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Better Memory and Neural Efficiency in Young Apolipoprotein E *ε4* Carriers

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The apolipoprotein E (*APOE*) *ε4* allele is the major genetic risk factor for Alzheimer's disease, but an *APOE* effect on memory performance and memory-related neurophysiology in young, healthy subjects is unknown. We found an association of *APOE ε4* with better episodic memory compared with *APOE ε2* and *ε3* in 340 young, healthy persons. Neuroimaging was performed in a subset of 34 memory-matched individuals to study genetic effects on memory-related brain activity independently of differential performance. E4 carriers decreased brain activity over 3 learning runs, whereas *ε2* and *ε3* carriers increased activity. This smaller neural investment of *ε4* carriers into learning reappeared during retrieval: *ε4* carriers exhibited reduced retrieval-related activity with equal retrieval performance. *APOE* isoforms had no differential effects on cognitive measures other than memory, brain volumes, and brain activity related to working memory. We suggest that *APOE ε4* is associated with good episodic memory and an economic use of memory-related neural resources in young, healthy humans.

Keywords: Alzheimer's disease, *APOE* gene, functional magnetic resonance imaging, hippocampus, learning, neuroimaging

Introduction

The *APOE ε4* allele (*APOE4*) has an extensive record of deleterious effects on several biological processes. The possession of at least one *ε4* allele increases the risk of Alzheimer's disease (AD) (Saunders et al. 1993) 3-fold, presumably through an association of *APOE4* with the pathological hallmarks of AD, amyloid plaque deposition, and neurofibrillary tangle formation (Ghebremedhin et al. 1998, 2001; Bennett et al. 2003, 2005; Tiraboschi et al. 2004; Thal et al. 2005). In contrast, the possession of an *ε2* allele appears to confer a protective effect against AD and AD-related neuropathology (Corder et al. 1994). Moreover, *APOE*2 is associated with a reduced decline of episodic memory in older persons (Wilson et al. 2002), whereas *APOE4* exerts detrimental effects in middle-aged and older subjects on memory performance (Hyman et al. 1996; Baxter et al. 2003), visual attention (Greenwood et al. 2000), executive functions (Rosen et al. 2005), memory-related brain activity (Bookheimer et al. 2000; Bondi et al. 2005; Trivedi et al. 2006), and resting brain glucose metabolism (Reiman et al. 2001, 2005). *APOE4* has also been experimentally related to impaired hippocampal plasticity (Levi et al. 2003) and lower density of dendritic spines (Ji et al. 2003) in aged transgenic mice and to increased neurotoxicity (Qiu et al. 2003) in vitro.

Although the frequency of the *APOE4* allele is low in humans (15% in Caucasians), studies in primates suggest that it is the ancestral allele (Finch and Sapolsky 1999). The common (75% in Caucasians) and uniquely human *APOE*3 allele appeared as a mutation, and its frequency increased during human evolution (Finch and Sapolsky 1999). Because the *APOE4* allele has been related to several deleterious biological effects, the question arises why it existed in the first place (Finch and Sapolsky 1999). From an evolutionary point of view, a possible advantageous effect of the *APOE4* allele in childhood and early adulthood could explain its existence and further persistence in humans. Support for this notion comes from studies where *APOE4* has been associated with higher IQ scores (Yu et al. 2000), a higher educational level (Hubacek et al. 2001), a reduced cardiovascular response to experimentally induced stress (Ravaja et al. 1997), and a protective effect against spontaneous abortion during embryogenesis (Zetterberg et al. 2002) and against perinatal death (Becher et al. 2006). Advantageous effects of the *APOE4* allele have also been found for memory-related functions in young animals. Hippocampal long-term potentiation (LTP) was enhanced at a young age in knock-in mice lacking mouse *APOE* but instead expressing human *APOE4* (Kitamura et al. 2004). This LTP enhancement was age dependent and disappeared in adult knock-in mice. Moreover, *APOE4*, but not *APOE*3, stimulated the transcriptional activity of cyclic adenosine 3′,5′-monophosphate response element-binding protein (CREB) by activating the extracellular signal-regulated kinase (ERK) cascade in rat primary hippocampal neurons (Ohkubo et al. 2001).

