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Hippocampal volume discriminates between normal cognition; questionable and mild dementia in the elderly

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Abstract

The sensitivity of MRI volumetric measures to detect cognitive dysfunction is examined in 39 participants of an epidemiological field study (age 75–85, MMSE 19–30). According to Clinical dementia rating (CDR), 17 subjects had normal cognition (CDR 0), 12 had questionable (CDR 0.5) and 10 mild dementia (CDR 1). Discriminant analysis based on four hippocampal measures resulted in a correct classification of 76.9% of all subjects. Left-sided and posterior hippocampal measures were more responsible for group discrimination than right-sided and anterior measures. In CDR 0.5, a significant hippocampal volume reduction of 14.3% vs.11.3% (left vs. right) relative to normal was found. The right hippocampus was significantly greater than the left in CDR 0 and CDR 0.5, but not in CDR 1. The magnitude of non-directional hippocampal asymmetry increased with decreasing cognitive state. We conclude that hippocampal atrophy is sensitive to detect cognitive dysfunction and subjects at risk for Alzheimer's disease in the elderly population.

Keywords: Hippocampus; MRI; Volumetry; Aging; Cognition; Mild cognitive impairment; Mild dementia; Alzheimer's disease; Asymmetry; Laterality; Clinical dementia rating; Population-based

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly.

The diagnosis of AD requires the presence of multiple cognitive deficits, including memory impairment, which are severe enough to interfere with activities of daily living [53]. The pathological processes underlying AD seem to be present years before the clinical diagnosis of AD can be made. Mild cognitive deficits are characteristic of the preclinical phase of AD. The transitional stage of mild cognitive impairment (MCI) in the elderly has become the subject of intensive investigation as a research category in the evaluation of preclinical Alzheimer's disease [1,42]. Subjects with MCI generally meet the criteria for "questionable dementia" when Clinical Dementia Rating (CDR) [22] is applied. "Questionable dementia" (CDR 0.5) refers to subjects with objective cognitive impairment who are not yet demented but have a high risk to develop dementia in the near future [46].

The hippocampal formation seems to be invariably involved in AD, which has led to the definition of AD as a hippocampal dementia [3]. Neurofibrillary tangles, i.e. histopathological changes typical of AD are found in large numbers in the hippocampus of demented patients with AD. The severity of neurofibrillary pathology in AD has been shown to correlate inversely with hippocampal volume measures in demented subjects [6,40].

Previous neuroimaging studies have consistently shown that hippocampal atrophy (HA) is a sensitive marker for AD and that it provides high accuracy in discriminating normal controls and subjects with AD in more advanced stages [9,23,28,36,41].

A number of studies on subjects with memory impairment in the absence of dementia or on subjects with mild dementia showed that hippocampal atrophy is present very

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early in the course of AD [24,26,30,34,36,41] and that it might even precede the onset of clinical symptoms [15,25, 29]. However, most of these studies comprised only small numbers of subjects specifically selected to fulfill research criteria for distinct diagnostic groups. Hence, little can be said about the accuracy of hippocampal measures in the delineation of mild cognitive impairment and/or mild dementia in a non-selected population with a continuous range of cognitive functions.

The aim of this study is to examine whether measures of HA may be useful for the delineation of questionable dementia in a sample of subjects aged 75 to 85 which were consecutively recruited from an epidemiologic field study. In addition, the question as to which hippocampal measures are most sensitive for the detection of cognitive dysfunction in the elderly is addressed.

2. Materials and methods

2.1. Subjects

We report on a subsample from the *Leipzig Longitudinal Study of the Aged, LEILA 75+* [44,45], a community-based study of 1692 randomly selected individuals aged 75 and older. The present sample includes the first 39 consecutively recruited subjects which will take part in an ongoing longitudinal neuroimaging study (LEILA-MCI).

As part of LEILA 75+, a fully structured interview was administered at a home visit during the time period January 1997 to June 1998. The core component of the interview was the SIDAM (Structured Interview for the Diagnosis of Dementia of Alzheimer type, Multi-infarct dementia and dementias if other etiology according to ICD-10 and DSM-III-R) [55]. Part of this interview is a cognitive test battery which contains all items of the Mini-Mental-State-examination (Folstein 1975) and a number of additional items yielding a maximum score of 55 (SIDAM score or SISCO). The SISCO can be subdivided into several cognitive domains (orientation, immediate recall, delayed recall, long term memory, intellectual abilities, verbal abilities/calculation, visuospatial function, and aphasia/apraxia).

