21 MRI of Entorhinal Cortex and Hippocampus in Alzheimer's Disease, Subcortical Ischemic Vascular Dementia and Mixed Dementia

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INTRODUCTION

After Alzheimer's disease (AD), cerebrovascular pathology is the next most frequent cause of dementia, accounting for perhaps one-fifth as many cases as AD (Esiri and Morris, 1997). Furthermore, both types of pathology often occur together to varying extents, making it difficult to determine which type played the major part in causing dementia in a particular case. Therefore, there is much interest in improving the accuracy of a differential diagnosis between AD and vascular dementia.

Early *in vivo* magnetic resonance imaging (MRI) studies of AD reported hippocampal atrophy that could to a high degree distinguish AD patients from cognitively normal elderly subjects (Saab et al., 1988; Kesslak et al., 1991). However, additional research has shown that these measurements may not be as accurate, at least for patients in mild stages of the disease (Jack et al., 1992; Lehericy et al., 1994). Furthermore, hippocampal atrophy is not specific to AD, limiting its usefulness for a differential diagnosis between AD and other types of dementia. MRI studies reported hippocampal atrophy in vascular dementia without concomitant AD pathology, as confirmed by autopsy (Chui et al., 1999) as well as in frontotemporal dementia (Frisoni et al., 1999) and Parkinson's disease (Laakso et al., 1996). In accordance with the theory that early AD pathology may start in the entorhinal cortex (ERC) before spreading to the hippocampus (Braak and Braak, 1995), several MRI studies also measured atrophy of ERC in AD (Bobinski et al., 1999;

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Juottonen et al., 1999) and in non-demented subjects at risk of AD ((Xu et al., 2000). Quantitative MRI studies of ERC changes in vascular dementia have not been reported. Therefore, the first aim of this study was to compare the volumes of ERC in patients with subcortical ischemic vascular dementia (SIVD) and mixed SIVD/AD with the volumes of ERC in AD patients and cognitively normal elderly subjects.

The diagnostic value of MRI-based volume measurements of ERC for AD is under debate. Bobinski et al. (1999) found that measurements of ERC atrophy in addition to hippocampus improved discrimination of AD from normal aging. In contrast, other studies found no advantage of ERC measurements (Juottonen et al., 1999; Xu et al., 2000). Comparing AD with frontotemporal dementia (FTD), another MRI study (Frisoni et al., 1999) found ERC atrophy in both AD and FTD, while hippocampal atrophy did not occur in FTD, implying that the relationship between ERC and hippocampal changes might aid the diagnostic process. In general, one would expect some information gain if ERC and hippocampal changes were dissociated and little improvement if the changes were strongly correlated. Therefore, the second aim of this study was to explore the relationship of ERC and hippocampal atrophy in AD, SIVD, and mixed SIVD/AD and, furthermore, to assess the value of using ERC and hippocampus findings together for differentiation between the groups.

METHOD

This study included 12 SIVD patients (7 men, 5 women, 76 ± 4 years of age), 17 patients with mixed SIVD/AD dementia (9 men, 8 women, 79 ± 7 years), 25 AD patients (12 men, 13 women, 77 ± 5 years), and 40 cognitively normal (CN) elderly controls (20 men, 20 women, age 75 ± 4 years). MRI results from this population have been reported previously in short publications (Chui et al., 1999). Diagnosis of SIVD and mixed SIVD/AD was established according to the criteria of Chui et al. (1992) and diagnosis of AD was established according to the NINCDS/ADRDA criteria (McKhann et al., 1984). The level of cognitive impairment, as measured by the Mini-Mental State Examination (MMSE) score (Folstein et al., 1975) was similar among the patient groups, with a mean MMSE score (standard deviation) of 20 ± 4 for SIVD, 21 ± 6 for SIVD/AD, and 20 ± 4 for AD. The Committee of Human Research at the University of California, San Francisco approved this study, and all subjects or their legal guardians gave written consent before participation in the study.

The MRI studies were performed on a 1.5-T MR scanner (Vision, Siemens Inc., Iselin, NJ) and consisted of sagittal T1-weighted images (3D MP-RAGE, TR/TI/TE = 10/250/4 ms, 15° flip angle) with $1.0 \times 1.0 \times 1.4\,\text{mm}^3$ resolution and axial proton density and T2-weighted MR images (TR/TE1/

TE2 = 3000/20/80 ms) with $1.0 \times 1.25 \times 3.0\,mm^3$ resolution. The volumes of ERC and hippocampus were determined manually by outlining the boundary of the structures on oblique coronal T1 weighted MR images. One rater (A.T.D.), who had no knowledge of the diagnosis and other clinical information, performed the volume measurements. Volumes of the ERC were measured following the editing protocol developed by Insausti et al. (1998), which starts one section caudal to the level of the limen insulae and ends one slice behind the posterior limit of the gyrus intralimbicus. Volumes of the hippocampus were measured following the guidelines by Watson et al. (1992), which include hippocampus proper, dentate gyrus, subiculum, fimbria, and alveus. Rater reliability was 2.9% for ERC and 1.8% for hippocampus. Finally, the volumes of ERC and hippocampus of each subject were normalized to the total intracranial volume.

