Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: An MRI study

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Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia:

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Article abstract—Hippocampal atrophy detected by volumetric MRI is a sensitive feature of early Alzheimer's disease (AD), but there are no studies evaluating hippocampal atrophy by MR volumetry in other dementing diseases. We therefore compared hippocampal volumes in a total of 113 subjects: 50 patients with mild to moderate AD, 9 patients with vascular dementia (VaD), 12 patients with idiopathic Parkinson's disease (PD) without dementia, 8 patients with PD and dementia (PDD), and 34 elderly control subjects. Thin, coronal, contiguous images were obtained by a 1.5-T MR imager. All patient groups had significantly smaller volumes of the hippocampus compared with the control group. In the PDD group, the absolute volumes were even smaller than in the AD group. In the PD group, the volumes were diminished to a lesser but significant extent. The volumes in the VaD group varied: of nine patients, two had no atrophy, three had unilateral, and four had bilateral atrophy. We postulate that hippocampal atrophy does not seem to be a specific phenomenon of dementia in AD but also occurs in VaD and PDD, and even in PD when no dementia is present. However, coexistence of AD pathology in our PD and VaD patients cannot be ruled out. Further studies with access to neuropathologic data are needed.

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In clinical practice, the diagnosis of Alzheimer's disease (AD) is based on typical features of the disease and exclusion of other conditions causing dementia. In AD, the hippocampus is atrophied early in the course of the disease,[1,2] and the atrophy can be reliably detected by volumetric MRI for diagnostic purposes.[3,4] With this technique, AD patients can be sensitively separated not only from cognitively normal control subjects, but also from subjects suffering from differentially important conditions, such as age-associated memory impairment[5] and depressive pseudodementia.[6] However, the specificity of MRI volumetry in the evaluation of hippocampal atrophy in dementing diseases other than AD has not been determined.

In the diagnostic process of dementias, AD and vascular dementias (VaD) constitute the largest and thus differentially most important groups of dementias. These two types of dementia together account for as much as 90% of all dementias.[7,8] Moreover, one of the most common diseases in the elderly that may be associated with dementia is Parkinson's disease (PD). In PD, the proportion of demented patients varies from 40 to 70%, the percentage increasing with age.[9]

In this study, we investigate the specificity of hippocampal atrophy by comparing hippocampal volumes of AD patients and cognitively normal control subjects with volumes of patients with VaD and PD with dementia (PDD) and without dementia. Our working hypothesis was that the volume loss of hippocampus would be most pronounced in AD and not present in PD.

Methods. We evaluated the volumes of hippocampus in 113 subjects: 50 patients with early probable AD according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria[10]; 9 patients with VaD according to the DSM-III-R criteria[11]; 20 patients with idiopathic PD, of whom 8 were demented; and 34 cognitively and neurologically normal subjects (table 1). In addition to the MRI, the investigation of the patients and the control subjects included clinical neurologic examination, EEG, and a comprehensive battery of neuropsychological and laboratory tests to exclude other causes of dementia and

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Table 1 *Clinical characteristics of patients and control subjects*

	AD	VaD	PDD	PD	Control	ANOVA
Number	50	9	8	12	34	NA
Women/men	26/24	3/6	5/3	6/6	14/20	NA
Age* (y)	70 ± 8	76 ± 4†	71 ± 2	68 ± 5	72 ± 4	2.6‡
Dementia duration* (y)	3.0 ± 1.6	3.5 ± 1.4	4.2 ± 1.5	NA	NA	1.6
PD duration* (y)	NA	NA	7.2 ± 3.3	5.4 ± 2.6	NA	1.9
MMSE score*	21 ± 4	16 ± 4§	19 ± 5	27 ± 2‖	28 ± 1‖	51.0¶
Ischemic score*	0.7 ± 0.9	7.8 ± 1.8**	2.0 ± 1.5**	0.2 ± 0.4	0.5 ± 0.9	96.1¶
Webster score*	2.1 ± 2.7	0.9 ± 1.5	9.2 ± 4.4††	5.8 ± 2.8††	ND	20.5¶

* Values are means ± SD.

