

Three-dimensional Patterns of Hippocampal Atrophy in Mild Cognitive Impairment

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Objective: To measure hippocampal volumes in patients diagnosed as having subtypes of mild cognitive impairment (MCI) relative to those of elderly control subjects and those of patients with Alzheimer disease (AD) using 3-dimensional mesh reconstructions.

Design: A magnetic resonance imaging volumetric study of MCI subgroups (MCI, amnesic subtype [MCI-A]; and MCI, multiple cognitive domain subtype) using 3-dimensional mesh reconstructions of the structure.

Setting: Referral dementia clinic.

Subjects: Twenty-six subjects with MCI (MCI-A, n=6; and MCI, multiple cognitive domain subtype, n=20), 20 subjects with AD, and 20 controls who were equivalent in age, education, and sex distributions.

Main Outcome Measures: Three-dimensional parametric mesh models of the hippocampus and total hippocampal volumes.

Results: The hippocampi of the patients with AD were significantly atrophic relative to those of the healthy controls. The MCI, multiple cognitive domain subtype, group did not differ from the controls, yet was significantly different from the MCI-A and the AD groups. The MCI-A patients had significant hippocampal atrophy compared with the controls, and did not differ significantly from the patients with AD.

Conclusion: These data add to the growing evidence that there are multiple forms of MCI, that they have distinct neuropathological correlates, and that MCI, multiple cognitive domain subtype, is not a more advanced form of the MCI-A subtype.

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MILD COGNITIVE IMPAIRMENT (MCI) is considered a transitional state between normal cognition and Alzheimer disease (AD).¹⁻⁴ Because memory disorders are the core clinical symptom in MCI and AD, and the earliest AD pathological changes have been noted in the entorhinal cortex and hippocampus,^{5,6} most of the magnetic resonance imaging (MRI) volumetric studies conducted in MCI patients have focused on these brain regions. The hippocampus and entorhinal cortex volumes are smaller than those of healthy individuals, appearing to be somewhere between those of patients with AD and those of healthy individuals,^{7,8} or as atrophic as those of patients with AD.^{9,10} Studies¹¹⁻¹³ that use whole brain techniques find that in addition to the loss of volume in mesial temporal lobe structures, MCI patients have atrophy in the other heteromodal association areas.

We report herein the results of the first study, to our knowledge, to use 3-dimen-

sional surface mesh models to evaluate the structural integrity of the hippocampus in MCI subgroups. This technique has advantages over other methods in that it permits visualization of the spatial profile of any neuropathological abnormalities, offering the possibility of more refined neuroanatomical localization if the changes seen in those with MCI are regionally selective. We analyzed data from healthy elderly control subjects, patients with mild probable AD, and 2 groups of MCI patients. We examined the presence, locus, and extent of hippocampal atrophy in the 3 patient groups, with specific reference to differences between the 2 MCI subgroups.

METHODS

The data for this study were derived from the archives of the University of Pittsburgh Alzheimer's Disease Research Center¹⁴ and the Mental Health Intervention Research Center for

Table 1. Selected Neuropsychological Test Data

Test	Score Range	Group*		
		MCI-A	MCI-MCD	AD
Rey-Osterreith figure				
Copy	0-24	20.8 (2.5)	19.8 (4.2)†	15.5 (8.7)
Delayed recall	0-24	13.3 (5.5)†	14.8 (3.6)†	5.7 (7.0)
Word list				
Learning	0-10	6.67 (0.58)	6.60 (1.7)	4.00 (2.8)
Delayed recall	0-10	2.17 (2.3)	4.89 (2.9)†‡	0.68 (1.4)
Category fluency	NA	19.7 (5.2)†	16.4 (5.5)†	10.3 (6.1)
Digit spans				
Forward	0-9	7.00 (1.3)	6.05 (1.6)	5.68 (1.6)
Backward	0-8	5.33 (1.0)†	4.42 (1.1)†	3.53 (1.3)
Visual discrimination	0-32	27.2 (4.0)	27.3 (3.6)	24.9 (4.5)

Abbreviations: AD, Alzheimer disease; MCI-A, mild cognitive impairment, amnesic subtype; MCI-MCD, mild cognitive impairment, multiple cognitive domain subtype; NA, data not available.

*Data are given as mean (SD).

