INTRODUCTION: Autopsy studies of brains from patients with Alzheimer's disease (AD) indicate early pathology in entorhinal cortex (ERC) progressing to hippocampus (HP). MRI studies of AD showed volume loss in ERC and HP correlated with cognitively normal subjects (CN) (1). MRI measurements of ERC improved discrimination of early AD from CN, compared to measurements of HP (2), indicating that ERC may be a more sensitive marker of AD than HP. However, another study did not show an advantage of ERC over HP measurement (1). ERC has not been measured in non-demented patients with mild cognitive impairment (MCI) thought to precede the diagnosis of AD. Therefore, the major purpose of this study was to measure and compare ERC and HP volumes in MCI subjects, who are known to have an increased risk for AD. Furthermore, we measured the relationship between ERC and HP volumes in AD, MCI, and CN. Our specific goals were to determine if: 1) ERC volume is significantly reduced in MCI compared to CN; 2) ERC is more sensitive than HP to distinguish AD or MCI from CN; 3) ERC and HP volume loss are correlated in MCI and AD. Finally, we explored whether ERC provided a better classification between the groups than HP, and the value of using ERC and HP together for classification.

METHOD: The study included 40 CN (age 75.1 ± 4.3 years, MMSE 29.0 ± 0.9), 36 MCI (age 75.1 ± 8.2 years, MMSE 25.8 ± 3.6) and 29 AD (age 75.8 ± 5.1 years, MMSE 17.7 ± 5.7). The criteria of AD accorded to the NINCDS/ADRDA criteria. The criteria of MCI was: subjects were old than 50 years old and were not demented by DSM-IV criteria presenting with complaints of memory loss, and had a Clinical Rating Scores of 0.5 (Clinical Dementia Rating). All subjects were scanned with volumetric MP-RAGE MRI (1.4 x 1 x 1 mm³ resolution). ERC and HP volumes were measured by the same rater, who was blind to clinical information. ERC (3) and HP (4) were volumed on MRI. ERC and HP differences between groups were analyzed using ANOVA with adjustment for age and sex. ERC and HP relationships were analyzed using linear regression. The discrimination power of ERC and HP was tested using classification tree analysis.

RESULTS: The Table shows the volume and comparison of ERC and HP in CN, MCI and AD.

<table>
<thead>
<tr>
<th></th>
<th>CN</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERC</td>
<td>2726 ± 608</td>
<td>2422 ± 659 $^*$</td>
<td>1662 ± 501 $^{**\dagger}$</td>
</tr>
<tr>
<td>% change</td>
<td>11%</td>
<td>9%</td>
<td>27%</td>
</tr>
<tr>
<td>HP</td>
<td>6327 ± 799</td>
<td>5763 ± 1125 $^*$</td>
<td>4595 ± 1009 $^{**\dagger}$</td>
</tr>
<tr>
<td>% change</td>
<td>9%</td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD mm³; % change as compared to CN
$^*$ p<0.05, ** p<0.01 for CN versus MCI or AD
$\dagger$ p<0.01 for % change of ERC is greater than HP

4) Classification: Using Classification Trees, ERC classified 86% and HP 86% of AD from CN. Similarly, ERC classified 72% and HP 72% of MCI from CN. Finally, ERC classified 83% and HP 80% of AD from MCI. Use of ERC and HP together slightly improved classification of AD from CN to 90%, MCI from CN to 80%, but not AD from MCI (83%).

DISCUSSION: The first major new finding was that MCI had significantly reduced ERC compared with CN. Furthermore, the ERC and HP losses in MCI were intermediate between CN and AD, implying some neurodegeneration in MCI. However, the % change of ERC in MCI was similar in magnitude to the % change of HP in MCI, and classification power was similar. Taken together these findings suggest that ERC may not provide any advantage over HP to detect AD at an early stage. The second major finding was that in AD the % change of ERC (compared to CN) of 39% was significantly (p<0.01) greater than the % change of HP. These results are consistent with those reported in early AD (2) but differ from another report (1). Although this might be taken to suggest that ERC measurements (compared to HP) might provide improved ability to diagnose AD, ERC and HP were very strongly correlated in AD and classification was no better with ERC. Finally, in MCI and AD there was a strong correlation between ERC and HP. This is consistent with autopsy data suggesting that both structures be affected in early AD. We conclude that ERC is reduced in MCI and shows greater changes than HP in AD.

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REFERENCE:

Table. Volume of ERC and hippocampus in CN, MCI and AD

Mean ± SD mm³; % change as compared to CN
$^*$ p<0.05, ** p<0.01 for CN versus MCI or AD
$\dagger$ p<0.01 for % change of ERC is greater than HP

( p<0.01).

3) Correlation: There was no significant correlation between ERC and HP volumes in CN. However, the correlation was significant in both MCI (r = 0.66, p<0.001) and AD (r = 0.68, p<0.001).