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Author:
Du, An-Tao
Schuff, Norbert
Chao, Linda L
Kornak, John
Jagust, William J
Kramer, Joel H
Reed, Bruce R
Miller, Bruce L
Norman, David
Chui, Helena C
Weiner, Michael W

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Age effects on atrophy rates of entorhinal cortex and hippocampus

An-Tao Du a, Norbert Schuff a,b, Linda L. Chao a,b,c, John Kornak a,b, William J. Jagust f, Joel H. Kramer c, Bruce L. Miller d, David Norman b, Helena C. Chui g, Michael W. Weiner a,b,c,d,e,∗

a Magnetic Resonance Unit (114M), Department of Veterans Affairs Medical Center, 4150, Clement Street, San Francisco, CA 94121, USA
b Department of Radiology, University of California, San Francisco, CA, USA
c Department of Psychiatry, University of California, San Francisco, CA, USA
d Department of Neurology, University of California, San Francisco, CA, USA
e Department of Medicine, University of California, San Francisco, CA, USA
f Department of Neurology, University of California, Davis, CA, USA
g Department of Neurology, University of Southern California, Los Angeles, CA, USA

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Abstract

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Keywords: Atrophy rate; Normal aging; Subcortical vascular disease; Hypertension; APOE ε4; The entorhinal cortex; The hippocampus

1. Introduction

The entorhinal cortex (ERC) and hippocampus are thought to be important structures in differentiating Alzheimer’s disease (AD) from normal aging. Cross-sectional MRI studies have shown that AD patients have significantly greater ERC and hippocampal atrophy than cognitively normal (CN) elderly subjects [9,21,26,48,57]. Longitudinal MRI studies have suggested that the rates of ERC and hippocampal atrophy may be useful in predicting AD before the onset of clinical symptoms and in assessing the potential usefulness of pharmacological interventions in treatment trials [10,22,24,27]. However, CN subjects often display ERC and hippocampal atrophy rates that are significantly greater than zero, although substantially less than that seen in AD patients [10,22]. Moreover, hippocampal atrophy rates tend to increase with age in CN subjects [41,42,44]. Raz and co-workers reported that normal aging has a greater effect on hippocampal than ERC atrophy rates and that ERC atrophy rate is not related to age [41,42]. Together these results suggest that hippocampal atrophy may be more closely associated with normal aging while ERC atrophy may be more closely associated with incipient AD pathologic processes. On the other hand, ERC and hippocampus are both strongly associated with memory function [51]. Since memory impairment typically increases with age [2,31], it is unclear why normal aging would differentially affect atrophy rates of ERC and hippocampus. Therefore, the first goal of this study was to examine the relationship...
between age and atrophy rates of the ERC and hippocampus. In an attempt to replicate the results of Raz and co-workers [41,42], we also examined whether the relationship between age and atrophy rates is different for ERC and hippocampus. Another risk factor for cognitive impairment, in addition to advanced age, is subcortical cerebral vascular disease, manifested as subcortical infarcts/lacunes and white matter hyperintensities (WMH) on MRI images [8,13,37,46,50,58]. A recent clinical study demonstrated that elderly individuals with silent brain infarcts were at greater risk for dementia and cognitive decline than elderly individuals without such lesions [53]. In addition to the subcortical cerebral vascular lesions visible on MRI, microinfarctions, which are usually not visible on MRI, may also be present, especially in subjects with hypertension [28]. Hypertension has been shown as a risk factor for late-life cognitive impairment [12,32]. Because cognitive decline is related to cerebral atrophy [15,36], cerebral vascular disease and hypertension may accelerate cerebral atrophy in CN subjects. Therefore, the second goal of this study was to determine if subcortical vascular disease and hypertension, independent of age, contribute to greater ERC and hippocampal atrophy rates.

The apolipoprotein E (APOE) e4 allele is a genetic risk factor for AD and vascular dementia [7,18]. APOE e4 lowers the age of AD onset [1], and healthy older women with APOE e4 have greater hippocampal atrophy rates than those without APOE e4 [6]. However, it is not known if APOE e4 is also associated with greater ERC atrophy rate in normal aging. Therefore, the third goal of this study was to examine if APOE e4 contributes to greater ERC and hippocampal atrophy rates in CN subjects.

