

Reduced hippocampal volume in non-demented carriers of the *apolipoprotein E* $\epsilon 4$: Relation to chronological age and recognition memory

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Abstract

Apolipoprotein E $\epsilon 4$ (*APOE* $\epsilon 4$) 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* $\epsilon 4$ 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* $\epsilon 4$ (age range: 49–79 years). We observed reduced right hippocampal volume in *APOE* $\epsilon 4$ carriers, and found that the difference was most pronounced before the age of 65. Further, the *APOE* $\epsilon 4$ 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. © 2005 Elsevier Ireland Ltd. All rights reserved.

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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 hippocam-

pus 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* $\epsilon 4$) as a major genetic risk factor for AD [8,31,38]. There are three different *APOE* isoforms: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. In western European and white American populations the allele frequencies of these isoforms are approximately 8, 78, and 14%, respectively [16,22]. Whereas *APOE* $\epsilon 2$ appears to be protective, *APOE* $\epsilon 4$ 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* $\epsilon 4$ is associated with more prominent hippocampal atrophy compared to other isoforms. This has been documented for AD patients [18] as

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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* $\epsilon 4$ 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* $\epsilon 4$. They noted that the lack of difference in cognitive functioning was inconsistent with previous findings of impaired cognitive performance in non-demented *APOE* $\epsilon 4$ 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* $\epsilon 4$; 10 were homozygotic (*APOE* $\epsilon 4/4$) and 20 were heterozygotic (*APOE* $\epsilon 4/3$). The remaining 30 subjects carried two copies of the *APOE* $\epsilon 3$ 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 recognition–memory test.

A T1-weighted 3D gradient echo sequence was used for the structural scans (TR = 24 ms, TE = 6 ms, flip angle = 35°, FOV = 180 mm × 180 mm). One hundred and twenty-four coro-

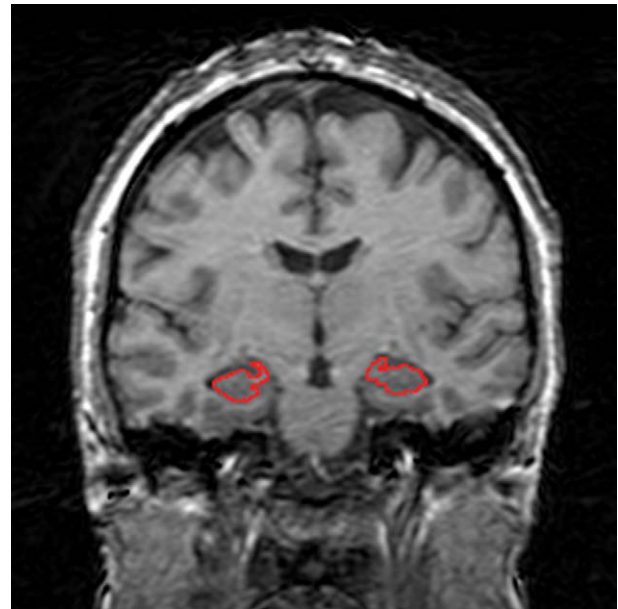


Fig. 1. The hippocampus was manually outlined on coronal MRI slices.

nal slices with a slice thickness of 1.8 mm 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 mammillary 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* $\epsilon 4$ carriers. The results from

Table 1
Demographic factors

	<i>APOE</i> $\epsilon 4$ (N = 30)	<i>APOE</i> $\epsilon 3/3$ (N = 30)
Female/male	19/11	18/12
Age	65.3 (7.9)	66.6 (8.3)
Range	49–74	49–79
Education (year)	10.6 (3.5)	10.2 (3.3)
Range	6–17	6–16
MMSE	28.2 (1.5)	27.9 (1.7)
Range	24–30	24–30
SRB	25.0 (2.4)	22.6 (4.8)
Range	16–29	11–29

Means and standard deviations (in parenthesis). MMSE = Mini-Mental State Examination (maximum = 30). SRB = vocabulary test (maximum = 30).

