compensatory increase in neuron recruitment. As the disease progresses and neuropathologies accumulate, processing capacity would further decrease and would pose limits on the capacity for compensatory neuronal recruitment (Prvulovic et al., 2005). Based on this model, it is expected that MCI persons situated on the mild end of the disease severity continuum would tend to show more brain activation than healthy controls, whereas MCI persons with more severe deficits and closer to AD would tend to show less brain activation than healthy controls. One study has reported results that are congruent with this hypothesis. Using a face–name associative encoding task, Celone et al. (2006) reported hippocampal hyperactivation in MCIs with less severe cognitive impairments relative to healthy controls, and hippocampal hypoactivation in MCIs with more severe cognitive impairments. It must be noted however that the MCI persons in this study were chosen based on different criteria than the ones used in the other studies. Generalizing these findings to individuals meeting current MCI criteria would have important implications for the assessment and follow-up of these individuals, for the understanding and integration of the results found in the literature, and for the comprehension of the brain response to neurodegenerative injuries.

The goal of this study was to assess the role of disease severity on the brain activation of persons with MCI during both the encoding and retrieval phases of a verbal episodic memory task. Furthermore, we wanted to explore the impact of performance on the nature and extent of brain activation. This was assessed in the prefrontal cortex and in the temporal lobe, two key regions for memory processes. In line with the literature, we hypothesized that more group differences in brain activation would be observed during the encoding phase than during the retrieval phase. We also hypothesized that performances would be correlated with brain activation in the prefrontal cortex for the healthy controls group, as this region has been linked to retrieval success in both healthy younger (Wagner et al., 1998) and healthy older adults. It is unclear whether a similar association is present or not in MCI as Dannhauser et al. (2008) have failed to find a correlation between prefrontal activation and performance in persons with MCI during a verbal memory encoding task that promoted interference effects. Presence of a larger activation of the prefrontal areas in MCI associated with a positive