A subsample of the LEILA population was subsequently invited for further clinical and paraclinical examinations (LEILA-MCI) which took place in the Memory Clinic of the University Department of Psychiatry. Inclusion criteria were: age 75–85, right-handedness, and a MMSE score above 18. Exclusion criteria were: physical and/or neurological disabilities (such as blindness, deafness, severe movement disorders or paralysis) which would have interfered with the ability of the subject to complete neuropsychological tests or paraclinical examinations (such as computed tomography, electroencephalography or magnetic resonance imaging).

Subjects were randomly selected for either CT or MR imaging with the exception of cases in which contraindications for MRI were present. To facilitate an adequate distribution along a presumed cognitive continuum, subjects were sampled in equal proportions according to their MMSE scores (group 1: MMSE 19–21, group 2: MMSE 22–24, group 3: MMSE 25–27, group 4: MMSE 28–30.)

The present study includes the first 39 subjects (10 males, 29 females) who had been consecutively recruited for LEILA-MCI and had received a MRI scan until November 1998. All subjects were clinically examined. Paraclinical tests included blood sampling, ambulatory blood pressure monitoring, magnetic resonance imaging (MRI), and quantitative electroencephalography.

2.2. Methods

2.2.1. Clinical assessment

All subjects were medically and neurologically examined by a trained physician and/or neurologist/psychiatrist (HW, HJG). In the neurological examination, focal neurological signs and symptoms, gait, balance, primitive reflexes and extrapyramidal signs (according to a subset of items of the Unified Parkinson's Disease Rating Scale, UPDRS) were assessed. Psychiatric assessment included the completion of the Montgomery-Asberg-Depression-Scale (MADR) [37] and a semistructured interview in order to assess cognitive and functional abilities of the subject as well as psychopathological features such as delusions and hallucinations.

In cases with questionable or significant cognitive deficits, a collateral source was also interviewed. According to the available information, the cognitive state was determined using Clinical Dementia Rating (CDR) [22] in a case conference (consensus rating of three clinicians). Of the 39 subjects, 17 had a CDR of 0 ("normal cognition"), 12 a CDR of 0.5 ("questionable dementia") and 10 a CDR of 1 ("mild dementia").

None of the subjects with a CDR-rating of 0.5 fulfilled the ICD-10 criteria for dementia. In one male subject with CDR 0.5, pronounced ventricular widening suggestive of normal pressure hydrocephalus was found.

Only five of the 12 subjects with CDR 0.5 had significant memory complaints. Only two of them had previously contacted a doctor because of memory problems. According to their cognitive performance in the SIDAM, four of the subjects with CDR 0.5 showed a cognitive profile with isolated memory impairment (defined by a delayed recall score which is at least 1.5 standard deviations [SD] below the mean of those who were judged to have CDR 0). Three subjects performed just within 1.5 SD in memory domains but showed significant decline in the domains visuospatial function, verbal abilities/calculation and/or aphasia/apraxia. The remaining subjects showed decline in both memory and other cognitive functions.

Of the subjects with a CDR-rating of 1, eight were diagnosed as having Alzheimer's disease and a mild dementia severity according to ICD-10 research criteria. Two of