†Significantly different from the AD group ($P < .05$).

‡Significantly different from the MCI-A group ($P < .05$).

Table 2. Subject Demographic and Neuropsychiatric Characteristics*

Characteristic	Group			
	Healthy Controls (n = 20)	MCI-A (n = 6)	MCI-MCD (n = 20)	AD (n = 20)
Age, y	70.1 (8.4)	74.8 (7.4)	71.4 (10.2)	69.1 (9.7)
Education, y	15.5 (1.9)	12.7 (3.3)	14.2 (3.4)	13.5 (4.8)
Male sex, No. (%)	8 (40)	3 (50)	12 (60)	10 (50)
MMSE score	NA	25.8 (2.7)	26.9 (2.5)	19.3 (5.8)
BDRS score for ADL	NA	1.58 (1.3)	1.63 (1.8)	3.43 (3.1)
CDR	0	0.42 (0.2)	0.47 (0.2)	1.12 (0.6)
NYU score	NA	7.67 (11.8)	2.88 (4.0)	10.16 (13.5)

Abbreviations: AD, Alzheimer disease; ADL, activities of daily living; BDRS, Blessed Dementia Rating Scale; CDR, Clinical Dementia Rating; MCI-A, mild cognitive impairment, amnesic subtype; MCI-MCD, mild cognitive impairment, multiple cognitive domain subtype; MMSE, Mini-Mental State Examination; NA, not applicable; NYU, New York University Scale for Parkinsonism.

*Data are given as mean (SD) unless otherwise indicated.

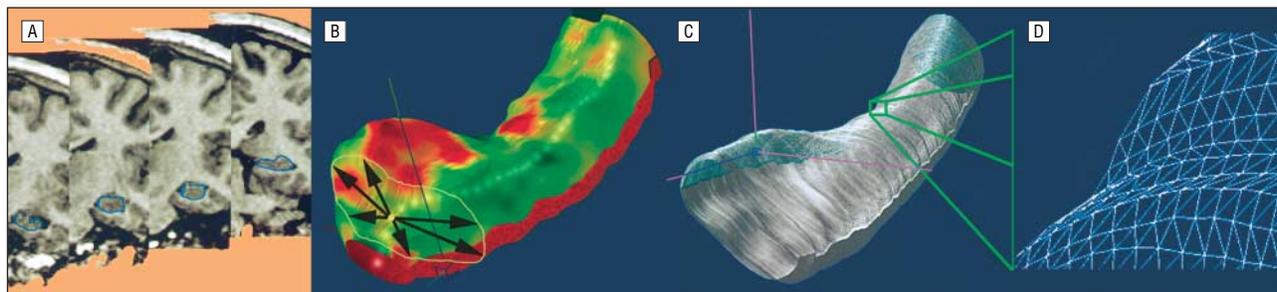


Figure 1. The boundary of the hippocampus traced in consecutive coronal magnetic resonance imaging sections (A); 3-dimensional parametric surface created using anatomical surface modeling software (B); the surface of the hippocampus, which is composed of discrete triangular tiles that are spatially uniform and can be averaged across subjects (C); and an average anatomical model for a group, produced from the triangular tiles (D). A 3-dimensional medial curve is derived from each individual hippocampus (arrows in part B), and the distance from this axis to the surface is the dependent variable in a regression analysis. See the "Methods" section of the text for details.

Late-Life Mood Disorders.¹⁵ The patients were all examined in the Alzheimer's Disease Research Center, and the images for the 20 control subjects were obtained through the Late-Life Mood Disorders and the Imaging Methods and Analysis in Geriatrics Research Group data repository. The subjects were selected (blind to imaging findings) to create groups of equivalent age, education, and sex distribution.

The 46 study patients underwent an extensive neuropsychiatric examination,^{14,16} and all patient records were reviewed at a multidisciplinary clinical consensus conference for assignment of a diagnosis. All patients with AD met the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD¹⁷; none of the patients with MCI had comorbid conditions that could in and of themselves cause cognitive dysfunction.