As yet, *APOE* effects on human memory at young age are unexplored. Here we combined human genetics with memory assessments and functional magnetic resonance imaging (fMRI) and structural magnetic resonance imaging (sMRI) to address the following questions: Does the *APOE ε4* allele have an effect on episodic memory performance in young adults? Do *APOE ε4* carriers exhibit altered learning- and memory-related brain activity compared with *APOE ε4* noncarriers within the medial temporal lobe? Our a priori hypothesis focused on the medial temporal lobe for 3 reasons: 1) the medial temporal lobe is the region where first neurofibrillary tangles can be detected in the course of AD (Ohm et al. 1995; Braak H and Braak E 1996; Delacourte et al. 1999), 2) alterations in the memory-related fMRI signal have been detected in the medial temporal lobe of healthy elderly *APOE ε4* carriers (Bookheimer et al. 2000; Bondi et al. 2005), and 3) hippocampal LTP has been found enhanced in young knockin mice expressing human *APOE4* (Kitamura et al. 2004). We also measured brain activity during a working memory task to find out whether potentially altered brain activity levels in *APOE ε4* carriers are restricted to episodic memory or extend to other forms of memory. Furthermore, we examined whether the *APOE ε4* allele influences brain morphology and cognitive functions other than memory functions.

We were testing for behavioral effects of the *APOE* gene's 3 allelic variants on verbal episodic learning and retrieval in

a large sample of 340 healthy young adults. Effects of the *APOE* gene's allelic variants on memory-related neurophysiology and brain morphology were then examined with fMRI and sMRI in 34 memory-matched subjects (see Materials and Methods) of the 340 original subjects. These 34 subjects underwent one fMRI experiment on episodic memory (Fig. 1) and a second fMRI experiment on working memory. Finally, the 34 subjects underwent an extensive neuropsychological assessment to uncover potential associations of *APOE* allele status with intelligence, executive functions, and spatial cognition.

Materials and Methods

Subjects

The large sample consisted of 340 healthy human subjects with an age of 22.8 ± 4 (mean ± standard deviation [SD]) years. There were no significant differences between *APOE ε4* carriers and *APOE ε4* noncarriers regarding age, gender, and education ($P \geq 0.2$; *APOE ε4* carriers [$n = 87$]: age 22.8 ± 3.9 years, sex 62 [71%] females, education 54 [62%] academics; *APOE ε4* noncarriers [$n = 253$]: age 22.8 ± 4.2 years; sex 171 [68%] females, education 177 [70%] academics). Information on genotyping procedures is provided elsewhere (de Quervain et al. 2003).

34 subjects (mean age 22.3, SD 2.53) participated in the fMRI experiments; 11 carried the *ε2/ε3* genotype, 10 the *ε3/ε3* genotype, and 13 the *ε3/ε4* genotype (Table 1). Importantly, these subjects were drawn from the large sample such that no statistically significant differences resulted between groups for age, years of education, the His452Tyr polymorphism of the 5-HT2a receptor–encoding gene (the His452Tyr polymorphism has been associated with poorer memory, see de Quervain et al. 2003), and the 5-min words recall performance in the previously applied verbal memory test (Table 1). The reason why we matched the 3 genotype groups for memory performance was to eliminate performance-related brain activity differences in order to sample only genetic effects on brain activity. The subjects reported neither past nor current psychiatric or neurological problems and denied taking illegal drugs or prescription medication. All subjects gave written informed consent to participate in the study after the nature and possible consequences of the study had been explained. The experiments were approved by the local ethics committee.

Experimental Procedure—Large Sample

The 340 subjects viewed 6 sets of words, each set containing 5 semantically unrelated nouns. These nouns were visually presented at a rate of one word per second. Subjects were instructed to learn the 5 nouns of a set for immediate free recall from short-term memory. An immediate free recall test followed the presentation of each of the 6 sets. In cognitive psychology, short-term memory is conceived as a limited capacity store capable of holding only about 7 "items" by the operation of rehearsal. Should rehearsal be interrupted, the material has a half-life of about 10–20 s (Reber 1995). Following the completion of the 6 sets, subjects performed a distracter task that kept them busy over 5 min. Thereafter, subjects engaged in a surprise delayed free recall test of the 30 studied nouns. Because this free recall followed a 5-min interval of distraction, it clearly exceeds short-term memory capacity and instead challenges episodic memory. Episodic memory is dependent on the intact functioning of the hippocampus (Scoville and Milner 1957; Squire and Alvarez 1995).