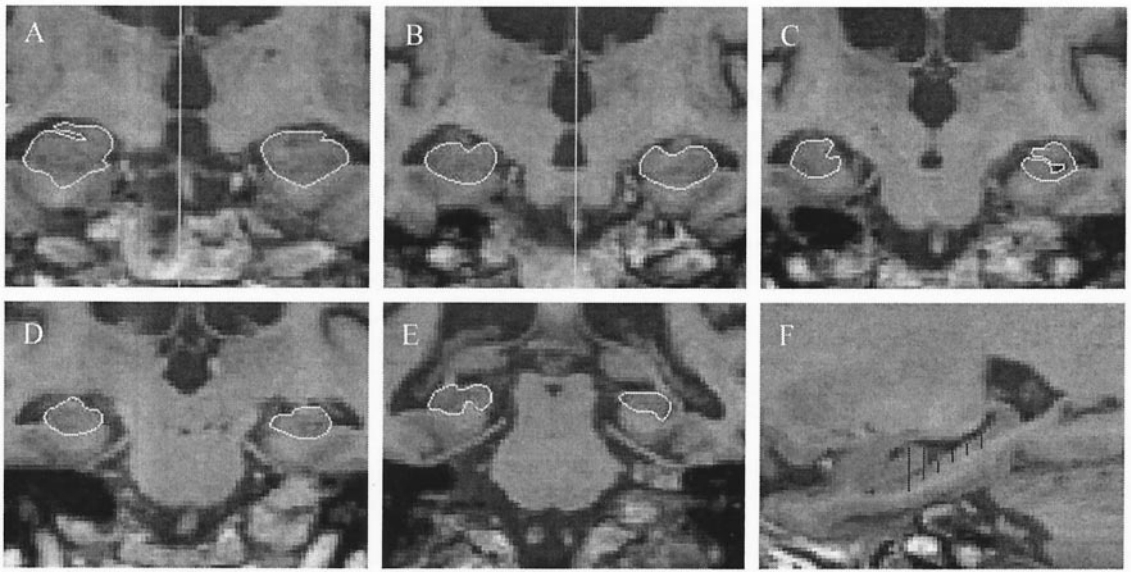

Fig. 1. Example manual segmentation of the hippocampus. The manual outlining of hippocampal cross-sections is demonstrated, (A) shows the first cross-section which is placed in the posterior part of the hippocampal head, measurements were continued posteriorly in 5 sections at 3-mm intervals (B–E), area 5 is not shown in this example. (F) shows the lateral aspect of the hippocampus in one of our datasets. The levels of area measurements are indicated.

the subjects with CDR 1 received a diagnosis of mixed Alzheimer's disease according to ICD-10 (atypical or mixed form of AD). One subject had a history of stroke with temporary right-sided paralysis, but no focal neurological signs could be found. In the other subject, a history of a stroke-like event was described (dizziness and muscle weakness without paralysis). No focal signs or symptoms were present at presentation in our study. In both cases, the course of the dementing illness was suggestive of Alzheimer's disease.

Six of the 39 subjects were clinically judged to have a mild to moderate degree of depression (1 with CDR 0, 4 with CDR 0.5, 1 with CDR 1). None had hallucinations or delusions. No other major psychiatric and/or neurological illnesses were diagnosed in the sample. A description of common medical illnesses and structural neuroimaging findings is given in Table 2.

2.2.2. Neuroanatomical imaging and analysis

All subjects underwent an MRI scan of the brain within four months after the clinical assessment. For each subject, a 3D T1-weighted high resolution MRI brain dataset was obtained on a Siemens Vision 1.5 T scanner using a 3D T1-weighted sequence (MPRAGE, TR 11.4 ms, TE 4.4 ms, 128 slices, matrix 256 × 256, voxel size 0.9 × 0.9 × 1.5 mm).

Collected datasets were analyzed within the BRIAN system [32] without knowing the cognitive state or other clinical data about the subjects.

Firstly, datasets were aligned with the stereotactical coordinate system [49] by identifying the crosspoint of the anterior and posterior commissure in the midsagittal plane and the angular misrotation along the body and the sagittal axes. Using these parameters, an affine transformation was defined to rotate, translate and interpolate the brain dataset to an isotropical voxel resolution of 1 mm.

Secondly, from the whole 3-D brain dataset the intracranial (i.c.) compartments, gray matter, white matter, internal and external cisterns (cerebrospinal fluid = CSF compartments) were automatically determined using a boundary-guided region-growing procedure [19]. The i.c. volume (ICV) was defined as the sum of the brain volume (BV) and the CSF volume (CSFV). The corrected brain volume (KBV) was defined as [(BV/ICV) ×100].

Thirdly, cross-sections of the hippocampus were segmented manually in the coronal plane on both sides. The first slice of hippocampal measurements was determined by moving posteriorily from the amygdala until the hippocampal head could be clearly distinguished from the amygdala. Hippocampal measures started behind the amygdala at the slice in which the area of the hippocampal head appeared maximal and were continued posteriorily in 5 sections at 3-mm intervals. The first cross-section measured was determined by visual estimation separately for each hemisphere. All hippocampal measures in this study were performed by one rater (SA) who had been extensively trained by an experienced operator (FK).

An example manual segmentation of the hippocampus is shown in Fig. 1.

To evaluate the reproducibility of the measures, an inter-rater experiment was carried out. The measurements were repeated in 5 cases by a second rater (AH). The mean differences (SD) between the two measurements were 3.5% (3.7) for the right hippocampus and 2.4% (3.5) for the left hippocampus. The correlation coefficient between the two readings was 0.996 ($P < 0.01$).