2. Subjects and methods

2.1. Subjects

All subjects were recruited from the community by flyers and advertisements in local newspapers as control subjects for a dementia study and had undergone two MRI and two neuropsychological evaluations approximately 3.5 ± 0.8 years apart. The subjects received standard neurological examinations [35] at the Memory and Aging Clinic at the University of California at San Francisco and the Alzheimer Center at the University of California at Davis, prior to participating in the study. Global cognitive function could be measured in a pair-wise fashion, as described earlier [11]. In contrast, hippocampal volumes were measured separately for each timepoint using a semi-automated high dimensional brain-warping algorithm (Medtronic Surgical Navigation Technologies, Louisville, CO) [20], which only measures gray matter of hippocampus. While measurements of ERC volumes were conducted in pairs with the rater blinded to chronological order to reduce scoring errors, semi-automated measurements of hippocampal volumes were conducted individually, because susceptibility to rater errors was substantially reduced with automation and whether performed individually or in pairs did not mat-
Table 1

Demographics

<table>
<thead>
<tr>
<th></th>
<th>CN without lacunes</th>
<th>CN with lacunes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-HTN</td>
<td>HTN</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 ± 7.6</td>
<td>74.3 ± 6.5</td>
</tr>
<tr>
<td>Interval (years)</td>
<td>3.6 ± 0.9</td>
<td>2.7 ± 1.0</td>
</tr>
<tr>
<td>APOE ε4</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.4 ± 0.8</td>
<td>38.0 ± 0.0</td>
</tr>
<tr>
<td>ΔMMSE (per year)</td>
<td>0.02 ± 0.22</td>
<td>0.14 ± 0.25</td>
</tr>
<tr>
<td>DLR</td>
<td>10.6 ± 1.4</td>
<td>10.5 ± 2.2</td>
</tr>
<tr>
<td>ΔDLR (per year)</td>
<td>−0.10 ± 0.79</td>
<td>−0.31 ± 0.31</td>
</tr>
<tr>
<td>WMH (cm³)</td>
<td>7.4 ± 10.5</td>
<td>2.5 ± 1.9</td>
</tr>
</tbody>
</table>

HTN: hypertension, MMSE: mini-mental state examination, DLR: delayed list recall. Twelve words need to be remembered in the DLR test, ΔMMSE: (first MMSE score – second MMSE score)/scan interval, ΔDLR: (first DLR score – second DLR score)/scan interval.

*p < 0.05, t-test, between subjects with and without lacunes.

2.3. Statistics

Atrophy rate is expressed as the annual percentage change from baseline volume [11]. Linear regression models were
used to determine the effects of age on ERC and hippocampal atrophy rates. In order to reduce the confounding effects of subcortical vascular disease and hypertension on atrophy rates, we initially analyzed data from only CN subjects without lacunes and hypertension in the linear model. Subsequently, the presence or absence of subcortical lacunes, baseline WMH volume, APOE e4 status, and presence or absence of hypertension were added to the linear model to evaluate the contribution of these additional factors to increased atrophy rates with aging. An analysis of variance (ANOVA) analysis was used to test the different effects of aging on ERC and hippocampal atrophy rates. The level of significance was set at $p < 0.05$.

3. Results

3.1. Effect of normal aging on atrophy rates of ERC and hippocampus

Fig. 2 shows ERC and hippocampal atrophy rates as a function of age in 27 CN subjects without lacunes and hypertension. ERC atrophy rate significantly increased with age by $0.04 \pm 0.02\%$ per year ($r = 0.38, p < 0.05$). After accounting for baseline WMH volume and APOE e4 status, the relationship between atrophy rate of ERC and age reduced to a trend ($p = 0.06$); however, both baseline WMH volume and APOE e4 status did not significantly contribute ($F$-tests, both $p > 0.1$) to increased atrophy rate of ERC. Therefore, the simpler model directly relating atrophy rate of ERC to age was chosen to estimate variations of atrophy rate of ERC with age. Similarly, hippocampal atrophy rate also increased significantly with age by $0.05 \pm 0.02\%$ per year ($r = 0.47, p < 0.05$). After accounting for baseline WMH volume and APOE e4 status, the relationship between hippocampal atrophy rate and age remained significant ($p < 0.05$). Neither baseline WMH volume nor APOE e4 status contributed significantly to increased atrophy rate of hippocampus (all $p > 0.1$). Atrophy rates of ERC and hippocampus were significantly correlated with each other ($r = 0.54, p < 0.01$) in the subjects without lacunes. There was no significant difference (paired $t$-test, $p > 0.5$) between atrophy rates of ERC and hippocampus; furthermore, there was no significant difference in the relationships between hippocampal and ERC atrophy rates and age ($F_{1,25} = 0.2, p > 0.5$). Based on the current sample size, however, there was virtually no power to detect significant differences of atrophy rates between ERC and hippocampus in relation to age. In addition, atrophy rates of both ERC and hippocampus were not related to baseline total brain tissue (both $p > 0.2$). In contrast to atrophy rates of the ERC and hippocampus, baseline volumes of the ERC and hippocampus were not significantly related (both $p > 0.5$) to age. Similar to volumes at baseline, there was no significant cross-sectional correlation between volumes of the ERC or hippocampus and age at follow-up (both $p > 0.1$).