Effects by group on ERC and hippocampal volumes were tested using analysis of variance (ANOVA) with adjustment for age and sex. Associations between ERC and hippocampal volume changes were tested using Pearson correlation coefficients. The power of ERC and hippocampal volumes to discriminate between the groups was tested using stepwise logistic regression.

RESULTS

Figure 21.1 shows representative oblique coronal images through the temporal lobe of a 73-year-old man with SIVD (left) and a 68-year-old man with AD (right), subvolumed to include ERC and hippocampus. The tracings indicate the boundaries of the entorhinal cortex (left) and hippocampus (right). Despite comparable levels of cognitive impairment (AD: MMSE = 21/30; SIVD: MMSE = 19/30), the patient with AD had a markedly smaller entorhinal cortex and a smaller hippocampus than the patient with SIVD. Mean volumes and standard deviations for ERC and hippocampus of each group are listed in Table 21.1. Differences between the groups are summarized in Table 21.2. This shows that AD patients had 25% ($p < 0.001$) smaller hippocampal volumes and 39% ($p < 0.001$) smaller ERC volumes than CN. The SIVD group had 18% ($p < 0.001$) smaller hippocampal volumes and 19% ($p < 0.05$) smaller ERC volumes than CN. Compared with AD, however, SIVD patients had 25% ($p < 0.001$) larger ERC volumes and no significantly different hippocampal volumes. Finally, patients with mixed SIVD/AD had 27% ($p < 0.001$) smaller hippocampal volumes and 34% ($p < 0.001$) smaller ERC volumes than CN, similar to AD. Compared to SIVD, mixed SIVD/AD had 11% ($p < 0.05$) smaller hippocampal volumes and no significantly different ERC volumes.

There was no significant correlation between the volumes of ERC and hippocampus in CN. In contrast, the volumes of ERC and hippocampus correlated weakly in SIVD ($r = +0.33$, $p < 0.05$), and strongly in both AD

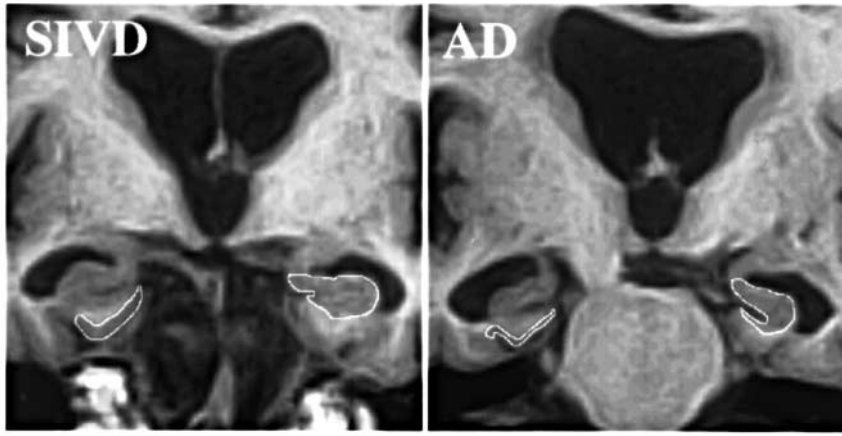

Figure 21.1. Oblique coronal T1-weighted MRI sections through the entorhinal cortex and hippocampus of a 73-year-old man with subcortical ischemic vascular dementia (left) and a 68-year-old man with Alzheimer's disease (right). The tracings indicate the boundaries of the entorhinal cortex (left) and hippocampus (right). Despite comparable levels of cognitive impairment, the AD patient has a markedly smaller entorhinal cortex and a smaller hippocampus than the SIVD patient

Table 21.1. Volumes (mm^3) of entorhinal cortex (ERC) and hippocampus (HP)

Group	ERC	HP
Normal	2720 ± 606	6314 ± 797
AD	1661 ± 456	4734 ± 972
SIVD	2211 ± 611	5188 ± 505
SIVD/AD	1796 ± 548	4602 ± 704

($r = +0.73$, $p < 0.001$) and mixed SIVD/AD ($r = +0.91$, $p < 0.01$). The correlation by group interaction was significant [$F(3,94) = 20$, $p < 0.04$].