The diagnosis of MCI, amnesic subtype (MCI-A), required impairments in delayed recall verbal memory, nonverbal memory, or both, defined as performance greater than 1.5 SDs below that of individuals of comparable age and education with otherwise normal cognitive function. For the diagnosis of the MCI, multiple cognitive domain subtype (MCI-MCD), there was deterioration in at least 1 cognitive domain (not including memory) or 2 abnormal test results in 2 different domains (which could include memory). Selected neuropsychological test data results are given in **Table 1**. The MRIs were not used to differentiate MCI sub-

types. **Table 2** shows the demographic and neuropsychiatric characteristics of the patients.

The MRI data were acquired in 3 dimensions to obtain 124 thin contiguous images throughout the entire brain. The contrast maximized the gray-white matter and cerebrospinal fluid differences (repetition time, 25 milliseconds; echo time, 5 milliseconds; slice thickness, 1.5 mm; 0-mm gap; 40° flip angle; and field of view, 24 × 18 cm). The individual brain volumes were first reoriented into the axial plane, then spatially realigned with the International Consortium for Brain Mapping nonlinear average brain template (ICBM152), using FLIRT (available at <http://www.fmrib.ox.ac.uk/fsl/>). The hippocampi from each brain were traced using a software program (Tracer) (available at http://www.loni.ucla.edu/Software/Software_Detail.jsp?software_id=10).

The hippocampi were manually traced bilaterally by one of us (S.W.D.), who was blind to diagnosis, sex, and demographics. Anatomical segmentation was performed using a standard neuroanatomical atlas of the hippocampus,¹⁸ according to previously described criteria.¹⁹⁻²¹ Hippocampal models were delineated in contiguous coronal brain sections using standard guidelines,²² including the hippocampus proper, dentate gyrus, and subiculum (**Figure 1A**). The borders of the hippocampus were determined by the temporal horn, the choroidal fissure, the uncus and ambient cisterns, and the gray-white junction between the subiculum and parahippocampal gyrus.

Anatomical mesh modeling methods^{23,24} matched equivalent hippocampal surface points across subjects and groups.²⁵

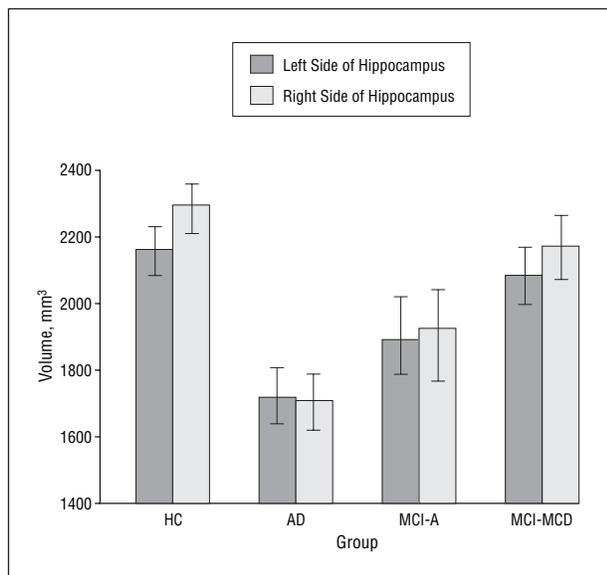


Figure 2. The mean \pm SEM total volume of the 2 sides of the hippocampus in each subject group (see also Table 3). HC indicates healthy control; AD, Alzheimer disease; MCI-A, mild cognitive impairment, amnesic subtype; and MCI-MCD, mild cognitive impairment, multiple cognitive domain subtype.

The manually derived contours were made uniform by modeling them as a 3-dimensional variable surface mesh (Figure 1B),^{23,24} allowing measurements to be made at corresponding surface locations in each subject (Figure 1C and D). This procedure also allows the averaging of hippocampal surface morphological features across all individuals belonging to a group and the recording of the amount of variation between corresponding surface points relative to the group averages.