3.2. Effect of other confounding factors on atrophy rates of ERC and hippocampus

In order to explore the extent to which atrophy rates of ERC and hippocampus in CN subjects were related to presence of lacunes, baseline WMH volume, APOE e4 status and presence of hypertension in addition to age, all subjects were combined in a larger linear model analysis. Atrophy rate of hippocampus was positively related with presence of lacunes ($p < 0.05$) in addition to age, suggesting that atrophy rate of hippocampus increases with presence of lacunes. After corrected for the age effect, atrophy rates of hippocampus was $1.0 \pm 0.09\%$ per year in subjects without lacunes and $2.0 \pm 0.9\%$ per year in subjects with lacunes. In contrast to the hippocampus, atrophy rate of ERC did not increase with presence of lacunes ($p > 0.3$). Atrophy rate of ERC was $1.0 \pm 0.8\%$ per year in subjects without lacunes and only $1.1 \pm 1.4\%$ per year in the subjects with lacunes after correcting for the age effect. The minimum difference in ERC atrophy rate between subjects with and without lacunes that could be detected with this sample size at 80% statistical power was $8\%$ per year ($\alpha = 0.05$). Furthermore, atrophy rates of ERC were no longer related to age ($p > 0.05$) after accounting for lacunes. WMH volumes, APOE e4 status and hypertension had no significant effect on atrophy rates of ERC and hippocampus (all $p > 0.1$) independent of age. Considering that the number of subjects who had each secondary condition (the presence of lacunes, APOE e4 or hypertension) was small, the analyses were repeated by successively removing subjects with the various conditions. The results remained the same. Fig. 3 shows atrophy rates of ERC and hippocampus in CN subjects with and without lacunes, after accounting for age. In contrast to atrophy rates of ERC and hippocampus, baseline volumes of both ERC and hippocampus were not significantly related (both $p > 0.4$) to presence of lacunes. Furthermore, no significant relationship was found between volumes of the ERC and hippocampus and baseline WMH volumes, APOE e4 status and hyperten-
4. Discussion

The main findings of this study were: (1) age was associated with increased ERC and hippocampal atrophy rates; (2) atrophy rate of hippocampus, but not atrophy rate of ERC increased with presence of lacunes; (3) WMH, APOE e4 and hypertension had no effect on atrophy rates of ERC and hippocampus.

The first finding was that ERC and hippocampal atrophy rates increased with increasing age in normal controls. Memory impairment is a prominent symptom of AD. Moreover, the ERC and hippocampus are both critical structures in the medial temporal lobe system that supports memory [51]. Over the last decade, modern stereological techniques to quantify the neuronal number in the ERC, reflecting the volume of all types of tissue, while stereological techniques quantify the neuronal number in the ERC. Raz and co-workers reported no relationship between age and ERC atrophy rates for subjects from age 26 to 82 years old [41,42], whereas our study included only 58–87 years old subjects. It is possible that rates of ERC atrophy increase disproportionately with age, which may explain the different findings. Furthermore, in our analysis of age effects, we excluded subjects with lacunes and hypertension that could have confounding effects. When subjects with lacunes and hypertension were included, we found that ERC atrophy rate was no longer related to age, similar to the report of Raz et al. [41,42]. In this study, we found that atrophy rates of ERC and hippocampus correlated with each other, suggests that common mechanisms, likely age, were driving the changes in ERC and hippocampus in CN elderly.

There are numerous imaging studies concerning the effects of age on brain structure [5,25,38,41,42,44,47,52], but most of them are cross-sectional studies [5,25,38,47,52]. Several cross-sectional studies, but not all found hippocampal volume decreases with age [5,25,38,47]. However, an aging effect is difficult to be determined in cross-sectional studies, because the volumes at baseline in individual subjects remain an unknown confound. In contrast, longitudinal studies can eliminate the baseline volume as a confounding factor. In this study, we performed both cross-sectional and longitudinal analyses in the same 27 elderly subjects from 58 to 87 years old and found a significant longitudinal, but not cross-sectional aging effect on hippocampal atrophy. This suggests that the longitudinal study may be more sensitive than the cross-sectional study to detect the aging effect on brain structure change.