Association studies in outbred populations such as the present one may be prone to false positivity because nonrandom genetic heterogeneity within the study sample (i.e., hidden population structure) can lead to spurious associations between a candidate marker and a phenotype. Hidden population structure within the study sample may be a result of sampling bias (an extreme example for such a condition would be to recruit both Caucasian participants and participants of Asian origin and to consider them as one homogenous group). In this case, alleles of high frequency in one subpopulation would be associated with any phenotype that is most prevalent in this one subpopulation. Thus, a subtle and unequal ethnic admixture may lead to spurious, false-positive associations with the phenotype of interest. Because allele frequencies at random marker loci may differ among ethnic groups, a consistent pattern of allele frequency differences between phenotypic groups will be detected if these groups are not well

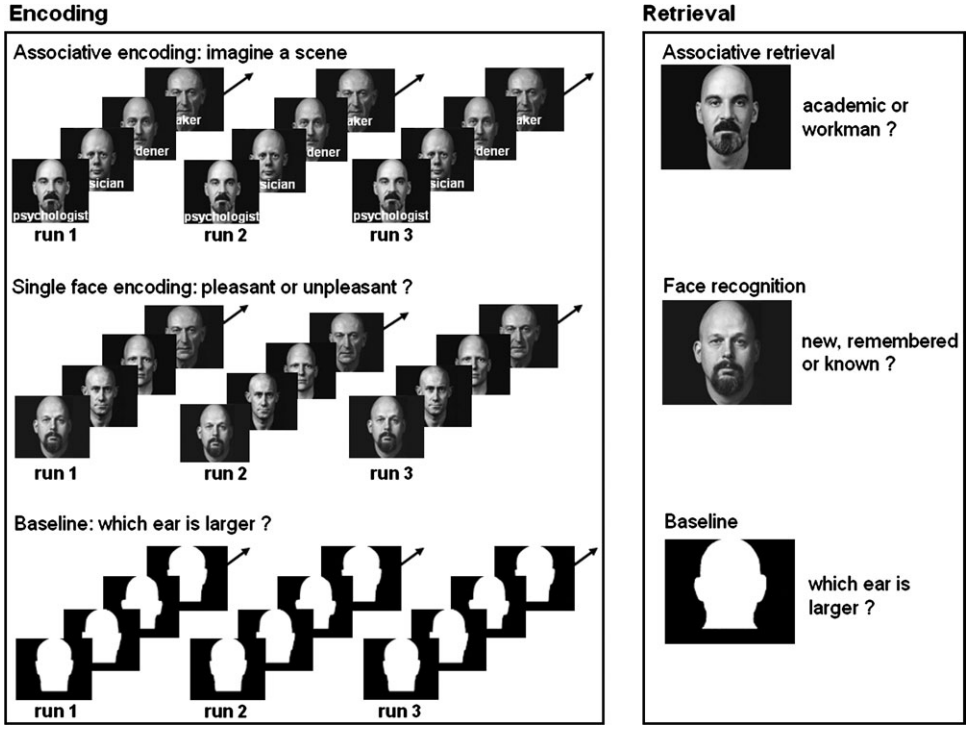

Figure 1. Study design. Left side (encoding fMRI time series): Displayed are examples of stimuli presented for associative learning, single-face learning, and the visual baseline task. Each stimulus appeared once in each run. Right side (retrieval fMRI time series): Displayed are examples of stimuli presented for associative retrieval, face recognition, and the visual baseline task. Alex Kayser granted us permission to use and reproduce faces from his book "Heads," 1985, New York: Abbeville Press.

Table 1
Matched *APOE* groups

APOE	ε2/ε3 (n = 11)	ε3/ε3 (n = 10)	ε3/ε4 (n = 13)
Age[a]	22.7 ± 1.7	21.6 ± 1.7	22.6 ± 3.5
Years of education[a]	14.5 ± 1.3	13.8 ± 1.5	14.3 ± 1.7
Words delayed recall[a]	7.2 ± 1.7	7.6 ± 2.7	7.7 ± 2.9
Sex (m/f)[b]	2/9	4/6	7/6
Handedness (R/L/A)[b]	11/0/0	8/2/0	11/1/1
His452Tyr[b]	4	4	5