Areas 1 to 6 were multiplied by slice thickness (3 mm), summed on each side (HcV L*, resp. HcV R*), and normalized by the i.c. volume to yield an estimate of the volume of the hippocampus (HcV L, resp. HcV R).

The first two hippocampal slices measured correspond optimally to the posterior part of the hippocampal head (Fig. 1). They were summed on both sides and normalized by the i.c. volume to yield a volume estimate of the hippocampal head (HcHead L/R). Likewise, the remaining slices of the hippocampus (area 3–6) were summed and normalized to give a volume estimate of the hippocampal body (HcBo L/R). The total hippocampal volume estimate was calculated by summing left and right hippocampal volume estimates.

The study was approved by the local Ethics Commission. All subjects gave informed consent to participate in this study.

2.3. Statistical analysis

The data were analyzed by SPSS package for Windows (Vers. 7.5.2).

ANOVA with LSD post-hoc analysis was used to compare the means over the study groups. Volumes normalized for the i.c. volume were used in all statistical analyses. The level of statistical significance of differences is $P < 0.05$. A discriminant analysis in which MRI measures were entered as independent variables was run in order to determine the structural measure most responsible for the discrimination of the three CDR groups. In the first discriminant function, all structural measures in which either CDR 0 and CDR 0.5 groups and/or CDR 0.5 and CDR 1 groups differed significantly after LSD post-hoc analysis were entered. In a second, hypothesis-driven approach, only left and right hippocampal measures were entered. Differences between left and right hippocampal volume measures were examined using the *t* test for paired samples (two-tailed).

3. Results

Table 1 summarizes the demographic characteristics of the population. No group differences were present with regard to age and years of education. Statistically significant between-group differences were found in both left and right hippocampal volume estimates, the total brain volume and the total CSF volume. The volume estimates of both hippocampal bodies differed significantly over all three groups. The volumes of the right hippocampal head differed only between CDR 0.5 and 1, the volumes of the left hippocampal head differed between the CDR 0 and CDR 0.5 group. With regard to CSF and total brain volumes, only CDR 0.5 and CDR 1 differed significantly from each other. For the ventricular volume, no group differences could be observed (*Tables 3 and 4*).

In the majority of subjects, the right hippocampus was greater than the left (11 of 17 in CDR 0; 9 of 12 in CDR 0.5; and 4 of 10 in CDR 1). The mean right hippocampal volume estimates tended to be greater than the left in all groups. These left-right differences were significant in the CDR 0 and CDR 0.5 groups (paired *t* test, $P < 0.0005$), but not in the CDR 1 group ($P = 0.9$) (*Table 5*, Fig. 2). When the direction of the lateralization was accounted for, the largest hippocampal left-right asymmetries were found in the CDR 0.5 group (in favor of the right hippocampus), however these differences did not

Table 1
Common medical diagnoses and neuroimaging findings

		CDR 0 N = 17	CDR 0.5 N = 12	CDR 1 N = 10
Known History of/Treatment for				
Arterial hypertension	N	16	9	8
	%	94	75	80
Diabetes mellitus	N	4	3	3
	%	24	25	30
Coronary heart disease	N	1	4	3
	%	6	33	30
Cerebrovascular disease	N	2	3	2
	%	12	25	20
MR evidence of				
Deep white matter hyperintensities	N	12	8	9
	%	71	67	90
Periventricular hyperintensities	N	17	12	10
	%	100	100	100
Dilated perivascular spaces	N	16	8	9
	%	94	67	90
Lacunar infarcts	N	6	5	3
	%	35	42	30

Table 2
Characteristics of the population

		ANOVA	CDR 0	CDR 0.5	CDR 1
	N		17	12	10
	M:F		4:13	2:10	4:6
Age	Mean		78.5	78.5	78.2
	SD		3.1	2.2	3.0
	Range		75–85	75–82	75–83
Years of education	Mean		11.4	10.5	10.7
	SD		2.8	1.5	1.8
	Range		8–17	7–12	8–15
MMSE	Mean	*†¶	28.3	25.7	22.4
	SD		(1.3)	(1.1)	(2.0)
	Range		30–26	27–24	26–19
SISCO	Mean	*†¶	50.1	43.7	37.5
	SD		(2.8)	(3.6)	(4.6)
	Range		55–45	49–39	44–30

