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Atrophy of presubiculum and subiculum is the earliest hippocampal anatomical marker of Alzheimer's disease

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Abstract

Background: There is no consensus about which hippocampal subfields become atrophic earliest in the course of Alzheimer's disease (AD).
Methods: Thirty AD patients, 41 mild cognitive impairment (MCI) patients, and 38 healthy controls (HCs) underwent cerebral magnetic resonance imaging (with an automated segmentation protocol for the volumetric analysis of hippocampal subfields) and a test of immediate and delayed recall of a 15-word list.
Results: The volumes of the presubiculum and subiculum presented the most remarkable reduction in the patient's groups. In the MCI group, only the volumes of presubiculum and subiculum predicted performance on the memory tests. In AD patients, the volumes of all hippocampal subfields (with the notable exception of the CA1) predicted memory scores.
Conclusions: Our data point to a prevalent atrophy of the presubicular-subicular complex from the early phases of AD. This finding is consistent with neuropathological observations in AD patients and probably reflects the severe degeneration of the perforant pathway while penetrating the hippocampus through the subicular field in its course from the entorhinal cortex to the dentate gyrus.

Keywords: Alzheimer's disease; Mild cognitive impairment; Memory; Structural MRI; Brain atrophy

1. Introduction

Neuropathological changes in patients with Alzheimer's disease (AD) typically affect the hippocampal formation very early [1,2]. Therefore, neuroradiological indexes of hippocampal atrophy [3,4] and, consistent with the well-known role of the hippocampus in human declarative memory [5], episodic memory deficits [6,7] are among the most powerful diagnostic indexes of AD from the very early phases, corresponding to the clinical condition of amnestic mild cognitive impairment (MCI).

The hippocampus is not, however, a unitary anatomical formation. Several subfields have been identified, which can be differentiated on both histological grounds [2,8] and according to their functional role in memory encoding and retrieval [9,10]. There is no consensus about which subfields become atrophic earliest in the disease course or which neuropathological change is primarily implicated in volume reduction. According to some authors, neuronal loss is the main cause of atrophy. However, the three studies that provided neuronal counts in the hippocampal subfields of patients with AD report discrepant data. West et al. [11,12] found the most striking AD-related neuronal loss at the level of the CA1 subfield, whereas Simic et al. [13] reported a reduced number of neurons in the subiculum and dentate gyrus of AD patients but not in other subfields. On the other side,

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neuronal loss might not be the only or even the main reason for regional volume reduction of the hippocampus in AD. Indeed, Rössler et al. [14] found a very weak correlation between the observed volume reduction and neuronal loss in the overall hippocampus of AD patients, and Mizutani and Kasahara [15,16] found that hippocampal atrophy in AD was mainly caused by degeneration of the stratum lacunosum-radiatum, which contains the perforant pathway that originates in the entorhinal cortex, rather than neuronal loss in the pyramidal layer of the hippocampus.

The aims of this cross-sectional study were to delineate the in vivo progression of atrophy in the main subfields of the hippocampus in patients diagnosed with either MCI or AD, and to determine whether atrophy in one or more specific hippocampal subfields best predict severity of episodic memory impairment.

2. Materials and methods

2.1. Subjects

A cohort of 109 individuals, 30 with a diagnosis of probable AD, 41 with diagnostic characteristics of single-domain amnestic MCI, and 38 healthy matched controls (HC), were enrolled in this study. AD and MCI patients were consecutively recruited from the specialist dementia clinics of Santa Lucia Foundation (Rome, Italy).

HCs were recruited from patients' relatives or through local advertisements. None of them showed cognitive problems or evidence of cognitive deficits on neuropsychological testing.

Patients with AD met the clinical criteria for Alzheimer's dementia established by the National Institute on Aging and the Alzheimer's Association [17].

Diagnosis of single-domain amnestic MCI was made according to established criteria [18] by trained neurologists. Inclusion criteria were as follows: (1) subjective memory impairment confirmed by a pathological score on at least one memory test of the neuropsychological battery; (2) nonfulfillment of the criteria for dementia according to the recommendations of the National Institute on Aging-Alzheimer's Association work groups [17]; (3) preserved general cognitive functions as confirmed by normal scores on the Mini-Mental State Examination (MMSE) (normality cutoff score, 24 [19]) and on tests of the neuropsychological battery; (4) no or very mild impact of the memory deficit on the subject's activities, as confirmed by a normal score on the instrumental activities of daily living and by a total Clinical Dementia Rating (CDR) score = 0.5; (5) lack of any evidence of neurological or systemic pathology able to induce memory disorders; (6) brain magnetic resonance imaging (MRI) negative for focal lesions (minimal diffuse changes or minimal lacunar lesions of white matter were admitted) [20]; and (6) absence of moderate to severe depression and/or anxiety, as confirmed by scores on Beck's Depression Inventory and the Hamilton Anxiety Rating scale (14 was the highest acceptable score for both scales). Finally, for a subsample of 46 patients (12 AD and 34 MCI patients), the investigation of *APOE* ε4 allele frequency was carried out, whereas for the HCs, no genetic data were available.

The principal demographic and clinical characteristics of the studied subjects are summarized in Table 1.

After the procedures were explained to them, the subjects gave their written informed consent in a protocol approved by the Joint Ethics Committee of the Fondazione Santa Lucia.

2.2. Neuropsychological examination

Consistent with the hypothesis of the study, two declarative memory tests were selected from the comprehensive neuropsychological battery administered to all participants: the immediate and the 15-minute delayed recall of a 15-word list.

In the 15-word list learning test [21], the examiner reads 15 words aloud (at a rate of 1 word/s) five times; immediately

Table 1
Number of females and males (F/M) and mean (and standard deviation) of other demographic, clinical, and genetic characteristics of the three groups of participants

Groups	AD (n = 30)	MCI (n = 41)	HC (n = 38)	Chi-square	*P*
F/M	16/14	16/25	22/19	1.7	.44
				$F_{2,106}$ (df)	
Age	71.2 (7.3)	70.6 (6.8)	69.7 (4.4)	0.5	.61
Years of formal education	8.4 (4.1)*,†	11.7 (4.1)	11.4 (4.3)	6.3	.003
MMSE (adjusted score)	19.7 (3.8)*,†	26.3 (2.3)*	27.2 (1.7)	102.0	.0001
15-Word list test					
Immediate recall	18.3 (9.4)*,†	26.6 (6.2)*	42.7 (8.3)	78.5	.0001
Delayed recall	1.5 (2.7)*,†	3.3 (2.7)*	9.0 (2.8)	72.8	.0001
APOE, n (%)	AD (n = 12)	MCI (n = 34)			
APOE ε2/ε3	0 (0)	1 (3)	—		
APOE ε3/ε3	10 (83)	20 (59)	—		
APOE ε3/ε4	2 (17)	13 (38)	—		

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; HC, healthy control; MMSE, Mini-Mental State Examination.
*Significantly less than in the HC group.
†Significantly less than in the MCI group.