Note: His452Tyr, polymorphism in the 5HT2a receptor-encoding gene. Carriers of this rare variant (His/Tyr) showed reduced memory performance (see de Quervain et al. 2003) when compared with homozygous carriers of the common variant (His/His). m/f, male/female; R/L/A, right/left/ambidextrous.
[a]values = means ± SD.
[b]values = number of subjects.

matched. Conversely, if the phenotypic groups are well matched, significant allele frequency differences will be located only near phenotype-related loci. We calculated the hidden population structure with the structured association method that uses unlinked genetic markers to detect possible population stratification (Pritchard and Rosenberg 1999). To this aim, we genotyped each subject for 55 random single nucleotide polymorphims distributed over the autosomes. This analysis revealed a low allele frequency divergence in our population (Kullback-Leibler distance = 0.15) and excluded nonrandom, gross genetic heterogeneity as a potential source of false positivity.

Experimental Procedure—Small Sample

Subjects were examined in 2 sessions. The first session took place in the magnetic resonance (MR) center and comprised the fMRI and sMRI examinations. Upon arrival, subjects took a medical questionnaire and practiced the fMRI tasks outside the scanner till they felt comfortable with task instructions and response mode. Then they were placed in the MR scanner and underwent the 2 fMRI experiments. The first fMRI experiment was the episodic memory experiment and the second the working memory experiment. In both fMRI experiments, trials were blocked per condition. Stimuli were the same for all subjects to avoid intersubject variance caused by stimulus-generated effects. Responses were collected with a response box that subjects held in their dominant hand. Finally, 2 anatomical brain scans were performed for the volumetric analyses. The second session followed 1–3 months (mean: 1 month) later and included an extensive neuropsychological assessment.

The fMRI Experiment on Episodic Memory—Encoding

We presented 16 face–profession pairs in the associative learning condition, 16 faces in the single-face–learning condition, and 24 head contours without physiognomy in the visual baseline condition (Fig. 1). All stimuli of the 3 conditions were presented in 12 task blocks (4 blocks per condition) in a first learning run consisting of one fMRI time series that ran over 6 min. This learning run/time series was repeated twice such that each stimulus was presented a total of 3 times within its condition—a condition comprising the stimulus presentations in all learning runs/fMRI time series. The 3 learning runs allowed us to monitor genotype-induced brain activity differences during the progressively deeper encoding of the material. The sequence of task blocks within a learning run/time series was counterbalanced across subjects but kept constant within subjects over learning runs/time series. In the 2 learning conditions, a task block contained 4 trials of 6 s each. In the visual baseline condition, a task block contained 6 trials of 4 s each. Consequently, each task block took 24 s. Instruction slides were presented for 6 s to announce each task block. The instruction for associative learning of the face–profession pairs was to imagine the presented person acting in a scene of the written profession. Subjects answered by button press whether they found it easy or hard to imagine a scene. The imagination of a scene automatically leads to the establishment of semantic person–occupation associations and activates the hippocampal formation (Degonda et al. 2005). Importantly, subjects were requested to imagine the same scene for a given face–profession pair during learning runs 2 and 3 as during run 1. This additional retrieval component in runs 2 and 3 was to enhance potential memory-related differences between genotype groups. The instruction for the learning of single faces was to decide whether a face was pleasant or unpleasant. This task leads to a semantic encoding of faces. The visual baseline task was to decide whether the area of the left or right ear was larger.

The fMRI Experiment on Episodic Memory—Retrieval

We applied a single fMRI time series for the retrieval of the previously learned face–profession associations and faces. This time series included an associative retrieval condition, a face recognition condition including the studied faces, a new face (distracter faces) detection condition, and the same visual baseline condition that was used for the encoding time series (Fig. 1). For the retrieval of the associations, the previously presented faces were shown again (without the professions) as retrieval cues with the instruction to recall each person's occupation and to indicate the superordinate professional category by button press: academic or workman. For the retrieval of the faces, we used a recognition test including the remember–know procedure (Tulving 1985; Gardiner 1988) to separate between full recollection (remember) and mere familiarity (know) with faces. Subjects were instructed to indicate by button press whether a face was fully remembered (remember) or appeared just familiar (know) or was completely new (Tulving 1985; Gardiner 1988). To conform to the standard fMRI block design, studied faces and new faces were presented in separate blocks. This procedure allowed for the measurement of fMRI signal solely related to either the recognition of old faces or the detection of new faces. A randomized presentation sequence of old and new faces, as typically used for recognition tasks, would have necessitated an event-related fMRI design. Yet, the number of stimuli required for the statistical analysis of event-related fMRI data exceeds normal mnemonic capacities in our difficult paired-associates learning task.

