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In vivo Quantification of Brain Volumes in Subcortical Vascular Dementia and Alzheimer's Disease

An MRI-Based Study

J. Pantel[a]
J. Schröder[a]
M. Essig[b]
M. Jauss[a]
G. Schneider[a]
K. Eysenbach[a]
R. von Kummer[c]
K. Baudendistel[b]
L.R. Schad[b]
M.V. Knopp[b]

[a] Section of Geriatric Psychiatry, Department of Psychiatry, University of Heidelberg,
[b] German Cancer Research Institute (DKFZ), Heidelberg,
[c] Department of Neuroradiology, University of Dresden, Germany

Abstract

Quantitative magnetic resonance imaging (MRI) was used to assess global and regional cerebral volumes in patients with a clinical diagnosis of subcortical vascular dementia (VD) and Alzheimer's disease (AD). Whole brain volume, cerebrospinal fluid volume, volumes of the temporal, frontal and parietal lobes, the cerebellum and the amygdala-hippocampus complex were determined using a personal computer-based software. Seventeen patients with VD, 22 patients with AD and 13 healthy controls were included. Analysis of covariance using age as covariate demonstrated significant mean differences between controls and dementia groups with respect to all morphological parameters. However, apart from the volume of the cerebellum no significant volumetric differences were found between VD and AD. These results indicate that MRI-based volumetry allows differentiation between AD or VD from normal controls and that measurement of cerebellar volume may be of use to separate vascular and degenerative dementia. However, since the distribution of cerebral atrophy in both dementia groups is very similar, it is suggested that the atrophic changes are not specific to the underlying cause but rather reflect the selective vulnerability of neuronal structures.

Key Words

Subcortical vascular dementia
Alzheimer's disease
MRI
Volumetry

Introduction

Neurodegenerative disorders and cerebrovascular disease are the most common causes of dementia in the elderly population. Epidemiological studies suggest that Alzheimer's disease (AD) and vascular dementia (VD) account for up to 90% of all dementia syndromes [1, 2]. Patients with subcortical lesions of vascular origin resulting in progressive dementia and the clinical picture of 'Binswanger's disease' represent an important subgroup of VD [3]. Although neuroimaging methods such as computerized tomography (CT) and magnetic resonance imaging (MRI) facilitated the in vivo diagnosis of both dementia types, clinical differentiation of AD from subcortical VD may still be difficult. Previous neuroimaging studies regarding the differentiation of VD, AD and normal aging focused mainly on frequency and type of cerebral infarcts and white matter changes [4]. Only few studies also investigated the diagnostic value of atrophic changes in the differentiation of the two disorders [5–8]. Those who did, however, were limited since they mainly used linear and planimetric measurements of ventricular size or did not restrict their investigations to patients with subcortical VD.

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Dr. med. Johannes Pantel
Department of Psychiatry, University of Heidelberg
Voss Strasse 4, D–69115 Heidelberg (Germany)
Tel. +49 6221 564452, Fax +49 6221 565477
E-Mail johannes_pantel@ukl.uni-heidelberg.de

Previous studies showed that MRI-based measurement of hippocampal size allows a separation of clinically diagnosed Alzheimer patients from age-matched nondemented controls with a sensitivity and specificity of 85–90% [9–15] and may also assist in the differential diagnosis of AD from age-associated memory impairment [16] and depressive pseudodementia [17]. However, the use of MRI-based volumetry in the differentiation of VD and AD remains to be established. Neuropathological studies show that atrophic changes are present in both disorders. In AD early and extensive pathological changes of the medial temporal lobe structures are found which only later spread to involve the temporal and parietal regions and finally affect nearly all isocortical association areas [18]. In subcortical VD white matter atrophy with progressive demyelination, neuronal loss and lacunar infarctions is the main pathomorphological feature leading to enlarged lateral ventricles, whereas the cortex characteristically appears intact [3, 19]. Based on these findings, it may be speculated that in vivo volumetry of the brain and its substructures could establish different patterns of atrophic changes in the two diseases. In particular, it has been suggested that hippocampal volume reduction may be a characteristic feature of AD and may therefore be useful in the differential diagnosis [20]. The aims of our study were accordingly: (1) to establish volumetric differences in the brain and its substructures between patients with subcortical VD and healthy age-matched controls, and (2) to compare volumes of brain structures from patients affected with VD with those from AD patients and to determine differences and/or similarities between these diagnostic groups.