ANOVA ‡ $p < 0.05$, ¶ $p < 0.0001$, Duncan post-hoc analysis $p < 0.05$: † differs from AD and PD; § differs from AD, PDD, PD, and control; ‖ differs from AD, VaD, and PDD; ** differs from AD, PD, and control; †† differs from AD and VaD.

NA = not applicable; ND = not done.

parkinsonism or other CNS pathology. The complete test battery that has been described elsewhere[4] also included tests of verbal and visual memory functions such as list learning test and story recall as well as the Heaton Visual Reproduction test. The degree of cognitive decline was evaluated by using the Mini-Mental Status Examination (MMSE).[12] The Webster scale[13] was used to estimate the severity of extrapyramidal signs. The modified ischemic score[14] was also included. The study was approved by the local ethics committee, and the study subjects gave their informed consent for participation in the study.

The study subjects were scanned with a 1.5-T imager using a magnetization prepared rapid gradient echo (TR 10 ms, TE 4 ms, TI 250 ms, flip angle 12°) resulting in sagittal T_1-weighted contiguous partitions with slice thickness of 1.5 to 2.0 mm, perpendicular to the long axis of the hippocampus. The hippocampus included the dentate gyrus, the hippocampus proper, and the subicular complex. The uncal portion of the rostral hippocampus that is located ventral to the caudal amygdala was included into the hippocampus. The caudal end of the hippocampus was determined from the section in which the fornices were still detectable in their full length. The fornices were not, however, included in the volume of the hippocampus. The boundaries of the hippocampus were outlined by a tract-ball driven cursor, and the number of voxels within the region creating the volume was calculated by using an in-house developed program. To exclude individual size variability, the volumes were normalized to coronal intracranial area measured at the level of anterior commissure (the volumes were multiplied by 100 and divided by intracranial area). All measurements were performed by the same rater without any knowledge of the clinical data and diagnostic category of the subjects. The methodology and reproducibility of the method have been described in detail elsewhere.[4,5]

Statistical analysis. The data were analyzed by SPSS-PC+ V.4.1 software (SPSS, Inc., Chicago, IL). ANOVA with Duncan post-hoc analysis was used to compare the means over the study groups. Volumes normalized for the intracranial area were used in all statistical analyses. Correlations were calculated by using two-tailed Pearson's correlation test. The results are expressed as mean ± SD. The level of statistical significance of differences is $p < 0.05$.

Results. The clinical data of the study groups are presented in table 1. ANOVA showed a significant difference in age ($F[4,107] = 2.7$, $p < 0.05$); the VaD patients were older than AD and PD patients (Duncan $p < 0.05$). Duration of dementia did not differ in the demented patient groups. Duration of PD was slightly longer in the PDD group than in the PD group but not significantly. As expected, the MMSE scores differed significantly ($F[4,105] = 49.4$, $p < 0.0001$) across the study groups; the control and PD groups had higher scores than AD, VaD, and PDD patients ($p < 0.05$), and the VaD group had lower scores than the AD and PDD groups ($p < 0.05$). The ischemic scores also differed significantly (ANOVA $p < 0.0001$): the VaD and PDD groups had higher scores than AD, PD, and control groups ($p < 0.05$). However, none of the PDD patients received an ischemic score higher than 4. The Webster scores were significantly higher in PD and PDD than in AD and VaD groups (ANOVA/Duncan $p < 0.05$).

Seven VaD patients had a history of cerebral infarctions, but at the time of the neurologic examination, right hemiparesis was present in one VaD patient and left hemiparesis in a second VaD patient. Two AD patients also had a history of cerebral infarction. The frequency of coronary heart disease was 19/50 38% in AD (19/50), 75% in VaD (6/8), 38% in PDD (3/8), 17% in PD patients (2/12), and 3% in control subjects (1/34). The frequency of hypertonia was 24% in AD, 100% in VaD, 0% in PDD, 8% in PD, and 12% in control groups.