The sequence of task blocks within the fMRI time series was counterbalanced across subjects. All conditions, except for the visual baseline condition (see above), consisted of 4 blocks, each block including 4 trials of 6 s each. All task blocks took 24 s and were announced by an instruction slide.

The fMRI Experiment on Working Memory

The experiment included one fMRI time series with a 2-back task for the assessment of working memory and a baseline task (x-target) for the assessment of concentration. The 2-back task required subjects to respond to a letter repeat with one intervening letter (e.g., **S**–f–**s**–g). The "x-target" task required subjects to respond to the occurrence of the letter "x." Each task was given in 5 blocks of 26 s each. Blocks were announced by an instruction slide. Stimuli were 50 upper- or lowercase letters typed in black on a white background. Thirteen upper- or lowercase letters were presented per block for the duration of 2 s each.

The fMRI Data Acquisition

MR measurements were performed on a 3-T Philips Intera whole body MR scanner equipped with an 8-channel Philips sensitivity-encoded (SENSE) head coil. Functional data were obtained from 32 transverse slices parallel to the AC–PC plane covering the whole brain with a measured spatial resolution of 2.8 × 2.8 × 4 mm^3 (acquisition matrix 80 × 80) and a reconstructed resolution of 1.7 × 1.7 × 4 mm^3. Data were acquired using a SENSE-single-shot echo planar imaging (Schmidt et al. 2005) sequence with an acceleration factor of R = 2.0. Other scan parameters were echo time (TE) = 35 ms, repetition time (TR) = 3000 ms, and flip angle θ = 82°. A standard 3-dimensional (3D) T_1-weighted scan was obtained for anatomical reference with a measured spatial resolution of 1 × 1 × 1.5 mm^3 (acquisition matrix 224 × 224) and a reconstructed resolution of 0.9 × 0.9 × 0.8 mm^3, TE = 2.3 ms, TR = 20 ms, θ = 20°, and no interslice gaps. A multislice T_1-weighted inversion-recovery anatomical scan, oriented perpendicularly to the long axis of the hippocampus, was obtained for hippocampal and parahippocampal volumetry over 33–39 slices with a measured spatial resolution of 0.5 × 0.6 × 1.5 mm^3 (acquisition matrix 400 × 320) and a reconstructed spatial resolution of 0.4 × 0.4 × 1.5 mm^3, TE = 15 ms, TR = 4200 ms, θ = 20°, inversion recovery delay = 400 ms, and no interslice gaps.

The fMRI Data Analysis

Image pre- and postprocessing and the statistical analyses were performed with SPM2 (http://www.fil.ion.ucl.ac.uk/spm). Standard

preprocessing procedures were applied, realignment, normalization, and spatial smoothing (8 mm) (Friston, Ashburner, et al. 1995). On the single-subject level, data were analyzed according to the fixed effects model (SPM2). The 6 head movement parameters were included in the model as confounding factors. Data were high-pass filtered with a specific filter value for each fMRI time series. This value was determined according to 2 × stimulus onset asynchrony × TR. On the second level, within-subject contrasts were entered into random effects analyses (analyses of variance [ANOVAs], *T*-tests, SPM2), which account for variance between subjects (Friston, Holmes, et al. 1995). We also computed correlations between the within-subject encoding contrasts (learning run 1–run 3) and behavioral measures (simple regression, SPM2). To determine the brain areas commonly activated in all *APOE* groups during working memory (2-back task vs. x-target task), we computed a conjunction analysis. To this aim, we inclusively masked the summed activation maps of all *APOE* groups in the ANOVA with the activation maps of each single *APOE* group in the ANOVA. The mask *P* value was 0.001, uncorrected. All thresholds were set at $P = 0.001$, uncorrected for multiple comparisons. An exception was made for the region of interest, the hippocampus, where the analyses were also run with the lower threshold of $P = 0.005$. This lower threshold is indicated where applicable. No region-of-interest analyses were computed with the fMRI data.