Methods

Patients and Control Subjects

The study was approved by a local ethical committee. Patients were consecutively admitted inpatients under the care of the Section of Geriatric Psychiatry of the University of Heidelberg and were prospectively included. Patients with a history of head trauma, birth injury, electroconvulsive therapy and a significant substance abuse were excluded. All patients underwent thorough standardized general and neurological examinations as well as a CT scan and laboratory studies in order to exclude metabolic, toxic and inflammatory causes of their dementia syndrome. CT scans were carefully screened for the presence and types of cerebrovascular lesions by an experienced neuroradiologist (R.v.K.) who was unaware of the patients' history and the results of the clinical examinations. Clinical grouping was based on the CT scans since MRI scans seem to be more sensitive but less specific to detect significant cerebral vascular changes. In contrast to CT studies, in most previous MRI studies white matter changes have not been correlated with overall cognitive decline. This indicates that MRI may have a ceiling effect, particularly when T2 weighted scans are used [4].

An extensive neuropsychological investigation was performed using a test battery which has been described in detail elsewhere [15]. Severity of cognitive impairment was established on the Mini Mental State Examination (MMSE) [21] and the Global Deterioration Scale (GDS) [22].

Diagnosis of VD was strictly based on the criteria of the NINDS-AIREN work group [23] and a modified Hachinski ischemic score [24]. Diagnosis of AD followed the criteria given by the NINCDS-ADRDA work group [25]. The diagnostic procedure used all relevant information concerning history, clinical, neuropsychological, and neuroradiological findings. Ambiguous cases in which no consensus about the diagnosis could be achieved were excluded. The NINDS-AIREN criteria for VD include the following: (1) presence of dementia, preferably established by clinical examination and documented by neuropsychological testing; (2) cerebrovascular disease, defined by the presence of focal signs on neurologic examination and/or evidence of *relevant* cerebrovascular disease on brain imaging; in case of Binswanger's disease this includes multiple basal ganglia and white matter lacunes or *extensive* periventricular white matter lesions, or combinations thereof; (3) a relationship beween the above two disorders, manifested by: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

Clinical features which support the diagnosis of VD include: (a) Early presence of gait disturbance; (b) history of unsteadiness and frequent falls; (c) early urinary symptoms not explained by a urologic disease; (d) pseudobulbar palsy, and (e) personality and mood changes.

The control subjects were volunteers from the local community and were all in a good mental and physical state of health with no history of hypertension, diabetes, neurological or psychiatric diseases. In order to exclude any latent brain disorders control subjects were investigated using the same neuropsychological and clinical measures. In total, 19 patients with VD, 29 patients with AD and 13 healthy control subjects were investigated. Patients who met the NINDS-AIREN criteria for VD but showed single or multiple cortical or extensive territorial infarcts were excluded, resulting in a group of 17 patients who exclusively displayed indications of subcortical small vessel disease such as extensive white matter lesions, basal ganglia and white matter lacunes or a combination of both. The AD group consisted of 22 patients who were classified as *probable* AD and 7 patients who were classified as *possible* AD according to the NINCDS-ADRDA criteria. In order to improve homogeneity of the AD group only the 22 patients with a diagnosis of *probable* AD were used for further analysis. In line with the NINDS-ADRDA criteria none of these 22 patients had evidence of cerebrovascular disease on CT. This was based on the judgment of the neuroradiologist (R.v.K.).

MR Image Acquisition and Image Processing

For each patient and control subject two sagittal image data cubes of the brain were measured: a set of T1-weighted images, providing differentiation between gray and white matter and a set of T2-weighted images providing differentiation between tissue and cerebrospinal fluid. Sagittal images were preferred, because due to anatomical reasons they provide a better volume resolution at a given slab thickness than transversal images. All measurements were performed on a 1.5-tesla MAGNETOM 63/84 SP Siemens scanner using

a 3D MPRAGE sequence (TR: 10 ms, TE: 4 ms) for the T1 and a 3D PSIF sequence (TR: 17 ms, TE: 7 ms) for the T2-weighted image data cubes. MR images were taken at 15° cranial to the orbitomeatal line. The total measurement time was about 15 min per patient. Both 3D image data cubes with a slab thickness of 160 mm consisted of 128 sagittal image slices, resulting in a slice thickness of 1.25 mm. The slices had an in-plane field of view of 260 mm, the volume pixels were of the size $1.02 \times 1.02 \times 1.25$ mm^3.