In the hippocampal volumes, ANOVA showed significant differences over the study groups both on the right and left ($p < 0.0001$) (table 2, figure, A and B). The control subjects had larger volumes on both sides than the other study groups ($p < 0.05$). The right hippocampal volumes of VaD patients were also larger than those of AD, PD, and PDD patients ($p < 0.05$). On the left side, the AD patients had significantly smaller volumes than VaD and PD patients. The raw volumes in the PDD group, although not significantly, were even smaller than in the AD group. In the VaD group, of the nine patients, two had no atrophy at all, four had bilateral atrophy, and three had unilateral atrophy. The limit of atrophy was taken as the average volume of the control group −1 SD, that is, 2,952 mm^3 on the right and 2,700 mm^3 on the left. These patterns of

Table 2 Hippocampal volumes (mm^3) for patients and control subjects

	Number	Right hippocampus*	Left hippocampus*
AD	50	2,337 ± 704	2,070 ± 562†
VaD	9	2,975 ± 572‡	2,406 ± 448
PDD	8	2,152 ± 391	2,042 ± 215
PD	12	2,557 ± 360	2,401 ± 380
Control	34	3,450 ± 498§	3,206 ± 548§
ANOVA, F		31.0‖	38.6‖

* Values are means ± SD.
ANOVA ‖ $p < 0.0001$, Duncan post-hoc analysis $p < 0.05$, § differs from all other groups; ‡ differs from AD, PDD, and PD; † differs from VaD and PD.

atrophy could not be explained by other findings in the MRI such as location infarcts.

The correlations between hippocampal volumes and performance on memory test scores were significant in AD and PDD groups but not in VaD, PD, or control groups. The left hippocampal volume correlated with delayed story recall ($r = 0.43$, $n = 48$, $p < 0.01$) in AD and with immediate list learning scores ($r = 0.93$, $n = 7$, $p < 0.01$) in PDD.

Discussion. A noninvasive method for the diagnosis of early AD is urgently needed. Hippocampal volumetry using MRI has shown potential as a promising and sensitive method for diagnosing early AD,[3,4] but this study indicates that hippocampal atrophy is not a specific finding to AD as also occurs in VaD and PDD as well as, to a lesser degree, in PD without dementia. Thus, hippocampal atrophy may be a common phenomenon to some dementias and not restricted only to AD. Atrophy of the hippocampus also occurs in amnestic conditions of temporal lobe pathology.[15] The volume of hippocampus correlates with memory functions as measured by tests assessing delayed recall[4,16] that are sensitive to dementia and spared by ageing.[17,18] In this study, left hippocampal volumes correlated with verbal memory scores in AD and PDD, although the number of PDD patients was small. In VaD, PD, or control subjects, there were no significant correlations between memory scores and hippocampal volumes. Yet, classical dementia in PD is not regarded as temporal but as subcortical.[19] In addition, vascular lesions should not necessarily affect the temporal lobe.

The dementia occurring in PD is not a single concept but consists of a variety of dementia syndromes, in which the clinical picture depends on separate pathogenetic mechanisms in different neurotransmitter systems. The typical dementia in PD is a mild subcortical dementia resulting from dopaminergic insufficiency. The most severe type of disease is PDD combined with AD pathology, which is present in 10 to 60% of the patients with PD.[19] Moreover, AD and PD share some neurochemical abnormalities in the brain such as deficits in the cholinergic, serotonergic, noradrenergic, and dopaminergic systems.[20-22] In AD, the disturbances in the medial temporal lobe structures, the hippocampus, entorhinal cortex, and adjacent cortical regions are a central phenomenon.[1] Neurofibrillary tangles are present in the entorhinal region in PD and AD.[23,24] The entorhinal cortex is a major relay station between the hippocampus and the isocortex, and its bilateral destruction isolates the hippocampus from isocortical inputs. Thus, the hippocampal atrophy in our PD and PDD patients may be explained by the neuropathologic changes resulting from PD on its own or coexistence of PD and AD, particularly in PDD patients.