Analysis of Anatomical Magnetic Resonance Imaging Data

Based on the 3D T_1-weighted sMRI images, which covered the whole brain, volumes of the total gray and white matter were computed with SPM2. Images were first normalized to the Montreal Neurological Institute T_1 template using a standard bounding box and then segmented into gray matter, white matter, and cerebrospinal fluid. Standardized gray and white matter volumes were then multiplied by the determinant of the linear transformation matrix to obtain gray and white matter volumes in cubic centimeter. Based on the multislice T_1-weighted high-resolution sMRI images, 2 independent raters (A.B. and H.M.) manually delineated the hippocampal formation (Henke, Kroll, et al. 1999) [cornu ammonis CA] regions, dentate gyrus, and subiculum, excluding the fimbria) and the parahippocampal gyrus using the software Pmod (http://www.pmod.com.). Cerebrospinal fluid was carefully excluded that resulted in conservative volume estimates. Raters relied on descriptions of anatomical landmarks and subdivisions of the medial temporal lobe as described by Duvernoy (1998) and Insausti et al. (1998). Interrater reliabilities ranged between $r = 0.8$ and 0.98. ANOVAs with *APOE* genotype and sex as independent variables were computed to determine group differences in brain volumes. Thresholds were set at $P < 0.05$ level, uncorrected for multiple comparisons (6 subjects were excluded from this analysis because of data loss).

Neuropsychology

Memory functions were assessed with the Wechsler Memory Scale Revised (Härting et al. 2000) in German and with a difficult verbal paired-associates word-learning test (Henke, Weber, et al. 1999). Intelligence was measured with the Hamburg Wechsler Intelligence Scale Revised Test (Tewes 1991). Spatial thinking abilities were tested with the Luria Mental Rotation Test (Christensen 1979). Executive functions were assessed with a verbal (S words) and nonverbal (5 point) fluency task (Regard et al. 1982), with the Kramer Card Sorting Test (Kramer 1970), which measures concept finding and shifting abilities, and with the Stroop Test (Stroop 1935), which measures the suppression of interference. ANOVAs with the *APOE* genotype as an independent variable were computed to determine group differences in cognitive performance. Thresholds were set at $P < 0.05$ level, uncorrected for multiple comparisons (one subject was excluded from this analysis because of noncompliance).

Results

Behavioral Results—Large Sample

The *APOE4* carriers, compared with *APOE4* noncarriers, exhibited better performance in the delayed but not the immediate recall (IR) of the 30 studied words (odds ratio = 1.6, $P = 0.009$; Fig. 2*a*). This result remained significant after excluding 6 homozygous *ε4* allele carriers from the analysis (odds ratio = 1.6, $P = 0.023$). Because the delayed recall of 30 words following only one stimulus presentation is difficult, our subjects' performance was rather low ranging around 25%. The recalled words derived from all sets of nouns, not just the last set. Multiple linear regression analysis revealed a significant linear relationship between the presence of no, 1, or 2 *ε4* alleles and the delayed recall of words ($\beta_{standardized} = 0.118$, $P = 0.023$; Fig. 2*b*). These performance differences in the delayed recall test are probably not attributable to differences in motivation or attention because the IR of words was comparable between genotype groups.