Image data processing was performed on a conventional 80486/66 MHz personal computer using the software NMRWin. This software provides segmentation and volumetry of MR brain images based on standard segmentation techniques which allows automatic quantification of cerebrospinal fluid (CSF) and brain matter compartment volumes requiring a minimum of manual interaction. Detailed structure and function of this software is described elsewhere [26].

Whole brain volume, CSF volume and total intracranial volume were assessed using the semiautomated segmentation function of NMRWin which segments the brain tissue and CSF slice by slice making use of both the T1-weighted and the T2-weighted data sets. The brain tissue compartment included gray and white matter structures as well as potential lacunes and white matter hyperintensities. The accuracy of the segmentation process could be controlled visually on the computer screen. The resulting areas were multiplied with the slice thickness, summed up and documented in a protocol file. The whole brain volume included the volume of the hemispheres, the cerebellum and the upper parts of the brain stem. The total intracranial volume was assessed by adding the whole brain volume and the CSF volume. The reliability of the method has been demonstrated by an independent study [27].

The volumes of the amygdala-hippocampus complex, the frontal lobes, the temporal lobes, the parietal lobes and the cerebellum were traced manually on 35–40 contiguous slices for each structure using the manual segmentation function of NMRWin. This requires the operator to place an exact region of interest (ROI) along the border lines of the structure to be analyzed, where each ROI has a color assigned to a specific structure. The measurements were obtained on the T1-weighted images providing a high gray matter/white matter contrast and were based on a detailed manual following anatomical landmarks. The use of a high number of thin slices (1.25 mm) should minimize partial voluming artifacts and overprojection errors. Measurements were performed 2 times by 2 independent raters who were unaware of the patients' diagnosis. In a previously published study a high test-retest reliability could be demonstrated for all volumetric measures [15]. Apart from the cerebellum all structures were measured on coronal slices which were reconstructed from the 3D dataset. The definitions of boundaries for the amygdala-hippocampus complex, the temporal and the frontal lobes were described in detail previously [15]. The boundaries of the parietal lobes were defined as follows:

The measurement of the parietal lobe started caudally in the coronal slice with the first appearance of the superior parietal gyrus. It was then continuously measured from caudal to rostral outlining the cortical surface of the parietal gyri including the superior parietal gyrus, inferior parietal gyrus, postcentral gyrus, precuneus and the paracentral gyrus. Subsequently, a straight line was drawn from the parietooccipital fissure to the intraparietal sulcus in order to separate the parietal lobe structures from the occipital and the temporal lobe. With the disappearance of the occipital lobe the subparietal sulcus served as the starting point of the straight demarcation line. Eventually, with the first appearance of the occipital horn of the lateral ventricles this line ended in the depth of the parallel sulcus. The measurement of the parietal lobe was terminated as the first slice which shows the cornu posterior, lateral and anterior of the lateral ventricle fused was reached.

The measurement of the cerebellum was carried out on about 50 sagittal slices and consisted of outlining the cerebellar surface with the cursor slice by slice. On the T1-weighted images the cerebellar boundaries could easily be separated from the adjacent brain structures and CSF. Pedunculi cerebellares were excluded.

Data Analyses

All computations were performed using the statistical analysis system [28]. To address potential interindividual differences in head size, all volumetric data were corrected for the subject's total intracranial volume. Total intracranial volume seems to be an appropriate indicator of premorbid brain size, since the brain drives the growth of the skull during childhood and adolescence. Therefore, we expected intracranial volume to be approximately the same in patients and healthy controls. Mathalon et al. [29] demonstrated that this method can be beneficial in brain imaging measurements because it improves the correlations with validity criteria, even if this may result in somewhat less reliable measures.

For statistical analysis we performed in a first step a comparison of the baseline features (i.e. age, sex, MMSE) between the AD group, VD group and healthy controls. Since there was a significant age difference between the VD group and the normal controls an adjustment for age was necessary.

To adjust for effects of age an analysis of covariance with age as a covariate was performed. An analysis of variance for the age-corrected values with a multiple comparison adjustment (Bonferroni) for the p values and confidence limits for the differences of least squares means was applied to test for differences between the patient groups and the normal control group respectively.