ANOVA/LSD post-hoc significance: * (CDR 0 vs. CDR 0.5); † (CDR 0.5 vs CDR 1); ¶ (CDR 0 vs. CDR 1)

SISCO = SIDAM-Score = Neuropsychological test battery of the Structured Interview for the Diagnosis of AD, Multi-infarct-Dementia and dementia of other aetiologies (Zaudig, 1991)

N number of subjects

M number of male subjects

F number of female subjects

Table 3
Quantitative MR measures

	ICV	BV		CSFV		VV		Total HcV (R+L)	
	Total [cm3] (SD)	Total [cm3] (SD)	Normalized [%] (SD)	Total [cm3] (SD)	Normalized [%] (SD)	Total [cm3] (SD)	Normalized [%] (SD)	Total [cm3] (SD)	Normalized [%] (SD)
CDR 0	1474.8 (190.1)	1065.1 (129.8)	72.2 (3.2)	409.7 80.7	27.8 (3.2)	40.2 (19.2)	2.7 (1.4)	3.7 (0.5)	0.25 (0.03)
CDR 0.5	1436.9 (155.8)	1054.1 (109.9)	73.4 (3.7)	382.8 75.38	26.6 (3.7)	36.7 (12.2)	2.6 (0.8)	3.2 (0.4)	0.22 (0.02)
CDR 1	1414.3 (164.9)	968.5 (97.4)	68.5 (5.5)	445.8 114.6	31.5 (5.5)	52.1 (22.5)	3.7 (1.4)	2.6 (0.4)	0.18 (0.02)
ANOVA/LSD	Ns	¶	†¶	Ns	†¶	Ns	Ns	*†¶	*†¶

ANOVA/LSD post-hoc significance: * (CDR 0 vs. CDR 0.5); † (CDR 0.5 vs. CDR 1); ¶ (CDR 0 vs. CDR 1), ns = non significant BV total brain volume, CSFV cerebrospinal fluid volume, VV ventricular volume, HcV hippocampal volume estimate, Total HcV total hippocampal volume estimate (left + right), Normalized volumes = total volume/ICV*100.

reach the level of statistical significance (ANOVA, $F(2,36) = 0.4$, $P = 0.6$) (*Table 5*). In contrast, the total hippocampal asymmetry (favoring neither hemisphere) was largest in the CDR 1 group (16% as compared to 6.1% and 6.6% in CDR 0 and CDR 0.5 respectively). The magnitude of non-directional asymmetry separated the CDR 1 group significantly from CDR 0.5 and CDR 0 (ANOVA, $F(2,36) = 6.2$, $P = 0.005$).

All hippocampal parameters reduced with advancing CDR stages. The left hippocampus of subjects with a CDR 0.5 was on average 14.3% smaller than in subjects with CDR 0, in subjects with mild dementia it was 28.1% smaller relative to CDR 0. In the CDR 1 group, the volume reduction was greatest in measures of the right hippocampal body (HcBo R) when compared with CDR 0. In the CDR 0.5 group, the left hippocampal body showed the greatest volume reduction (*Table 6*).

All structural parameters were entered into a partial correlation matrix, which was controlled for age and gender. The volume estimate of the left hippocampal body correlated most highly with the CDR rating (correlation coefficient 0.71, $P < 0.0005$).

In the first discriminant function analysis, all MRI measures that differed significantly between the groups were entered, i.e. CSFV, BV, and the total hippocampal volume. This resulted in two significant canonical discriminant functions (Wilks-Lamba 0.37, $P < 0.0005$) which led to a correct classification of 74% of all subjects. The total hippocampal volume correlated most highly with the group classification. When, in the same procedure, the total hippocampal volume was replaced by left and right hippocampal volumes, the left hippocampus was the variable which most highly correlated with the discriminant function.