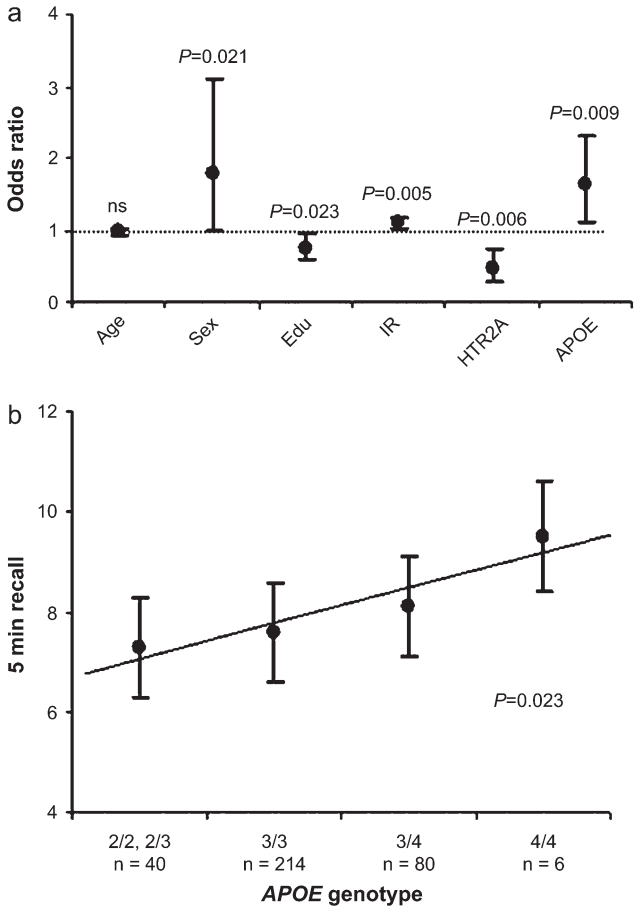

Figure 2. *APOE* effects on verbal memory in 340 subjects. (*a*) Displayed are forward and backward logistic regression analyses after median split for the 5-min recall of words (dependent variable). Factors significantly associated with better memory performance (>median of 8) were female sex, good immediate recall (IR), and the *APOE* ε4 allele. Dotted line indicates odds ratio of 1. Error bars reflect 95% confidence interval of odds ratio per independent variable. Edu, education. (*b*) Displayed are multiple forward and backward linear regression analyses with the 5-min recall performance as the dependent variable, adjusted for sex, education, immediate recall and the His452Tyr substitution of the HTR2A gene, which has been related to memory performance (de Quervain et al. 2003). Dots depict mean, bars depict standard error of mean. Forty subjects carried either the *ε2/ε2* or the *ε2/ε3* variant, 214 subjects the *ε3/ε3* variant, 80 subjects the *ε3/ε4* variant, and 6 subjects the *ε4/ε4* variant.

Behavioral Results—Small Sample

In the fMRI experiment on episodic memory, response latencies decreased significantly from learning run 1 to run 3 within each *APOE* group for both faces and face–profession pairs confirming effective learning in each *APOE* group. *APOE* group differences in response latencies occurred neither within nor

between runs (Table 2). The number of "easy" (to imagine) answers during associative learning increased over learning runs for each *APOE* group (Table 2; effect did not quite reach significance in *APOE* $\varepsilon 3/\varepsilon 4$ carriers with $P = 0.06$). This facilitation of imagining a scene was also indicative of effective learning over runs. There were no *APOE* group differences in the number of easy answers within or between runs. The number of "pleasant" decisions for the single faces remained constant over the 3 learning runs for each *APOE* group. *APOE* groups did not differ in the number of given pleasant answers within or between runs (Table 2). Retrieval accuracies and response latencies for faces and face–profession associations were statistically equal between *APOE* groups (Table 2).

In the fMRI experiment on working memory, neither accuracy nor response latency differed significantly between *APOE* groups for the x-target and the 2-back task (Supplementary Table S1).

Performance measures acquired during the neuropsychological examination of the 34 subjects—measures of memory, intelligence, spatial cognition, and executive functions—were also statistically equal between *APOE* groups (Supplementary Table S2).

Imaging Results—Small Sample

One-sample *t*-tests including all 34 subjects revealed brain activation in a memory-related neocortical network and robust bilateral hippocampal activation for face–profession associative learning and for single-face learning (each compared with the visual baseline condition) supporting previous evidence (Degonda et al. 2005) that our tasks reliably activate the hippocampus (Fig. 3). One-way ANOVAs (SPM2) with the *APOE* genotype as independent variable and contrasts for associative and single-face learning/retrieval and working memory as dependent variables were followed by post hoc *t*-tests between the $\varepsilon 3/\varepsilon 4$ and $\varepsilon 2/\varepsilon 3$ carriers. We directly compared the $\varepsilon 3/\varepsilon 4$ and $\varepsilon 2/\varepsilon 3$ carriers because the $\varepsilon 4$ and the $\varepsilon 2$ allele might confer opposite effects not only on the risk of AD (Corder et al. 1994) but also on the normal memory-related neurophysiology. Therefore, we were expecting to see the largest brain activity differences between the $\varepsilon 3/\varepsilon 4$ and the $\varepsilon 2/\varepsilon 3$ carriers.

