Reduced hippocampal volume in non-demented carriers of the apolipoprotein E ε4: Relation to chronological age and recognition memory

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Abstract

Apolipoprotein E ε4 (APOE ε4) is the main known genetic risk factor for Alzheimer’s disease (AD). Some previous studies have reported structural brain changes as well as cognitive deficits in non-demented APOE ε4 carriers, but the pattern of results is inconsistent and studies with larger sample sizes have been called for. Here we compared hippocampal volume and recognition–memory performance between AD-symptom-free carriers (N = 30) and non-carriers (N = 30) of the APOE ε4 allele (age range: 49–79 years). We observed reduced right hippocampal volume in APOE ε4 carriers, and found that the difference was most pronounced before the age of 65. Further, the APOE ε4 carriers made significantly more false alarms in the recognition–memory test, and the number of false alarms correlated significantly with right hippocampus volume. These results indicate that relatively young individuals at genetic risk for AD have smaller hippocampal volume and lower performance on hippocampal-dependent cognitive tasks. A question for the future is whether smaller hippocampal volume represents early-onset hippocampal volume reduction or an inherent trait.

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Alzheimer’s disease (AD) is a neurodegenerative disorder, characterized by neurofibrillary tangles and neuritic amyloid plaques, and by progressive cerebral atrophy [3,12]. As the neural degeneration accumulates, subsequent behavioral symptoms are initiated until a generalized cognitive decline prompts a diagnosis of dementia. At early stages of AD, the most prominent neuropsychological feature is a progressive decline in episodic memory [1,13,40]. This is consistent with studies showing that the first and most severe cellular damage occurs in the medial temporal lobe; in particular the entorhinal cortex and hippocampi are affected [4,12,28,32], both of which are important structures for episodic memory [5,26,35].

Genetic studies have identified the apolipoprotein E type 4 allele (APOE ε4) as a major genetic risk factor for AD [8,31,38]. There are three different APOE isoforms: ε2, ε3, and ε4. In western European and white American populations the allele frequencies of these isoforms are approximately 8, 78, and 14%, respectively [16,22]. Whereas APOE ε2 appears to be protective, APOE ε4 increases the risk for and decreases the onset age of AD in a dose-dependent manner such that homozygotic carriers are most at risk [8,10].

Brain-imaging studies have found that APOE ε4 is associated with more prominent hippocampal atrophy compared to other isoforms. This has been documented for AD patients [18] as
well as for non-demented subjects [7,34,41]. Tohgi et al. [41] reported that right hippocampal atrophy may be detectable as early as at age 40 in non-demented APOE e4 carriers. These investigators used the Mini-Mental State Exam [11]—a test for global cognitive functioning—to evaluate cognitive performance, and observed no difference between carriers and non-carriers of APOE e4. They noted that the lack of difference in cognitive functioning was inconsistent with previous findings of impaired cognitive performance in non-demented APOE e4 carriers [6,15,29,33], and called for future studies with larger sample sizes. The purpose of the present MRI study was to examine this issue further, using data from an ongoing population-based study [23,24].

The study was approved by the Ethics committee of Umeå University, and written informed consent was obtained in accordance to the Declaration of Human Rights of Helsinki, 1975. Sixty subjects who had undergone extensive psychometric and medical examination, including APOE genotyping (see [39] for details), were included. They were carefully screened to ensure that they were all AD-symptom free. Thirty subjects were carriers of at least one copy of APOE e4; 10 were homozygotic (APOE e4/e4) and 20 were heterozygotic (APOE e3/e4). The remaining 30 subjects carried two copies of the APOE e3 and served as controls. The subjects ranged in age from 49 to 79 years. The genotype groups were indistinguishable on age, education, and sex distribution (Table 1).

Magnetic resonance imaging was performed on a Philips Intera 1.5 T scanner (Philips Medical Systems, Netherlands). The scanning session included both functional and structural scans. The results from the functional scanning have been reported elsewhere [20]. Briefly, subjects performed a word categorization task that promoted incidental encoding of the words. About 15 min after the scanning session ended, a self-paced unexpected recognition test was administered during which participants made yes/no recognition decisions on 240 words: 80 new (not presented during the categorization task) and 160 previously studied words. Two subjects did not complete the post-scan recognitions-memory test.

A T1-weighted 3D gradient echo sequence was used for the structural scans (TR = 24 ms, TE = 6 ms, flip angle = 35°, voxel size = 180 mm × 180 mm × 1.8 mm). One hundred and twenty-four coronal slices were acquired in 160 × 160 matrices and reconstructed to 256 × 256 matrices. Two averages were used. All images were sent to a PC and converted to analyze format. After acquisition, the T1-weighted images were aligned to correct for undesirable effects of head tilt, rotation, and pitch, using the computer program Brain Image 5.2.5 (available at http://www.stanford.edu/group/cap/research/neuroimaging/imageanalysis/) (see [27] for details). The geometrical operations required an isotropic voxel size; in order to get a slice thickness equal to the pixel size (0.703 mm), bicubic interpolation between the slices was performed using Matlab 6.1 (Mathworks Inc., MA, USA). One subject was excluded from the hippocampus measurements due to poor image quality.

