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Featured Articles

Structural MRI discriminates individuals with Mild Cognitive Impairment from age-matched controls: A combined neuropsychological and voxel based morphometry study

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Abstract

Background: Several previous studies have reported that amnestic mild cognitive impairment (aMCI), a significant risk factor for Alzheimer's disease (AD), is associated with greater atrophy in the medial temporal lobe (MTL) and posterior cingulate gyrus (PCG).

Method: In the present study, we examined the cross-sectional accuracy (i.e., the sensitivity and specificity) of voxel-based morphometry (VBM) in discriminating individuals with MCI (n = 15) from healthy age-matched controls (n = 15). In addition, we also sought to determine whether baseline GM volume predicted aMCI patients that converted to AD from those that did not approximately 2 years after the baseline visit.

Results: MCI patients were found to display significantly less GM volume in several hypothesized regions including the MTL and PCG relative to the age-matched controls ($p < 0.01$). Logistic regression analysis and receiver operating characteristic (ROC) curves for GM volume in the anterior MTL and PCG revealed high discriminative accuracy of 87%. By contrast, baseline GM volume in anterior MTL and PCG did not appear to be sensitive to changes in clinical status at the follow-up visit.

Conclusion: These results suggest that VBM might be useful at characterizing GM volume reductions associated with the diagnosis of aMCI.

Keywords: Mild cognitive impairment; Alzheimer's disease; Voxel-based morphometry; Hippocampus; Posterior cingulate gyrus; Sensitivity and specificity

1. Introduction

Mild cognitive impairment-amnestic type (aMCI) is a term typically used to describe the earliest stage of Alzheimer's disease (AD) [1]. Peterson et al. [2] have sought to establish clinical criterion for the diagnosis of aMCI. These criteria include the presence of subjective memory complaints preferably corroborated by an informant, objective episodic memory impairment (1.5 standard deviations below age-matched normal subjects), intact activities of daily living, and cognitive/functional status not consistent with the diagnosis of dementia [1]. Using these criterion, the large-scale, multi-center, Alzheimer's Disease Cooperative Study found that 212 of 214 (99%) cases of aMCI eventually met the clinical criteria for possible or probable AD, indicating that the enrollment criteria for aMCI were highly specific [3].

Several recent structural MRI studies using primarily region of interest (ROI) tracing methods have reported that

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individuals with aMCI display greater atrophy in the medial temporal lobes (MTL) relative to age-matched controls [see 4 for review]. Furthermore, longitudinal MRI studies have found that MTL atrophy was a good predictor of individuals with aMCI who subsequently developed AD from those who did not over a 3-5 year follow-up periods [5–7].

Recent advances in structural MRI image analysis such as voxel-based morphometry (VBM) allow an unbiased mapping of gray matter (GM) volume [8]. The automated VBM procedure has a high degree of reproducibility, and has been previously used to examine GM volume in both AD and aMCI. These studies generally report findings consistent with observations from studies using manual ROI or histopathological methods. For example, Karas et al. [9] found that individuals with aMCI had significantly reduced GM volume in the MTL relative to age-matched controls. Furthermore, AD patients had significantly less GM volume in both posterior cingulate gyrus (PCG) and MTL relative to the aMCI and control groups. However, no differences in GM volume in the PCG were found between the aMCI patients and controls. Together, these results suggest that VBM might be useful at characterizing neuropathological changes associated with the early stages of AD.

In the present study, we used VBM to 1) replicate previous findings of regional GM volume reductions in a group of patients who met the criteria for aMCI, 2) the area under the curve (AUC) of receiver-operating characteristic (ROC) analysis to determine the sensitivity and specificity of VBM at separating aMCI patients from age-matched controls, and 3) determine whether baseline GM volume was associated with longitudinal changes in clinical status in the aMCI patients. The combined use of different ROIs might result in better accuracy than the use of one ROI (e.g., hippocampus) alone. Based on previous studies, we hypothesized that aMCI patients would display reduced GM volume in the MTL, PCG, and temporal/parietal cortices.

2. Methods

2.1. Participants

Fifteen individuals were identified that met the Petersen [1] criteria for aMCI. These individuals were then matched to 15 healthy elderly control participants based on gender, age, and education (see Table 1). Each group consisted of nine men and six women. All subjects received a detailed neuropsychological evaluation examining several cognitive domains. aMCI patients were referred from the several memory disorders clinics at a university-based medical center. The diagnostic criteria for aMCI were those recommended by Petersen [1] including: a) presence of memory complaints by the patient that was preferably corroborated by an informant, b) objective memory impairment defined as performance that was 1.5 SD below the cutoff for normal aging on at least one of four memory measures, c) essentially intact activities of daily living, and d) cognitive and functional status not consistent with a diagnosis of dementia. Prior to inclusion in this study, the aMCI patients were presented to a diagnostic consensus panel for support of the diagnosis. Longitudinal follow-up data (mean follow-up interval = 1.83 ± 0.68 years) were available for 12 aMCI patients (80%). Follow-up data for the majority of the elderly controls was not available because the design of our longitudinal study is to follow individuals meeting the criterion for aMCI.

Table 1
Demographic and neuropsychological data

	Controls		MCI	
	Mean	SD	Mean	SD
Age (years)	73.6	7.1	73.3	6.72
Education (years)	16.7	2.5	16.3	2.81
Gender Ratio: Female / Male	6/9		6/9	
% APOE e4 carriers *	17%		54%	
MMSE †	29.7	0.5	27.8	1.8
RAVLT total recall trials 1-5 †	46.8	6.5	30.5	5.2
RAVLT long delay recall †	8.9	1.8	1.9	1.9
BVMT total recall trials 1-3†	23.5	8.0	12.8	5.3
BVMT long delay recall†	9.3	1.8	4.3	2.8
Boston Naming Test	57	3.2	55.7	3.6
COWAT adjusted raw score	46.5	8.9	37.5	9.7
Clock Drawing Test	9.6	1.3	9.4	0.5
JLO Test	25.7	3.01	25.7	3.03
Trail Making Test A (sec)	33.7	7.6	42.2	18.6
Trail Making Test B (sec)‡	65.9	15.7	92.8	22.5
WRAT-3 reading subtest – Standard Score	118.7	19.7	110.3	7.8

Note: Unless otherwise indicated, all data represent raw scores and are presented as mean (SD).

MMSE = Mini Mental Status Exam, BVMT = Brief Visual Memory Test, COWAT = Controlled Oral Word Fluency Test, JLO = Judgement of Line Orientation Test, RAVLT = Rey Auditory Verbal Learning Test, BNT = Boston Naming Test, WRAT = Wide Range Achievement Test-3. See text for further discussion of test measures.

* = significant difference ($p < .01$), † = significant difference ($p < 0.0001$), ‡ = significant difference ($p < 0.001$).

Subjects that met the clinical criterion for multi-domain or non-amnestic MCI were excluded from the statistical analyses. Additional exclusion criteria for both groups included Hachinski score greater than four, prior neurological disease or neurosurgery, current diagnosis of major psychiatric disorder (including depression), or chronic major medical conditions (e.g., diabetes, poorly controlled hypertension, or cardiac disease). Elderly control participants were recruited from the community, predominantly by advertisement, mailings, and community outreach events. Control participants exhibited normal baseline performance across cognitive domains as assessed by the same battery of neuropsychological measures used to determine cognitive impairment in the aMCI patients (see Table 1).

2.2. Neuropsychological assessment

The aMCI patients and elderly controls received a battery of neuropsychological tests using standardized admin-