

Higher Atrophy Rates of Entorhinal Cortex than of Hippocampus in Alzheimer's Disease

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Objectives: Because Alzheimer's disease (AD) is thought to begin in the entorhinal cortex (ERC) before spreading to the hippocampus and cerebral cortex, it might be expected that the atrophy rate of ERC is greater than that of hippocampus in AD; if so, measurement of ERC atrophy rate may be a more sensitive approach to early detection of AD. Therefore, the main objectives of this study were:

- To compare atrophy rates of ERC and hippocampus in patients with AD and in subjects at risk for AD, including cognitive impaired (CI), and normal elderly individuals.
- To determine if cerebral vascular pathology (i.e white matter lesions) is associated with increased atrophy rate of ERC and hippocampus.

Methods:

- 18 AD patients, 12 CI subjects, and 42 cognitive normal elderly subjects were studied. Demographic data is listed in Table 1 and 2.
- AD was diagnosed according to NINCDS/ADRDA criteria; CI subjects were 50 years or older, presented memory loss, but were not demented by DSM-IV criteria. CI and normal subjects did not change diagnosis between first and second scans.
- Volumetric T1-weighted MRI (MP-RAGE); TR/TE/TI=10/4/300ms, 1.5mm³ resolution and proton density and T2 weighted images, TR/TE1/TE2 = 5000/20/80ms, 3.0mm³ resolution;
- Hippocampal volume was measured using a semi-automatic method based on high dimensional brain mapping (SNT Inc., Boulder Co.). ERC volume was measured manually according to the protocol by Insausti.¹ Volumes of white matter (WM) lesions were determined by semi-automatic tissue segmentation.²
- Atrophy rate of ERC and hippocampus was expressed annual percent atrophy rate.
- Paired t-tests were used to compare hippocampal and ERC atrophy rates. ANOVA, followed by post-hoc Scheffe test, was used to determine significance of group effects.

Results:

- **Table 1** lists annual percent atrophy rate of hippocampus by group. AD had significantly larger atrophy rates of hippocampus than CI (F[1, 27] = 16, p < 0.001) and controls (F[1,57] = 76; p < 0.001). The difference in hippocampal atrophy rates between CI and controls was not significant.
- **Table 2** lists annual percent atrophy rate of ERC by group. Similarly to hippocampus, AD had larger atrophy rates of ERC than CI (F[1,13] = 7, p < 0.05) and controls. Similarly to hippocampus, AD had larger atrophy rates of ERC than CI

Table1. Annual percent atrophy rate of hippocampus

	Age	No.	MMSE	Period (ys)	Atrophy rate %
Controls	74 ± 7	42	29 ± 2	3.2 ± 1.1	1.0 ± 1.6
CI	72 ± 8	12	28 ± 2	2.8 ± 0.8	2.0 ± 2.5
AD	76 ± 7	18	24 ± 5	2.2 ± 1.3	6.0 ± 2.9*

Data represented as mean ± SD.

* p < 0.01 AD vs controls, AD vs CI

Table2. Annual percent atrophy rate of ERC

	Age	No.	MMSE	Period (ys)	Atrophy rate %
Controls	77 ± 5	19	30 ± 0	2.9 ± 1.0	1.6 ± 3.5
CI	70 ± 7	7	28 ± 2	2.4 ± 0.8	4.2 ± 6.2
AD	75 ± 8	9	26 ± 2	2.2 ± 1.3	10.7 ± 3.9*

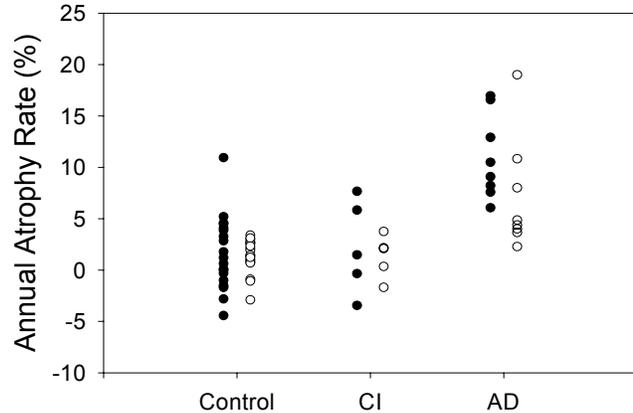
Data represented as mean ± SD.

* p < 0.01 AD vs controls, AD vs CI

($F[1,13] = 7, p < 0.05$) and controls ($F[1,25] = 36, p < 0.001$). The difference in ERC atrophy rates between CI and controls was not significant.

- **Figure 1** depicts annual percent atrophy rate of ERC and hippocampus in AD, CI, and control subjects graphically. AD had significantly larger atrophy rates of ERC than of hippocampus ($p < 0.05$). However, there was no difference of atrophy rates of ERC and hippocampus in CI or controls.
- In addition, there was significantly correlation between annual atrophy rates of hippocampus and WM lesions ($r = 0.28, p < 0.01$) in all groups. In contrast to hippocampus, contributions of WM lesions to atrophy rates of ERC were not significant.

Figure 1. Atrophy rate of ERC (●) and hippocampus (○) in controls, CI and AD.



Conclusions:

- Larger atrophy rates of ERC than hippocampus in AD are consistent with the theory that AD involves initially ERC before spreading to the hippocampus.
- Higher atrophy rates of ERC than hippocampus suggest that measurements of ERC changes may be a more sensitive marker for AD progression than hippocampal changes.
- The association between increased atrophy rates of hippocampus and WM lesions implies that cerebral vascular disease can accelerate decline of brain integrity.

Reference:

1. Insausti R et al. AJNR 1998; 19:659-71.
2. Tanabe JL et al. AJNR 1997; 18:115-123.