Correlations between the clinical variables and volumetric data were calculated for each group separately by Spearman rank correlation.

Results

The clinical characteristics of the investigated groups is shown in table 1. The VD patients were significantly older than the other groups, gender distribution of the diagnostic groups was similar. 3/17 (17.6%) VD patients but 3/29 (10.3%) AD patients had a history of regular but moderate alcohol consumption. As expected, impairment of cognitive performance of both dementia groups was highly significant when compared to the controls. However, severity of dementia did not differ significantly between VD and AD.

Table 2 shows a comparison between controls, VD, and AD with respect to the corrected morphometric values and to the age adjusted values. As expected, the total intracranial volume did not differ significantly between the groups.

Table 1. The clinical characteristics of the population under investigation

	Controls	VD	AD
n	13	17	22
Mean (± SD) age, years	68.23 ± 5.31[1]	76.47 ± 6.62[1]	71.04 ± 8.56
Sex, m/f	3/10	7/10	5/17
Mean (± SD) MMSE	29.33 ± 0.78[1,2]	18.65 ± 5.85[1]	16.92 ± 6.1[2]
Mean (± SD) duration of illness, months	NA	49.53 ± 66.33	43.32 ± 29.14
Mean (± SD) GDS	1.17 ± 0.39[1,2]	4.29 ± 0.85[1]	4.12 ± 0.88[2]
Stroke and TIA	0/13 (0)	11/17 (65)	3/22 (9)
Hypertension	3/13 (23)	11/17 (65)	4/22 (18)
Coronary heart disease	3/13 (23)	7/17 (41)	0/22 (0)
Diabetes	1/13 (8)	3/17 (18)	2/22 (9)
Focal signs	0/13 (0)	11/17 (65)	1/22 (4)
Mood disturbances	0/13 (0)	15/17 (88)	13/22 (59)
Gait disturbances/dysarthria	0/13 (0)	12/17 (71)	3/22 (14)
Stepwise progression	NA	8/17 (47)	4/22 (18)
Hachinski score [24] (0–10)	NA	4.47 ± 1.59[3]	0.41 ± 0.73

Values are absolute (sex) and means with standard deviation. Statistically significant differences ($p < 0.05$, Duncan's multiple-range test) are marked with: [1] VD compared to control; [2] AD compared to control; [3] AD compared to VD. NA: Not applicable. Percentages in parentheses.

Table 2. Comparison between controls, VD and AD

	Controls (n = 13)		VD (n = 17)		AD (n = 22)	
	unadjusted	adjusted	unadjusted	adjusted	unadjusted	adjusted
Total intracranial volume, cm^3	1,193.4 ± 129.2	1,182.0 ± 121.7	1,239.4 ± 105.5	1,256.0 ± 127.5	1,215.5 ± 123.3	1,209.6 ± 119.8
Whole brain, %	74.1 ± 3.7[1,2]	73.7 ± 4.1[1,2]	66.1 ± 4.0[1]	66.7 ± 4.3[1]	65.1 ± 4.2[2]	64.9 ± 4.0[2]
CSF, %	25.9 ± 3.7[1,2]	26.4 ± 4.3[1,2]	33.5 ± 4.3[1]	32.5 ± 4.6[1]	34.7 ± 4.5[2]	35.0 ± 4.2[2]
Amygdala-hippocampus						
right, %	0.4 ± 0.053[1,2]	0.4 ± 0.061[1,2]	0.29 ± 0.057[1]	0.3 ± 0.064[1]	0.28 ± 0.064[2]	0.27 ± 0.06[2]
left, %	0.39 ± 0.056[1,2]	0.38 ± 0.051[1,2]	0.28 ± 0.047[1]	0.29 ± 0.054[1]	0.27 ± 0.048[2]	0.27 ± 0.05[2]
Temporal right, %	4.00 ± 0.52[1,2]	4.0 ± 0.47[1,2]	3.05 ± 0.44[1]	3.06 ± 0.5[1]	3.22 ± 0.44[2]	3.22 ± 4.7[2]
Temporal left, %	3.99 ± 0.58[1,2]	3.95 ± 0.47[1,2]	3.11 ± 0.43[1]	3.17 ± 0.5[1]	3.25 ± 0.41[2]	3.23 ± 0.47[2]
Frontal right, %	4.41 ± 0.52[1,2]	4.41 ± 0.45[1,2]	3.46 ± 0.41[1]	3.46 ± 0.47[1]	3.56 ± 0.47[2]	3.59 ± 0.44[2]
Frontal left, %	4.51 ± 0.62[1,2]	4.48 ± 0.51[1,2]	3.49 ± 0.49[1]	3.52 ± 0.53[1]	3.53 ± 0.43[2]	3.55 ± 0.5[2]
Parietal right, %	5.13 ± 0.55[1,2]	5.17 ± 0.52[1,2]	3.92 ± 0.49[1]	3.87 ± 0.53[1]	3.82 ± 0.46[2]	3.83 ± 0.49[2]
Parietal left, %	5.23 ± 0.52[1,2]	5.27 ± 4.9[1,2]	4.02 ± 0.48[1]	3.98 ± 0.5[1]	3.96 ± 0.42[2]	3.97 ± 4.7[2]
Cerebellum, %	10.38 ± 0.75[1,2]	10.4 ± 0.79[1,2]	8.00 ± 0.84[1,3]	8.00 ± 0.81[1]	9.26 ± 0.66[2,3]	9.26 ± 0.76[2,3]