Finally, Table 21.3 lists sensitivity, specificity, and overall classification of ERC and hippocampal volumes for discrimination between the groups, tested using stepwise logistic regression. This shows that using hippocampus alone helped to discriminate between AD and NC with an overall classification of 82% ($p < 0.01$, 68% sensitivity, 90% specificity), between SIVD and CN with an overall classification of 87% ($p < 0.01$, 67% sensitivity, 93% specificity), and also between mixed SIVD/AD and CN with overall classification of 72% ($p < 0.05$, 67% sensitivity, 76% specificity). In contrast, SIVD and AD could not be classified by hippocampus better than by chance. However, adding ERC helped to discriminate between SIVD and AD with an overall classification of 81% ($p < 0.05$, 96% sensitivity, 50% specificity). Finally, adding ERC improved further the discrimination between AD and CN with an overall classification of 85% ($p < 0.05$, 76% sensitivity, 90% specificity).

Table 21.2. Percentage differences in entorhinal cortex (ERC) and hippocampus (HP) volumes between the groups

		AD	SIVD	SIVD/AD
Normal	ERC	−39*	−19†	−34*
	HP	−25*	−18*	−27*
AD	ERC		+25*	+8
	HP		+9	−3
SIVD	ERC			−18
	HP			−11†

*$p < 0.001$; †$p < 0.05$.

Table 21.3. Discriminations between the groups using volumes of hippocampus (HP) and entorhinal cortex (ERC)

	HP alone			HP+ERC		
	Sensitivity	Specificity	Overall	Sensitivity	Specificity	Overall
Normal vs. AD	68	90	82*	76	90	85*
Normal vs. SIVD	67	93	87*	58	93	85
Normal vs. SIVD/AD	76	93	88*	76	95	89
SIVD vs. AD	88	8	62	96	50	81†
SIVD vs. SIVD/AD	67	76	72†	67	82	72

Values in percentage of number of subjects in the groups.
*$p < 0.01$; †$p < 0.05$.

DISCUSSION

A major finding of this study was that the volume of ERC was reduced in SIVD compared to CN. This implies that ERC atrophy is not a specific marker for AD. However, autopsy data is necessary to determine that these SIVD subjects had no AD pathology. Recently, ERC atrophy was also reported in frontotemporal dementia (Frisoni et al., 1999), where—unlike in AD—amyloid deposition does not occur.

Another finding was that ERC and hippocampal volume losses were of similar magnitude in SIVD, while the volume losses of ERC markedly exceeded those of hippocampus in both AD and mixed SIVD/AD. In addition, ERC and hippocampal volumes were moderately correlated in SIVD and much stronger correlated in AD and mixed SIVD, while healthy subjects showed no correlation. Greater atrophy of ERC than hippocampus in AD and mixed SIVD/AD is consistent with the distribution of AD pathology, which is thought to arise in the ERC before progressing to the hippocampus (Braak and Braak, 1995). Furthermore, as AD progression impacts ERC and hippocampus equally, one would expect a strong correlation between changes

in these two structures. In contrast, cerebrovascular pathology can impact ERC and hippocampus randomly, inducing changes that are not expected to correlate strongly. These differential patterns of ERC and hippocampal changes might potentially be helpful to differentiate between AD and vascular dementias.

Finally, this study showed that discriminations between SIVD and AD, as well as between AD and NC were significantly improved after hippocampal volume was combined with ERC volume. This implies that ERC and hippocampus provide partially independent information about dementia that assists classification. However, 100% discrimination between the groups could not be achieved.

Our results imply that ERC atrophy is not a specific marker for AD, but volume measurements of ERC assist classification, particularly the discrimination between AD and vascular dementia.

SUMMARY

MRI shows hippocampal atrophy in both Alzheimer's disease (AD) and subcortical ischemic vascular dementia (SIVD), limiting the ability to differentiate between AD and SIVD of hippocampal measurements. MRI shows also atrophy of the entorhinal cortex (ERC) in AD, but little is known about ERC volume changes in SIVD and mixed SIVD/AD dementia. Therefore, the aims of this study were: (1) to measure ERC volumes in SIVD and mixed SIVD/AD, and (2) to test whether ERC measurements help to discriminate SIVD and mixed SIVD/AD from AD and cognitive normal elderly. Quantitative MRI volume studies were performed on 12 patients with SIVD, 17 patients with mixed SIVD/AD, 25 patients with AD, and 40 cognitively normal elderly subjects. Dementia severity was similar among the patients and all groups were comparable with respect to age and sex. Results showed that both SIVD and SIVD/AD patients had significantly smaller ERC volumes ($p < 0.001$) and significantly smaller hippocampal volumes ($p < 0.05$) than cognitive normal controls. Compared to AD, however, SIVD had markedly larger ERC volumes ($p < 0.001$) and slightly larger hippocampal volumes, while mixed SIVD/AD patients had ERC and hippocampal volumes of a similar size to those with AD. A combination of ERC and hippocampal measurements improved discrimination between SIVD and AD and between AD and controls. MRI measurements of ERC atrophy could be useful for a differential diagnosis between AD and vascular dementia.

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