The right and left hippocampus formation was manually traced on every other coronal slice using a computer mouse, and measured with NIH Image public domain software (version 1.20; http://rsb.info.nih.gov/nih-image/) (Fig. 1). Beginning rostrally, the first slice used was the one where the mamillary bodies were clearly visible, whereas the caudal boundary was marked by the slice showing the fornices rising from the fimbria. To separate the rostral part of the hippocampus from the adjacent amygdala, the temporal horn of the lateral ventricle was used as a border-indicator. Medially, the subiculum was demarcated from the cortex of the parahippocampal gyrus by tracing the subiculum to its most medial position and drawing a horizontal line at its medial curve. Any part of the subiculum above this line was included as a part of the hippocampus. The total number of slices used to outline the hippocampus varied between 17 and 23 per subject. All measurements were performed by the same operator (J.L.), who was blind to the characteristics of the participants. Body height was used to adjust the hippocampal volumes via the analysis of covariance formula, similar to [27,30].

Based on previous studies [6,15,29,33] we predicted impaired cognitive performance for APOE e4 carriers. The results from
the post-scan memory test provided support for this prediction by revealing a significant group difference for false-alarm rate, whereas there was no significant difference in hit rate or overall recognition accuracy (hits–false alarms) (Table 2). Comparison of memory test performance and the hippocampal size (Table 2). Importantly, right hippocampal volume was significantly correlated with numbers of false alarms in the APOE e4 group (r = −0.40, P < 0.01, two-tailed) but not in the APOE e3 e3 group (r = −0.15, P > 0.40).

Analyses of the correlation between hippocampal volume and chronological age revealed a significant relationship in the APOE e3 e3 group (right HC: r = 0.37, P < 0.01, one-tailed; left HC: r = 0.41, P < 0.01, one-tailed). This pattern of correlation suggests that hippocampal volume decreased with age in the APOE e3 e3 group but not in the APOE e4 e4 group. A plot of right as well as total hippocampal volume as a function of age (≤65 years versus >65 years) for the two genotype groups confirmed this impression (Fig. 2). There was a significant difference between the younger (but not the older) genotype groups for the right HC [t(19) = 1.8, P = 0.05, one-tailed] hippocampal volume, and a tendency in the expected direction for total hippocampal volume [t(19) = 1.3, P = 0.10, one-tailed].

In keeping with previous findings [41] we observed reduced right hippocampal volume in APOE e4 carriers that ranged in age between 49 and 79 years. We found that the difference in hippocampal volume between carriers and non-carriers was most pronounced before age 65 (Fig. 2). Thereafter, the difference was attenuated, possibly as a function of age-related hippocampal atrophy in the APOE e3 e3 group. Taken together, the present study and that of Tohgi et al. [41] suggest early-onset hippocampal atrophy in subjects at genetic risk for AD. It cannot be ruled out, however, that APOE e4 carriers have a smaller hippocampal volume already from birth or early childhood. A related issue is whether reduced hippocampal volume in persons diagnosed with posttraumatic stress disorder is a consequence of exposure to stress or a trait that make some individuals more vulnerable to stress; there is some evidence that smaller hippocampal volume is a pre-existing vulnerability factor rather than a consequence [14]. Studies with even younger subjects than those included in this study will be needed to address this issue.

A behavioral consequence of smaller right hippocampal volume in APOE e4 e4 carriers seems to be a heightened false-alarm rate in tests of recognition memory. That is, the APOE e4 e4 carriers exhibited an increased tendency to say that non-studied items were familiar. This finding may relate to difficulties assessing relative novelty/familiarity. There is ample evidence that hippocampus, notably right hippocampus, is implicated in novelty detection [21,25,36,37,43,44]. Novel items tend to be remembered better than familiar items [42,45] but this novelty advantage (in terms of recognition accuracy) was reported to be eliminated in patients with medial temporal lobe damage [17]. In line with this, it has been argued that intact hippocampal function is particularly critical for correctly rejecting novel (i.e. non-studied) words in tests of recognition performance [19]. Relatedly, increased false-alarm rates have been associated with an increased reliance on familiarity-based processes, and a decrease of conscious, recollective operations in making recognition judgments [2]. Towards this end, it is of interest to note that hippocampal activation during recognition was greater for items where subjects had a vivid recollection of the encoding situation than for items that merely evoked a feeling of familiarity [9]. Substantiating this link further, in a study of schizophrenic patients, Weiss et al. [46] found that right hippocampal atrophy correlated with false-alarm rate.

In summary, the present results indicate that relatively young individuals at genetic risk for AD have smaller hippocampal volume, which seems to translate into certain memory deficits. An...
important task for future research will be to determine whether smaller hippocampal volume in APOE ε4 carriers represents early-onset atrophy or an inherent trait.

Acknowledgements


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