The second finding was that atrophy rate of hippocampus, but not atrophy rate of ERC increased with presence of lacunes. This finding is consistent with previous human and animal studies showing that the hippocampus is selectively vulnerable to ischemia/hypoxia [4,29,30]. Furthermore, since an effect of lacunes on the rate of ERC atrophy was not detectable, our finding suggests that ERC atrophy rate may be more specific for AD pathology than hippocampal atrophy rate. However, AD patients have often co-existing cerebrovascular pathology, and further, AD and cerebrovascular disease may have an additional or even synergistic effect on dementia development [37,58]. Effect of lacunes on hippocampal atrophy rate but not ERC atrophy rate suggests that hippocampal atrophy rate may be a better marker for predicting the onset of dementia in subjects with cerebrovascular diseases than ERC atrophy rate. Furthermore, it may pro-
vide a possibility to separate AD pathology from concomitant vascular pathology leading to dementia. However, more data are needed to further explore this possibility. Lacunes have been shown to be a significant risk factor for dementia and cognitive impairment [53]. In this study, we found greater hippocampal atrophy rates in CN subjects with lacunes than those without lacunes, which suggests that lacunes may accelerate the deterioration of brain reserve in CN subjects before cognitive decline becomes apparent. This may explain at least in part why subjects with lacunes are at increased risk for AD [33]. In contrast to lacunes, there were no significant relationships between WMH and atrophy rate of ERC or hippocampus. Lacunes are small, deep cerebral infarcts attributed from microatheroma, lipohyalinosis and emboli [16], however, the cause of age-related WMH remains uncertain. Histological study showed that some of age-related WMH were not associated with ischemia [14] and therefore may not be a specific marker for generalized cerebrovascular disease. In addition, we did not find a relationship between hypertension and atrophy rate of ERC or hippocampus.

Previous reports concerning effects of APOE ε4 on hippocampal atrophy from cross-sectional MRI are quite variable [23,33,39,45]. The longitudinal MRI study by Cohen et al. showed that atrophy rate of hippocampus was higher in CN subjects with APOE ε4 than those without APOE ε4 [6]. However, in the current longitudinal MRI study, we did not find a significant relationship between APOE ε4 status and increased hippocampal atrophy rate in CN. Further, we did not find a significant relationship between APOE ε4 status and increased ERC atrophy rate. Differences in subject demographics may partially explain the discrepant findings. Subjects without APOE ε4 in the longitudinal MRI study by Cohen et al. were 60.6 ± 10.2 years old and subjects with APOE ε4 were 55.1 ± 6.0 years old [6]. In contrast, subjects in the present study were much older (i.e., CN without APOE ε4: 73.6 ± 7.6 years old; CN with APOE ε4: 73.4 ± 6.4 years old). Previous cross-sectional MRI studies suggest that APOE ε4 only affect hippocampal volume loss in subjects who are younger than 70 years old [23,33]. Thus, the effects of APOE ε4 on ERC and hippocampal atrophy rates may be modulated by age.

Studies on the effects of normal aging on brain structures are very influenced by sample selection. One problem is to distinguish the effects of normal aging per se from the age-associated disease. In this study, we have attempted to determine the effect of normal aging on atrophy rates of ERC or hippocampus, separately from age-associated disease processes, such as lacunes, WMH, or hypertension in a highly selected elderly population who had – based on clinical examinations – no diseases, normal cognition and no cognitive decline at follow-up over more than 3 years as well as no neuropathological lesions on MRI except WMH. Therefore, our findings should truly reflect the effect of normal aging on ERC and hippocampal atrophy. However, despite our efforts, there still remains the possibility that the development of preclinical AD, cerebrovascular disease, or other age-associated disease processes may be, in part, responsible for our findings. In this study, we assumed that the increase of atrophy rate of ERC and hippocampus with age was linear, but this may not be the case. Rodrigue and Raz found a quadratic relationship between atrophy rate of hippocampus and age in a group of CN subjects from 26 to 82 years old [42]. Adding a quadratic term for age in this study, however, made no significant contribution. The different findings between this study and that by Rodrigue et al. may be related to the fact that age range in our study was limited from 58 to 87 years old, while atrophy rate of hippocampus starts to increase in subjects who are around 40 years old, as shown by Rodrigue et al. Although we found a significant effect of lacunes on atrophy rate of hippocampus, it has to be aware that lacunes were not confirmed by pathological evaluation but merely by their morphological appearance and signal intensity on MRI data. In addition, the small number of subjects, who had lacunes in each subcortical location, prevented a rigorous analysis of an association between lacunar location and atrophy rates.

In summary, our results suggest that both ERC and hippocampal atrophy rates increase with increasing age and presence of lacunes increase atrophy rate of hippocampus in CN subjects. Therefore, age and presence of lacunes should be considered in the analysis of longitudinal MRI studies for early diagnosis and treatment assessment of AD.

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