To define the hippocampal subsection which is most responsible for group discrimination, the volume estimates of hippocampal head and body of both sides were entered into another discriminant function analysis. With this procedure, two significant canonical discriminant functions were produced (Wilks-lamda 0.4, $P < 0.0005$) which resulted in a correct classification of 76.9% of all subjects. The volume of the left hippocampal body correlated most highly with the discriminant functions, followed by the right hippocampal body and the left hippocampal head, indicating that left-sided measures seem to be superior to right-sided measures and that measures of the posterior part of the hippocampus (hippocampal body) seem to be superior to

Table 4
Normalized hippocampal measures

	ANOVA	CDR 0#	CDR 0.5#	CDR 1#
Hippocampal volume estimate (head + body)				
Left	*†¶	0.124 (0.016)	0.106 (0.013)	0.089 (0.014)
Right	*†¶	0.128 (0.020)	0.114 (0.012)	0.095 (0.019)
Hippocampal head				
Left	*¶	0.059 (0.010)	0.051 (0.007)	0.044 (0.008)
Right	†¶	0.062 (0.013)	0.056 (0.008)	0.046 (0.008)
Hippocampal body				
Left	*†¶	0.065 (0.008)	0.056 (0.007)	0.045 (0.008)
Right	*†¶	0.067 (0.009)	0.058 (0.006)	0.049 (0.013)

* ANOVA/LSD post-hoc significance: * (CDR vs. CDR 0.5); † (CDR 0 vs. CDR 1), (CDR 0 vs. CDR 1), $P < 0.05$.
All measures are relative volumes (total volume/ICV*100).

Table 5
Amount that right hippocampal measures are greater than left

	ΔL/R% (sd)[†]		
	CDR 0	CDR 0.5	CDR 1
HcV	2.5% (7.3)**	6.5% (4.8)**	3.2% (21.0)
HcHead	3.5% (11.9)**	9.9% (6.6)**	3.2% (23.3)
HcBo	1.7% (9.4)**	3.3% (9.8)*	−0.4% (22.3)

[†] ΔL/R% = 100* (Right normalized volume—Left normalized volume)/(right normalized volume). Positive values indicate a smaller left hippocampus
$p < 0.05$; ** $p < 0.0005$ (paired t-test, left vs. right)
HcV hippocampal volume, HcHead hippocampal head, HcBo hippocampal body.

Table 6
Mean hippocampal volume reduction relative to subjects with CDR 0

	% Difference as compared to CDR 0	
	CDR 0.5 Left: Right	CDR 1 Left: Right
HcV	−14.3:−11.3	−28.1:−25.9
HcHead	−13.9:−8.9	−25.4:−24.9
HcBo	−17.7:−16.7	−23.6:−30.9

measures of the hippocampal head in discriminating the three groups.

In this discriminant function 82.4%, 75% and 70% of the subjects with CDR 0, CDR 0.5 and CDR 1 respectively were classified correctly. Of the subjects with CDR 0, three were misclassified as CDR 0.5. Of the subjects with CDR 0.5, two were misclassified as demented and one was misclassified as CDR 0. Of the mildly demented subjects, two were misclassified as CDR 0.5, one as CDR 0. Both subjects with CDR 0.5 misclassified as demented had severe isolated memory impairment without evidence of decline in other cognitive areas and intact activities of daily living at their presentation in our study. When one of them re-visited our memory clinic six months later, she appeared disoriented and had noticeable difficulties in managing her medical appointments, hence she certainly met the ICD-10 criteria for mild dementia.

4. Discussion

In this study involving a well characterized sample of elderly community-dwelling subjects with a continuous range of cognitive functions, we demonstrated that MRI volumetric measures of the hippocampus are sensitive in discriminating subjects with questionable dementia from subjects with normal cognition and mild dementia respectively.