Table 2
Comparison of memory test performance and the hippocampal size

	<i>APOE</i> ϵ 4	<i>APOE</i> ϵ 3/3	<i>P</i>
Post-scan recognition test			
Hits ^a (%)	78.0 (14.3)	74.7 (13.8)	0.18
False alarms ^b (%)	33.0 (20.9)	24.5 (17.2)	0.05*
Hits – false alarms ^c (%)	61.5 (11.0)	62.5 (13.2)	0.39
Hippocampus volume (mm ³)			
Right	2823 (328)	2952 (384)	0.09
Left	2758 (295)	2759 (317)	0.49
Total	5581 (539)	5711 (641)	0.20

^a Correctly recognized items (max = 160).

^b New items (presented for the first time) that are incorrectly claimed to be recognized (max = 80).

^c Total number of hits – false alarms represents overall recognition accuracy (max = 160), X% = (hits – false alarms/160) × 100. Means and standard deviations (in parenthesis).

* $P < 0.05$, Student's *t*-test, one-tailed.

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 hippocampal volumes revealed an effect in the expected direction (*APOE* ϵ 4 < *APOE* ϵ 3/3) for the right but not the left hippocampus (Table 2). Importantly, right hippocampal volume was significantly correlated with numbers of false alarms in the *APOE* ϵ 4 group ($r = -0.5$, $P < 0.01$, two-tailed) but not in the *APOE* ϵ 3/3 group ($r = -0.15$, $P > 0.40$).

Analyses of the correlation between hippocampal volume and chronological age revealed a significant relationship in the *APOE* ϵ 3/3 group (right HC: $r = -0.31$, left HC: $r = -0.37$, $P < 0.05$, one-tailed), but not in the *APOE* ϵ 4 group (right HC: $r = -0.05$, $P > 0.30$, one-tailed; left HC: $r = -0.28$, $P > 0.05$, one-tailed). This pattern of correlation suggests that hippocampal volume decreased with age in the *APOE* ϵ 3/3 group but not in the *APOE* ϵ 4 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 [$t(19) = 1.8$, $P < 0.05$, 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* ϵ 4 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* ϵ 3/3 group. Taken together, the present study and that of Tohogi et al. [41] suggest early-onset hippocampal atrophy in subjects at genetic risk for AD. It cannot be ruled out, however, that *APOE* ϵ 4 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

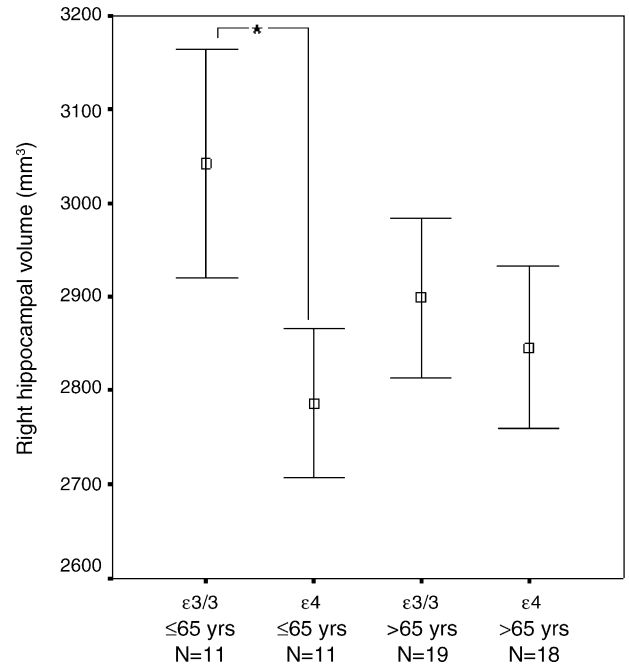


Fig. 2. Group differences in hippocampal volume as a function of *APOE* (ϵ 4 vs. ϵ 3/3) and chronological age (≤ 65 years vs. > 65 years). Bars show mean ± 1 standard error of the mean. * $P < 0.05$, Student's *t*-test, one-tailed.

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* ϵ 4 carriers seems to be a heightened false-alarm rate in tests of recognition memory. That is, the *APOE* ϵ 4 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* ϵ 4 carriers represents early-onset atrophy or an inherent trait.

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