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Effects of age, cerebrovascular disease and APOE ε4 on entorhinal and hippocampal atrophy rates

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Background: MRI measured volume changes of entorhinal cortex (ERC) and hippocampus over time may be useful in predicting AD before clinical symptoms develop and in assessing treatment effects. However, significant rates of ERC and hippocampal atrophy are also observed in cognitive normal (CN) elderly, although magnitudes are substantially smaller than in AD. In addition, subcortical lacunes, white matter hyperintensities (WMH) and apolipoprotein E ε4 allele (AOPE ε4) may affect the atrophy rates of ERC and hippocampus in CN elderly. **Objective:** To explore the extent to which age, presence of subcortical lacunes, WMH and APOE ε4 are associated with increased atrophy rates of entorhinal cortex (ERC) and hippocampus in normal aging. **Methods:** Longitudinal MRI studies were performed on 53 CN elderly with an average interscan period of 3.4 ± 1.0 years. CN subjects remained cognitively normal within the duration of the study. Cerebral vascular disease was assessed by quantifying the number of subcortical lacunes and the extent of WMH. ERC and hippocampal volumes were measured on volumetric T1-weighted images.17 subjects had subcortical lacunes. 13 subjects had at least one APOE ε4 allele. A multivariate linear regression model was used to test for effects of age, presence of subcortical lacunes, extent of WMH and APOE ε4 on atrophy rates of ERC and hippocampus. **Results:** In absence of subcortical lacunes, atrophy rates of both ERC ($F_{1,34} = 5.8$, $p < 0.05$) and hippocampus ($F_{1,34} = 10.6$, $p < 0.01$) increased with increasing age, independent of WMH volume and APOE ε4 status. When CN subjects with subcortical lacunes were included, both increasing age (both $p < 0.03$) and presence of subcortical lacunes (both $p < 0.02$), but not WMH volume and APOE ε4 status, explained increased atrophy rates of ERC and hippocampus. Estimations from linear regressions indicated that presence of subcortical lacunes increases atrophy rates from 0.8 ± 0.7%/year to 1.7 ± 1.3%/year for ERC and from 0.9 ± 0.9%/year to 2.0 ± 1.3%/year for hippocampus in normal aging. **Conclusion:** Age and presence of subcortical lacunes, but not WMH and APOE ε4 status, were associated with higher rates of ERC and hippocampus. Therefore, age and presence of subcortical lacunes should be considered when using longitudinal MRI data to predict development of AD and assess treatment effect.