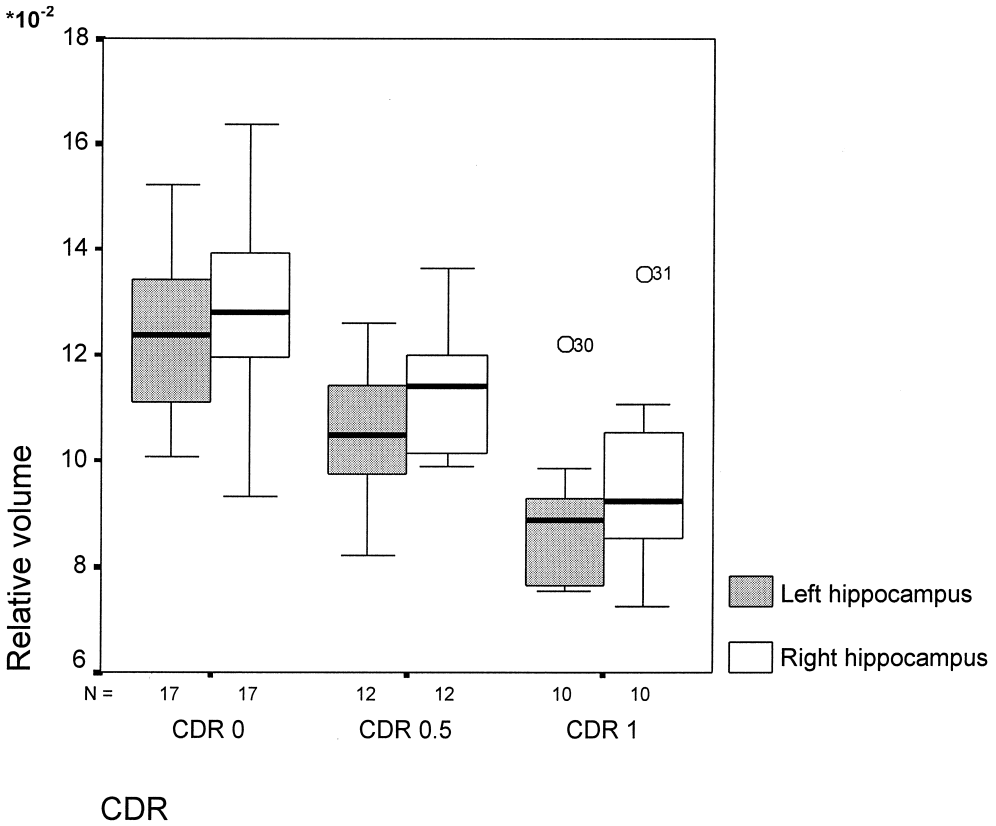

Fig. 2. Left and right hippocampal volume estimates in CDR 0, CDR 0.5 and CDR 1. Boxplots: Upper and lower end of boxes indicate upper and lower quartile, the line within the box represents the median, ○ represent outliers (points more than 1.5 times the interquartile range).

Of the hippocampal parameters, the left hippocampus seemed to be more responsible for group discrimination than the right. Furthermore, measures of the more regular-shaped posterior part of the hippocampus discriminated the groups better than measures of the anterior part of the hippocampus (hippocampal head).

The results will be discussed with special regard to 1) the discriminative power of hippocampal measures, 2) the possible significance of hippocampal asymmetry in mild cognitive impairment and Alzheimer‘s disease.

4.1. Discriminative power of hippocampal measures

Compared to subjects with normal cognition, we found significant in-vivo hippocampal volume reductions of 14% vs. 11% (left vs. right) for the questionably demented and of 28% vs. 26% (left vs. right) for the mildly demented group. In a discriminant function analysis, 82%, 75% and 70% of our normal, questionably and mildly demented subjects were correctly classified based on four hippocampal measures.

Our results add evidence to the consistent disclosure of hippocampal atrophy in Alzheimer’s disease, which seems to be present even in the early stages of the illness [13,26, 30,34,36,51].

Few studies exist with a comparable design and special focus on MCI [10,11,51]. Convit et al. reported that elderly subjects with MCI defined by a GDS score of 3 could be distinguished from normal controls and demented subjects cross-sectionally [11]. The results of this study compare with our findings with regard to the amount of hippocampal volume reductions in MCI and mild dementia. Comparable to our study, a 74% overall correct classification of their normal and mildly impaired subjects was reported based on a hierarchical logistic regression analysis. Contrary to our results, in another study involving a population-based sample, hippocampal measures did not separate subjects with minimal dementia as defined by the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) from normal controls and subjects with mild dementia respectively [51]. In the latter study subjects with minimal dementia were in the MMSE range of our mildly demented subjects. Two studies involving subjects with age-associated memory impairment; a milder form of memory impairment in the elderly than MCI [4]; failed to demonstrate hippocampal volume differences relative to normal controls [35,48].

Following a study involving patients with mild dementia, Laakso et al. [34] reported 92% accuracy of hippocampal volume measures in the discrimination of AD patients from nondemented elderly subjects. The lower accuracy in our study is most likely due to the relatively close and continuous range of cognitive functions in our subjects which makes a cross-sectional discrimination more difficult. Furthermore, the differential involvement of hippocampal, temporal lobe and other brain structures in the process of cognitive decline and dementia development which have been suggested by neuropathological [8,16] and previous MRI studies [11,29,51] might hamper the discriminative power in analyses that include both MCI and demented subjects. We do not know to which extent cerebrovascular and non-specific morbidity factors may have influenced the cognitive state and/or volumetric measures in our subjects. Even though such factors did not feature as exclusion criteria in our study, hippocampal measures were able to discriminate the CDR groups. This demonstrates the robustness of the hippocampal volume as a correlate of global cognitive performance and memory.

