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Structural and functional bases of visuospatial associative memory in older adults

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Abstract

Impaired visuospatial associative memory may be one of the earliest changes predicting cognitive impairment and Alzheimer's disease. We explored the relationship between performance on a visuospatial associative memory task (the Placing Test) and brain structure and function in cognitively healthy older adults. First, we performed a voxel-based morphometry correlational analysis on structural magnetic resonance imaging (MRI) data from 144 healthy older adults with their scores on the Placing Test. Second, we carried out a functional MRI study on another group of 28 healthy older adults who performed a similar task during functional MRI. Decreased performance on the Placing Test was associated with increased atrophy in medial-temporal regions. Functional activation of the same regions—controlling for the effect of atrophy—occurred during successful performance of the same task. The colocalization of structural and functional MRI correspondents of visuospatial associative test performance within medial-temporal regions validates multimodal imaging in describing behaviorally relevant variability in the aging brain and suggests that the Placing Test has the potential for detecting early cognitive changes occurring in preclinical phases of Alzheimer's disease.
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1. Introduction

Memory impairment, in particular the loss of the ability to form and retain new episodic memories, is the hallmark of early Alzheimer's disease (AD) (Elias et al., 2000; Galton et al., 2000; Grady et al., 1988; Tierney et al., 1996). As it has been shown that the earliest neuropathological changes associated with AD occur years before a diagnosis of dementia can be given clinically (Ohm et al., 1995; Smith, 2002a), increasing research into the neuropsychology of aging has focused on identifying cognitive tests that are sensitive to these early pathological changes occurring in the preclinical or "prodromal" phase of AD, i.e., those in whom the pathological process due to AD is present but whose symptoms are currently subclinical (Dubois et al., 2010). The best candidate among such cognitive tests should be specific in detecting the earliest memory dysfunctions but relatively insensitive to the effect of age and other demographic variables. If proven, its specific association with brain structures known to be particularly vulnerable to AD pathology (Braak and Braak, 1997; Delacourte et al., 1999) would further corroborate its role in potentially detecting early signs of disease.

Research into the brain correspondents of cognitive dysfunction occurring in AD has been extensive and focused mainly on stages when the cognitive decline is already

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clinically evident and the degree of brain atrophy advanced. Several studies performed in patients with a clinical diagnosis of AD or mild cognitive impairment (MCI; i.e., cognitive decline greater than expected for an individual's age and education level but not interfering with activities of daily life) have found correlations between performance on tests of episodic memory and volumes of the hippocampi and other medial temporal lobe structures, consistent with the long-established role of these structures in episodic memory (Cahn et al., 1998; Deweer et al., 1995; Di Paola et al., 2007; Heun et al., 1997; Jobst et al., 1992; Köhler et al., 1998; Sarazin et al., 2010). However, given the current importance of focusing on the earliest changes occurring before cognitive decline manifests clinically, it is important to explore whether the association between tests of episodic memory and their potential brain correspondents is also true in populations of healthy older adults and at the time of onset of AD or MCI. In addition, it is important to show if the brain-behavior association specifically reflects successful cognitive performance and does not depend on nonspecific and stage-related effects of the disease. Indeed, those candidate cognitive tests that are thought to be able to detect early or predictive changes of later cognitive impairment are usually standardized and validated in cognitively normal older adults. If these associations between cognitive test and brain correspondents were to be proven even in cognitively healthy older adults, it would support the notion that decreased performance on the cognitive test specifically reflects early brain dysfunction and not general effects of the disease when it is already in the advanced stage.

Among the several possible cognitive tests thought to be sensitive to early changes occurring in the preclinical or "prodromal" phase of AD, visuospatial paired associate learning task performance has been shown to be impaired at an early stage and to have very good sensitivity and specificity in discriminating older adults who will develop AD (Ahmed et al., 2008; Blackwell et al., 2004; Johnson et al., 2009). These tasks are thought to specifically index the hippocampal function of new memory encoding by binding sensory inputs (Squire and Zola-Morgan, 1991).

We have previously shown that a visuospatial associative learning test designed in our research center, namely the Placing Test, could detect early deficits suggestive of cognitive impairment in a population of healthy older adults (Anderson et al., 2006). The test had high discriminative capacity in distinguishing controls from patients with MCI and AD (de Jager et al., 2003), suggesting that it may prove to be useful for detection of MCI. Importantly, performance on this test was not affected by age, education, or gender. The Placing Test is an episodic memory test that measures the ability to remember associations between objects and their locations. It was designed to specifically reflect the medial-temporal lobe function of forming new memories by binding together the disparate features of experiences as they occur. This was hypothesized on the basis of widely accepted theories on the role of the hippocampus and related medial temporal lobe structures in episodic memory (Bunsey and Eichenbaum, 1993; Rajji et al., 2006; Wallenstein et al., 1998). However, the neuroanatomical correlates of the Placing Test have not been directly investigated.

The first aim of the present study was to explore the neuroanatomical correlates of visuospatial associative learning, and more precisely to test the hypothesis that variability in the performance of the Placing Test in a population of healthy older adults specifically correlates with the variability in the morphology of medial temporal lobe structures. We used voxel-based morphometry (VBM), which allows the measurement of the degree and the distribution of regional gray matter loss throughout the whole brain and without an a priori hypothesis (Ashburner et al., 2003) and carried out a correlational analysis on a group of 144 healthy older adults who had performed the Placing Test. VBM allows for regression analyses to test for correlations between performance and regional gray matter volume (correlational analyses). VBM correlational analyses have been extensively used in patients with neurodegenerative dementias and in healthy older adults to unravel the neuroanatomical correlates of cognitive and behavioral symptoms (Di Paola et al., 2007; Sarazin et al., 2010).

The second aim of the present study was to further explore the link between visuospatial associative memory and brain function by establishing if the regions of significant correlation resulting from the VBM analysis were those whose actual activation enables successful visuospatial memory. In fact, a plausible concern regarding structural magnetic resonance imaging (MRI)-related measurements is that volume alone does not provide direct and immediate information about function. We therefore used functional MRI (fMRI) on another group of healthy older adults to directly explore neural activity during successful performance of a similar task. Participants underwent fMRI scanning while they were performing an fMRI-adapted version of the Placing Test. Intersubject variability in brain structure was included as a covariate in the analysis of functional MRI data, to disentangle the effect of atrophy on functional activity and test if structural and functional MRI would provide independent evidence on the role of medial temporal lobes in visuospatial associative memory. Indeed, the assumption that the regions resulting from VBM correlational analyses are those whose neural activity is actually enabling a certain cognitive function has not been directly demonstrated in older adults. Therefore, we combined VBM and fMRI studies (in different groups) to study the correlates of visuospatial learning from both structural and functional perspectives. This multimodal approach should better define those brain regions exhibiting performance related properties within the networks involved in episodic memory and therefore also related to the earliest symptomatic changes occurring in the diseased brain.

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