To assess global hippocampal atrophy, the volumes of these 3-dimensional models were measured in cubic millimeters. To measure local atrophy, a medial 3-dimensional curve was derived from each hippocampus down the central axis (Figure 1B). The distance of each surface point from this center line measures the radial size of the hippocampus. Regressions were performed at each surface point to map linkages between radial size and as many as 3 covariates. The resulting maps were visualized, and their significance was assessed by permutation to correct for multiple comparisons within each statistical map.²⁴

RESULTS

At a global level, the total volume of the hippocampus differed significantly between controls and all MCI and AD subjects ($F_{2,63}=13.54$, $P<.001$, $\eta^2=0.30$). The total volume of the hippocampus was significantly smaller in the patients with AD compared with the controls (least significant difference test, $P<.001$) and with all of the MCI patients ($P<.001$). The hippocampi of the MCI patients, as a group, did not differ from those of controls ($P=.09$). When we examined the 2 MCI subgroups, there were significant differences among the study groups in terms of the volumes of the right side of the hippocampus ($F_{3,65}=11.4$, $P<.001$, $\eta^2=0.36$), the left side of the hippocampus ($F_{3,65}=6.46$, $P=.001$, $\eta^2=0.23$), and the total hippocampus (bilateral) ($F_{3,65}=9.97$, $P<.001$, $\eta^2=0.32$) (**Figure 2** and **Table 3**).

Table 3. Hippocampal Volumes by Study Group*

Hippocampus	Group			
	Healthy Controls	MCI-A	MCI-MCD	AD
Right side	2292.7 (342)	1889.4 (347)	2167.7 (337)	1709.2 (333)
Left side	2161.9 (287)	1923.7 (295)	2084.3 (380)	1718.7 (362)
Total	4454.6 (572)	3813.1 (592)	4252.0 (702)	3427.9 (641)

Abbreviations: See Table 1.

*Data are given as mean (SD) volumes, measured in cubic millimeters.

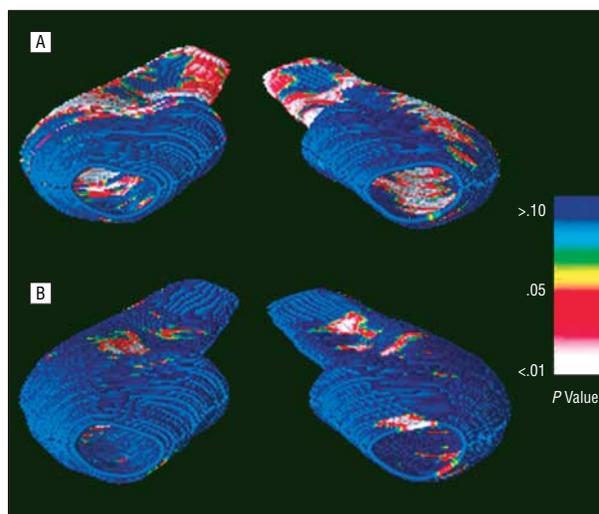


Figure 3. Statistical 3-dimensional maps showing local differences in hippocampal structures between patients with Alzheimer disease and control subjects (A) and between all patients with mild cognitive impairment and control subjects (B). The right hippocampus is on the left side of the figure.

Significant local atrophy in the hippocampus in the patients with AD compared with the controls is shown in **Figure 3A** on the right ($P<.001$ by permutations tests) and left ($P<.001$) sides. By contrast, there was only a small amount of local atrophy in the hippocampi of the MCI patients (as a group) compared with the controls (Figure 3B).

The MCI-MCD patients did not have significant volume loss in the hippocampus, examined either on the maps (all permutation tests, $P>.05$) or by the measured volumes ($\eta^2<0.05$, $P>.25$ for all values). Compared with the patients with AD, the MCI-MCD patients showed significant sparing of the hippocampi on the maps (left side, $P=.002$; and right side, $P=.002$) and by the measured volumes (right side, $P<.001$; left side, $P=.001$; and total, $P<.001$; $\eta^2>0.25$).

The MCI-A patients had significant atrophy on the inferior hippocampal surface (left side, $P=.02$; and right side, $P=.03$), but there was no difference vs the patients with AD ($P>.05$ for all). The overall volumes showed a similar pattern; there was significant atrophy on the right side and in total hippocampal volume measures compared with the controls (right side, $P=.01$ [$\eta^2=0.21$]; left side, $P=.14$ [$\eta^2=0.11$]; and total, $P<.03$ [$\eta^2=0.19$]) and no differences vs the patients with AD (right side, $P=.25$; left side, $P=.20$; and total, $P=.20$) (**Figure 4**).