Values are given as percentage of the total intracranial volume and cm^3 (total intracranial volume) respectively. Values are means and standard deviation. The unadjusted values and the age-adjusted values are listed. Statistical significant differences ($p < 0.05$, analysis of variance with age as the covariate and with Bonferroni correction) are marked with: [1] VD compared to control; [2] AD compared to control; [3] AD compared to VD.

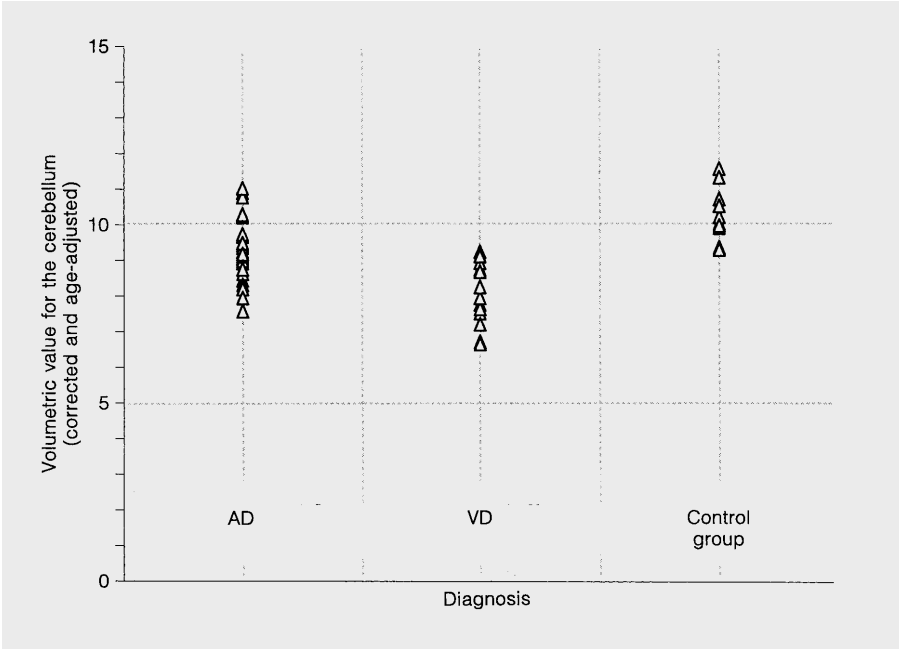

Fig. 1. Corrected and age-adjusted values for the cerebellar volume in patients with AD, subcortical VD and controls. All three groups show significantly different distributions ($p < 0.05$). Means and standard deviations are given in table 2.

After correction for total intracranial volume, both dementia groups demonstrated significantly lower volumes than controls with respect to all volumetric parameters. The greatest mean difference was observed for the volume of the amygdala-hippocampus complex bilaterally. Only the volume of the cerebellum differentiated between AD and VD and was significantly smaller in the latter group (see also fig. 1). However, no significant differences were found between VD and AD with respect to the whole brain volume, the amygdala-hippocampus complex and the frontal, temporal, and parietal lobes. Within both dementia groups no significant correlations were found between the volumetric data age and duration of the disease (Spearman rank correlation).

