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Featured Article

Differential medial temporal lobe morphometric predictors of item- and relational-encoded memories in healthy individuals and in individuals with mild cognitive impairment and Alzheimer's disease

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Abstract

Introduction: Episodic memory processes are supported by different subregions of the medial temporal lobe (MTL). In contrast to a unitary model of memory recognition supported solely by the hippocampus, a current model suggests that item encoding engages perirhinal cortex, whereas relational encoding engages parahippocampal cortex and the hippocampus. However, this model has not been examined in the context of aging, neurodegeneration, and MTL morphometrics.

Methods: Forty-four healthy subjects (HSs) and 18 cognitively impaired subjects (nine mild cognitive impairment [MCI] and nine Alzheimer's disease [AD] patients) were assessed with the relational and item-specific encoding task (RISE) and underwent 3T magnetic resonance imaging. The RISE assessed the differential contribution of relational and item-specific memory. FreeSurfer was used to obtain measures of cortical thickness of MTL regions and hippocampus volume.

Results: Memory accuracies for both item and relational memory were significantly better in the HS group than in the MCI/AD group. In MCI/AD group, relational memory was disproportionately impaired. In HSs, hierarchical regressions demonstrated that memory was predicted by perirhinal thickness after item encoding, and by hippocampus volume after relational encoding (both at trend level) and significantly by parahippocampal thickness at associative recognition. The same brain morphometry profiles predicted memory accuracy in MCI/AD, although more robustly perirhinal thickness for item encoding ($R^2 = 0.31$) and hippocampal volume and parahippocampal thickness for relational encoding ($R^2 = 0.31$).

Discussion: Our results supported a model of episodic memory in which item-specific encoding was associated with greater perirhinal cortical thickness, while relational encoding was associated with parahippocampal thickness and hippocampus volume. We identified these relationships not only in HSs but also in individuals with MCI and AD. In the subjects with cognitive impairment, reductions in hippocampal volume and impairments in relational memory were especially prominent.

Keywords: Recognition memory; Item encoding; Relational encoding; Mild cognitive impairment; Alzheimer's disease; Hippocampus; Parahippocampus; Perirhinal cortex

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1. Introduction

A current model of episodic memory proposes that different subregions of the medial temporal lobe (MTL) support different cognitive operations during memory processing [1–4]. Convergent rodent and subhuman primate data support a distinction in which perirhinal cortex (PRC)/entorhinal cortex (ERC) appear responsible for encoding information about individual items and their features, and the parahippocampus (PHC) and hippocampus (HC) appear responsible for relational binding of items that co-occur in scenes or in associative pairs to form a coherent memory event [5]. The functional neural underpinnings of such processing have been examined in a variety of functional magnetic resonance imaging (fMRI) paradigms in healthy humans, including those relating to transitive inference (a type of relational processing), and item-context association binding [2,6–9]. Generally, increased activations in the hippocampus, as well as dorsolateral prefrontal cortical regions, were prominent during relational encoding. In contrast, during judgments after item-specific encoding, PRC was activated. Data from human amnestic patients with acquired lesions are also consistent with this distinction [10,11] (but see [12] for an alternative view).

These encoding distinctions may also have potential relevance for neurodegenerative diseases. In Alzheimer's disease (AD), and its prodrome mild cognitive impairment (MCI) in particular, early changes in the MTL are characterized by prominent atrophy and degeneration in ERC and PRC (usually related to tau pathology), and may precede or coincide with atrophy of the HC. Changes to these subregions are usually evident in MCI and AD in structural magnetic resonance imaging (sMRI) [13–18]. It is unknown if morphometric measures from MTL subregions are predictive of accuracy in item- and relational-encoding paradigms in these neurodegenerative disorders. A hypothesis-driven examination of the relationship of MTL subregional morphometrics on memory performance after directly manipulating these two types of encoding processes, followed by recognition tests within the same subjects, has not been yet undertaken.

The relational and item-specific encoding task (RISE), a newly developed test of episodic memory, permits such an investigation [19–21]. We have recently demonstrated RISE impairments in a large MCI/AD sample and found that it had good psychometric properties (including equivalent difficulty level for the subtests) and to be predictive of functional capacity [22].

In the present study, our goals were twofold. First, we sought to determine the validity of a model of episodic memory in which item-encoded material and relationally encoded material were supported by different prespecified subregions in the MTL in healthy older individuals using structural morphometric measures of cortical thickness and volumes, and RISE memory accuracy scores. Second, we sought to determine if RISE measures might be sensitive to measurable pathology in the MTL in subjects suffering from a neurodegenerative disorder (MCI and AD). This information might be helpful for designing clinical trials using better and more sensitive memory measures, as well as detecting clinical differences between amyloid and tau pathology.

2. Methods

2.1. Subjects

2.1.1. Diagnostic groups

2.1.1.1. General

All subjects were between the ages of 50 and 85 years. There were no restrictions based on gender or ethnicity. Exclusion criteria are in Supplementary Material.

2.1.1.2. Healthy subjects

Forty-four older subjects had Mini–Mental State Examination (MMSE) scores greater than or equal to 24 and did not meet psychometric or clinical criteria for MCI or AD disease. All formal neurocognitive test scores for these subjects were within 1.5 standard deviation (SD) of normative data in published studies or manuals.

2.1.1.3. Mild cognitive impairment

The diagnosis of MCI was made according to Petersen's criteria for "amnestic" MCI in nine individuals. Individuals had memory impairments of greater than 1.5 SDs on either Selective Reminding [23,24] or Logical Memory [25] and had relatively preserved activities of daily living (ADLs). Individuals who had additional impairments in other nonmnemonic domains of cognition were also included, so long as ADLs were ostensibly preserved (i.e., "multidomain MCI"). All MCI subjects had MMSE scores greater than 23 (i.e., "nondemented") and Clinical Dementia Rating (CDR) score of 0.5 [26].

2.1.1.4. Alzheimer's disease

Nine individuals met NINCDS-ADRDA criteria for probable AD. Diagnostic criteria include memory impairment (defined below that for MCI) and at least one other area of impaired cognition, including speed of processing, executive ability, and/or semantic processing/language; report of decline in memory and other areas of cognition; and impairments in ADLs. AD participants had MMSE scores below 24 and greater than 15 (i.e., in the mild-to-moderate stage) and CDR scores of 1 or greater on the global scale.

2.1.2. Staging instruments

2.1.2.1. Clinical Dementia Rating Scale

This instrument consists of items relating to memory, orientation, problem solving, personal care, function at home and in hobbies, and function in community affairs [27].