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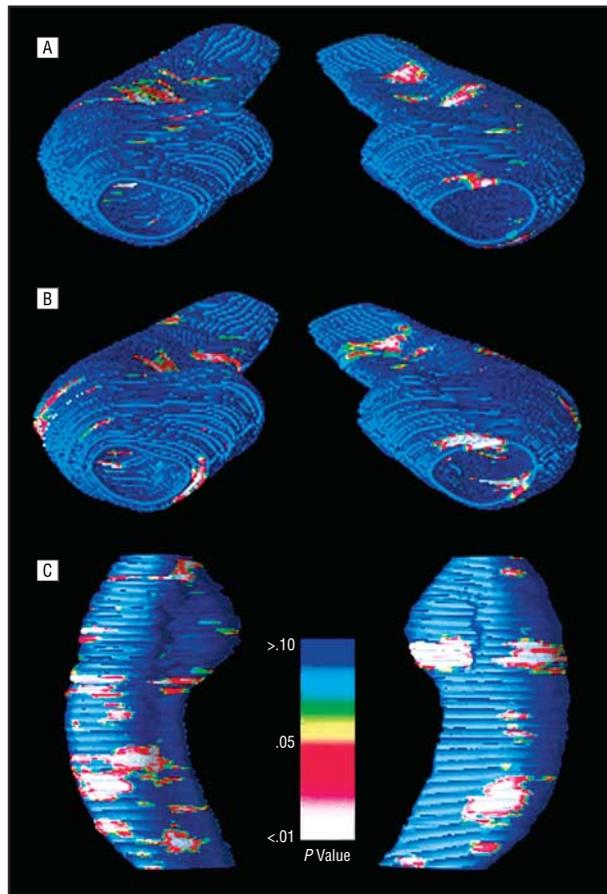


Figure 4. Statistical 3-dimensional maps showing local hippocampal atrophy in patients with mild cognitive impairment (MCI) compared with control subjects. The right hippocampus is on the left side of the figure. A, Patients with MCI, multiple cognitive domain subtype, vs controls ($P > .05$ for all). B, Patients with MCI, amnesic subtype (MCI-A), vs controls. C, Patients with MCI-A vs controls, showing bottom sections of the map ($P < .03$ for all).

COMMENT

These data show that there are neuropathological differences (reflected as MRI measured volumes) between MCI as an idiopathic amnesia (MCI-A) and the MCI that includes other cognitive deficits (MCI-MCD), supporting the clinical differentiation of the 2 subgroups. Furthermore, these data and those of others¹¹ demonstrate that MCI-MCD is not a more advanced stage of MCI-A. The lack of extensive hippocampal atrophy and the presence of significant cortical atrophy in those with MCI-MCD means that the starting point for the 2 syndromes differs. However, only longitudinal data will be able to compare and contrast the trajectories of the cerebral atrophy over time. Finally, these data emphasize the importance of care-

ful clinical characterization of MCI. Differences in the method of case ascertainment, the extent of the neuropsychological examination, and the use of subgroup analysis may explain the discrepancies among clinical and neuroimaging studies of MCI.^{2,4,11,13,26-30}

Our clinical definition of MCI was based on the nature and extent of neuropsychological impairment; in the case of MCI-A, cognitive dysfunction was limited to memory. By contrast, the MCI-MCD patients, while often having mild memory impairments, also had deficits in other domains. Although the entire MCI group had only a small degree of hippocampal atrophy, this was an artifact of combining the 2 subgroups. The MCI-MCD group had no atrophy, masking the shrinkage in the MCI-A group. The focal nature of the cognitive loss in MCI-A patients is, thus, consistent with the focal atrophy within the hippocampal complex.

Our analysis was aided by the fact that these cases were taken from a referral-based clinic. In all cases, someone (patient, family member, or physician) believed that there was a significant change in cognition and, consequently, the MCI patients studied herein are likely "closer" to conversion to clinical AD than they might be otherwise. Were we to study patients from a population study without such referral bias, we would be able to evaluate central nervous system structural changes before their clinical expression, and then the locus and extent of atrophy might differ from what was observed herein.

These data provide further evidence for the existence of subtypes of MCI, and they are also consistent with the parsimonious explanation that MCI represents a mild form of AD that has yet to convert to the full expression of a dementia syndrome. The differences among the subtypes of MCI are a consequence of different patterns of atrophy, which express themselves as different patterns of neuropsychological dysfunction.

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