Discussion

The results of our study indicate that: (1) subcortical VD is associated with a significant global and regional decrease in cerebral and cerebellar volume which can be quantified by MRI-based volumetry; (2) mildly to moderately impaired patients with subcortical VD and patients with AD show a similar distribution of cerebral volume reduction including a marked volume loss of the medial temporal lobe structures, and (3) volume of the cerebellum is significantly smaller in patients with VD when compared to patients with AD.

Previously, MRI-based volumetry was used by several investigators to quantify cerebral atrophy in patients with AD [9–15]. Most of these studies revealed a significant volume reduction of the entire brain and its substructures when groups of AD patients were compared with age-matched healthy controls. The results of our study show that significant global and regional volume loss also occurs in patients with a clinical diagnosis of subcortical VD. This confirms and extends several findings derived from CT studies which suggested that cerebral atrophy is a common finding in VD. Pullicino et al. [30] reported a frequency of 83% of atrophy in a group of patients with VD. In the series of Erkinjuntti et al. [5] 88% of patients with a moderate VD but all patients with a severe VD showed indications of cortical atrophy. Based on MRI findings, Schmidt [8] reported a frequency of 58.1% of moderate to severe cortical atrophy and 80.7% of moderate to severe ventricular enlargement in a group of 31 patients with VD. However, all these studies used either visual rating or linear measurement of atrophy. Our study for the first time uses MRI-based volumetry in order to quantify these changes.

Vascular dementia is a heterogeneous syndrome which can be associated with different cerebrovascular lesions including multiple large vessel infarcts, strategic single infarcts, small vessel disease with single or multiple lacunar lesions, and diffuse white matter lesions. It is therefore conceivable that a cerebral volume deficit in VD may

be caused mainly or solely by the cerebral substance loss induced by single or multiple large territorial infarcts. In order to address this problem we restricted our investigations to patients suffering from the subcortical or Binswanger's type of VD. Accordingly, the volume loss in our VD patients may reflect the diffuse process of white matter atrophy which has been described pathologically in this patient group. Previous MRI studies showed that nondemented and demented patients with cerebrovascular disease differed with respect to the prevalence of diffuse cerebral volume loss insofar as the presence of cerebral atrophy in a patient with cerebrovascular disease increased the likelihood that this patient belonged to the demented group [31, 32]. Our findings support the view of Liu et al. [32] who concluded from their data that the global brain tissue loss in VD is one of the most important factors leading to the severe cognitive deficits.

According to our data no global or regional measure of cerebral volume differentiated significantly between AD and subcortical VD. These results are in agreement with the findings of previous studies [5, 6, 8] who failed to demonstrate significant differences between VD and AD when using measures of cortical and central cerebral atrophy. Our findings are of particular interest with regard to the specificity of the medial temporal volume reduction in the differential diagnosis of AD which yet has not been fully established. For at least two reasons, it has been argued that medial temporal lobe atrophy may be an early and specific marker in the diagnosis of AD. Firstly, the medial temporal lobe appears to be the area of the greatest and probably the earliest pathological changes in AD [18, 33]. Secondly, a hippocampal-type amnesia is an early and prominent clinical feature of AD which has led some authors to refer to AD as being mainly a 'hippocampal dementia' [34, 35]. Indeed, several MRI-based volumetric studies revealed early and severe medial temporal lobe atrophy in AD patients and demonstrated a sensitivity and specificity of 85–90% in separating clinically diagnosed patients from age-matched nondemented controls [36]. In view of our data, AD patients tended to have a greater mean volume reduction of the amygdala-hippocampus complex when compared to VD (~ 33% in AD vs. ~ 27% in VD). However, these differences were not significant and considerable volume reduction of the amygdala-hippocampus complex also occurred in VD. These findings are supported by the recent results of Laakso et al. [37] who compared hippocampal volumes in AD, Parkinson's disease with and without dementia, VD, and healthy controls. In this MRI study, a significant volume reduction of the hippocampus was not only observed in AD patients but also in the other patient groups. This is further confirmed by the results of Frisoni et al. [38], who performed linear measurements of medial temporal lobe structures in patients with frontotemporal dementia in comparison to AD patients and found that the measure of hippocampal atrophy was the least specific in the differentiation of the two dementia syndromes, showing as much atrophy in frontotemporal dementia as in AD. Ohnishi et al. [39] conducted a SPECT study and found that hippocampal hypoperfusion was observed in demented patients regardless of etiology including AD, VD and dementia with motor neuron disease. On the basis of these and our findings, hippocampal volume reduction is probably not a specific phenomenon of AD, but also occurs in other types of dementia such as VD. Our in vivo results correspond to recent postmortem findings in patients with VD showing that hippocampal volume reduction is also present in patients with dementia of pure vascular origin [40, 41]. Olsson et al. [41] stated that vascular factors seem to be of pathogenetic significance for the appearance of hippocampal sclerosis at least in some cases of senile dementia. In the adult human brain, acute hypoxic episodes result in a certain pattern of nerve cell damage from which a hierarchy of neuronal vulnerability can be formed [42]. Among the most sensitive regions are the phylogenetically 'older' brain structures like the hippocampal formation including the neurons of the Sommer sector (CA1) and the end folium (CA 3–4) which are particularly sensitive. Subsequent to nerve cell damage in VD there is in these regions of the hippocampus activation of glial cells and finally gliosis. Thus, hippocampal volume reduction in VD and AD are probably caused by a different pathological mechanism. This points toward the selective vulnerability of several neuroanatomical structures which may be independent of the nature of a particular noxious agent. Animal experiments support the hypothesis that chronic cerebrovascular insufficiency and acute hypoxia can result in a pattern of brain damage that shows many parallels to Alzheimer type changes [43, 44]. The hippocampal volume reduction observed in our VD patients could be explained on the basis of these experimental findings.