Regarding the subjects with MCI, the crucial factor from a clinical point of view is not necessarily that of an accurate cross-sectional classification, but more so the question whether those subjects at highest risk for further cognitive decline can be identified by hippocampal measures and furthermore how accurate such a prediction is in comparison to neuropsychological, electrophysiological and functional neuroimaging measures. In our study, the prognostic value of hippocampal volume measures is indicated by the fact that two subjects with MCI who had been classified as demented by our discriminant function analysis suffered from severe isolated memory impairment, a condition which is known to show a very high rate of progression to dementia [7,35].

4.2. Possible significance of hippocampal asymmetry in MCI and AD

A number of findings in our study point toward an asymmetrical hemispheric involvement of hippocampal structures in questionable dementia and AD. Our discriminant analysis suggested that the left hippocampus might be more responsible for group discrimination than the right. This finding implies that the left hippocampus might be preferentially involved in the development of MCI and AD. On the other hand, the better correlation of left hemispheric measures with clinical classification could be due to the fact that the specific functions processed by the left hippocampus are clinically and neuropsychologically more easily detectable (verbal memory). We found significantly smaller left hippocampi as compared to right only in our normal and questionably demented group. We think that this finding most likely reflects the physiological hemispheric asymmetry of the human hippocampus which has been consistently demonstrated in a large number of studies involving healthy subjects of all age groups [5,17,20,21,27,43,48,50,54].

Our study lacks the statistical power to prove whether or not the increased left-right asymmetry of the hippocampus in subjects with questionable dementia could be due to a preferential atrophy (shrinkage) of the left hippocampus in MCI and/or early AD. Previous studies on a possible early asymmetrical involvement in AD with a hemispheric direction are inconsistent [15,29–31,33,36,47,51]. In a prospective study of seven at-risk members of a familial AD ped-

igree, Fox et al. found significantly smaller initial left hippocampi in those subjects who became demented over a 3 year observation period. The authors concluded that hippocampal asymmetry may be an early sign of the presence of a degenerative process [15]. Laakso et al. found smaller left hippocampal volumes in AD compared to Parkinson's disease and vascular dementia [33]. In agreement with our observation of a higher discriminative power of the left hippocampus, Krasuski et al. reported that left-hemispheric volumetric measures of medial temporal lobe structures provided a higher accuracy of group discrimination in a sample of mildly demented AD patients versus controls [31]. A number of studies failed to demonstrate left-right hippocampal differences in subjects with preclinical [29,51] and/or mild AD [30,36].

With regard to mild dementia with AD, our study confirms previous results from neuropathological [38,39] and functional neuroimaging studies [18] suggesting an increased magnitude of total hemispheric asymmetry, i.e. left-right differences favoring neither hemisphere in several brain regions.

Contrary to Jack et al. [26] who found that the head of the hippocampus is more susceptible to age-related atrophy as well as degenerative change associated with AD, our data suggest that the degenerative change in MCI and AD is most extensive in the posterior part of the hippocampus. The differing methods used for hippocampal measurements may account for such inconsistent findings. However, our findings are supported by a previous neuropathological study showing that tangles and granulovacuolar degeneration demonstrate a stronger propensity for occurring in the posterior part of the hippocampus in AD [2].

4.3. Limitations and conclusions

The main limitation of our study lies in the small number of subjects. Therefore our results should be interpreted with caution. Since our study examines a cross-sectional sample, we cannot tell whether the subjects clinically identified as "questionable dementia" will progress to dementia or not, neither do we know if the underlying disease process of their cognitive impairment is that of Alzheimer's disease. Previous studies demonstrated a high risk of progression to dementia of the Alzheimer type in subjects with CDR 0.5 [46], but there is also evidence for a high heterogeneity in this difficult diagnostic subgroup [14,52]. It has been shown that hippocampal atrophy is non-specific and that other processes such as hippocampal sclerosis may also lead to hippocampal atrophy and memory impairment [12].

In conclusion, this study demonstrates the sensitivity of hippocampal measures in discriminating normal cognitive function from questionable and mild dementia in subjects aged 75 to 85. The inclusion of anterior-posterior and interhemispheric gradients may improve the accuracy of diagnostic and prognostic models for dementia and AD.

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