The patterns of atrophy in the VaD group are more difficult to explain. In a previous study with aged rats, chronic vascular insufficiency, without infarctions, mimicked AD-type changes, including high signal intensities in the hippocampal region predominant on the right side, MR spectroscopic changes, alterations in local cerebral blood flow, spatial memory dysfunction, and CA1 neuron damage.[25] Yet, this

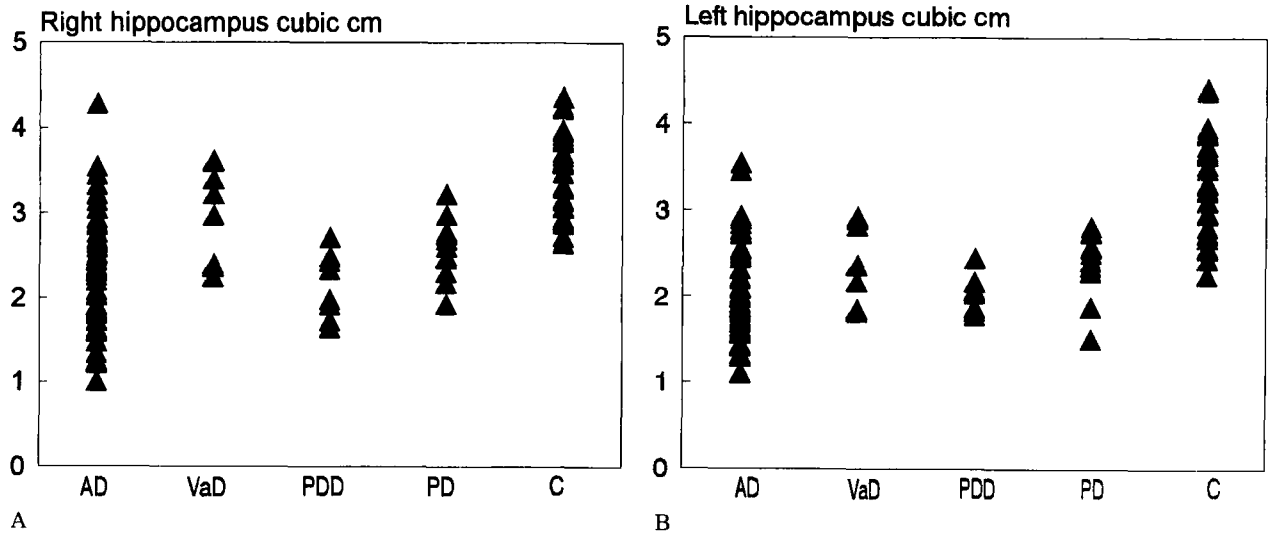

Figure. Right (A) and left (B) hippocampal volumes for patients and control subjects.

does not explain our findings where of the nine VaD patients, four had bilateral atrophy, two had no atrophy, and three had unilateral atrophy. In three of the four patients with unilateral atrophy, the right hippocampus was larger. Other findings in T_2-weighted axial MRI could not clarify the nature of these findings. There were no large or strategic infarcts or other lesions in the temporal lobes or in the area of the posterior cerebral artery responsible for the circulation to the hippocampus. However, these patterns of atrophy probably represent the results of different vascular lesions or etiologies. In the two VaD patients without atrophy, the lesions causing the dementia probably did not affect the size of hippocampus. Likewise, in cases with unilateral atrophy, the lesions affect the hippocampus on only one side. The cases with bilateral atrophy have vascular lesions affecting the hippocampus bilaterally, or alternatively they may present mixed dementia, that is, the combination of AD and VaD. In a previous autopsy study, the presence of mixed dementia was surprisingly high: three of four patients considered to have VaD had also AD, and 5 of 16 patients considered to have mixed dementia had AD alone.[26]

We conclude that hippocampal atrophy is a sensitive feature of AD, but specificity of this atrophy seems to limit its use in clinical practice.

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