According to our results, patients with VD are characterized by a significantly greater cerebellar volume reduction when compared to patients with AD. Our findings may be explained by the observation that lacunar cerebellar infarcts occur regularly in Binswanger's disease [3] and multi-infarct dementia [45]. In a CT study of Barclay and Brady [45], cerebellar atrophy was absent in AD but a common finding in patients with a mixed AD and VD

pathology. Chan et al. [46] reported recently that MRI-derived multifocal hypointense lesions in the cerebellum were associated with the diagnosis of chronic hypertension which is believed to be the most important risk factor for the development of VD. This is further supported by the results of positron emission tomography studies which indicate that cerebellar glucose metabolism is reduced in patients with stroke [47] and VD [48] but not in normal aging and patients with pure AD. However, neuropathological investigations show that AD pathology does not spare the cerebellum [49] and our own results suggest that cerebellar volume reduction can also be found in AD. Thus, cerebellar volume reduction shows a great overlap when VD and AD patients are compared and may hence only be of limited use in the differential diagnosis of the two dementia syndromes.

The main limitation of our study is the fact that the diagnostic classification of the dementia type was based solely on clinical and neuroradiological information. Although the diagnosis was strictly based on internationally accepted criteria, there is still some uncertainty concerning the reliability of the standardized diagnostic tools [50. 51]. It may well be that some of our patients have been misclassified or that our patient groups are heterogeneous, possibly owing to a certain proportion of patients with so-called 'mixed dementia'. There is growing evidence from the literature that coexisting vascular pathology in AD is far more common than previously acknowledged [52]. Conversely, it may be argued that satisfaction of the NINDS-AIREN criteria can not be taken as a sufficient proof that ischemic mechanisms are the exclusive explanation for an individual patient's dementia. Our failure to find significant differences between VD and AD may therefore reflect insufficient selectivity of the in vivo applicable diagnostic criteria resulting in an inhomogeneity of the diagnostic groups. However, a recent clinicopathological correlation study showed that the use of the NINDS-AIREN criteria led to 0.80 specificity with respect to the diagnosis of VD when the neuropathological diagnosis was used as a gold standard and by the application of these criteria 91% of patients with Alzheimer's disease could be successfully excluded [53]. Nonetheless, it will be necessary to carefully follow-up our patients in order to confirm the clinical diagnosis.

Taking into account the above-mentioned limitation, we conclude that although MRI-based volumetry is sufficiently sensitive to detect atrophic changes in dementia patients, it may only be of limited use in the differentiation between clinically diagnosed patients with AD and subcortical VD. The pattern of volume reduction does not seem to be specific to the underlying cause but rather reflects the selective vulnerability of neuronal structures.

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