Significant *APOE* group differences in the signal change from learning run 1 to run 3 were observed in both the ANOVA and the post hoc *t*-tests within bilateral hippocampus during associative learning (Table 3 and Fig. 4) and within the left hippocampus during single-face learning (Table 3). Further effects were situated in neocortical areas, namely, within the left orbital gyrus and within a left posterior middle temporal area during associative learning (Fig. 4) and within the middle frontal gyrus during single-face learning (Table 3). Whereas the $\varepsilon 3/\varepsilon 4$ carriers decreased their learning-related hippocampal and neocortical activity from the first to the third learning run, the $\varepsilon 2/\varepsilon 3$ carriers increased their learning-related hippocampal and neocortical activity from the first to the third learning run (Fig. 4). These differences in the slope of activity changes between the $\varepsilon 3/\varepsilon 4$ and $\varepsilon 2/\varepsilon 3$ carriers over learning runs were not caused by unequal starting levels of brain activity during the first run of associative learning and single-face learning because the comparison of run 1 brain activity (vs. the visual baseline condition) barely revealed significant differences between $\varepsilon 3/\varepsilon 4$ and $\varepsilon 2/\varepsilon 3$ carriers (Fig. 5). One-sample *t*-tests computed for each *APOE* group revealed that $\varepsilon 2/\varepsilon 3$ and $\varepsilon 3/\varepsilon 3$ carriers exhibited transcortical activity increases (contrast run 3–run 1) during repeated associative and single-face learning, whereas $\varepsilon 3/\varepsilon 4$

Table 2
ANOVA on the groups' latency and accuracy values in the learning and retrieval tasks

	$\varepsilon 2/\varepsilon 3$	$\varepsilon 3/\varepsilon 3$	$\varepsilon 3/\varepsilon 4$	*F*	*P*
Associative learning					
# easy (run 1)	8.9 ± 2.2	8.6 ± 2.5	8.8 ± 2.1	0.5	0.951
# easy (run 2)	9.3 ± 2.8	9.9 ± 2.6	8.9 ± 1.8	0.465	0.632
# easy (run 3)	10.9 ± 1.9	10.4 ± 2.9	10.8 ± 2.9	0.104	0.902
# easy (run 1–run 3)	−2 ± 2*	−1.8 ± 2.3*	−1.7 ± 2.8	0.056	0.946
RT run 1	3212.6 ± 841	3179.1 ± 599.5	3164.5 ± 624.9	0.015	0.985
RT run 2	2944.8 ± 922	2934.4 ± 514.4	2884.2 ± 639.9	0.261	0.772
RT run 3	2628.5 ± 798.5	2725 ± 706.4	2717.8 ± 840.3	0.117	0.89
RT run 1–run 3	584 ± 633.3*	454.1 ± 607*	472.9 ± 507.5*	0.158	0.855
RT run 1–run 2	267.7 ± 595.7	244.7 ± 423	366.1 ± 332.8*	0.221	0.803
RT run 2–run 3	316.3 ± 253.1*	209.5 ± 358.1	116.1 ± 331.2	1.107	0.344
Single-face learning					
# pleasant (run 1)	6.8 ± 2.9	7.2 ± 1.2	7.9 ± 3	0.566	0.573
# pleasant (run 2)	7.2 ± 3.2	6.8 ± 2.3	7.7 ± 2.8	0.267	0.768
# pleasant (run 3)	7.5 ± 2.9	7.1 ± 2	7.5 ± 3.3	0.062	0.94
# pleasant (run 1–run 3)	−0.6 ± 1.3	0.1 ± 1.2	0.5 ± 1.4	1.758	0.19
RT run 1	2132.9 ± 511.9	1945.2 ± 227	2081.5 ± 324.4	0.699	0.505
RT run 2	1924.5 ± 477.9	1944.3 ± 343.4	1963.2 ± 402.1	0.025	0.975
RT run 3	1541.8 ± 508.9	1702.5 ± 312.4	1581.6 ± 388.6	0.426	0.657
RT run 1–run 3	591.1 ± 392.8*	242.7 ± 243.4*	490.3 ± 500.4*	2.075	0.143
RT run 1–run 2	208.4 ± 340.1	0.9 ± 222.1	153.4 ± 345.3	1.237	0.305
RT run 2–run 3	382.7 ± 207.2*	241.7 ± 244.4*	314.4 ± 273.9*	0.879	0.426
Associative retrieval					
# correct	12.3 ± 2.2	11.4 ± 2.3	12.2 ± 2.4	0.442	0.647
RT correct answers	2597.1 ± 338.6	2621.9 ± 425.8	2888.1 ± 413	1.928	0.163
Single-face retrieval					
Remember answers (hits–false alarms)	10.2 ± 4.5	10.3 ± 3.1	10.2 ± 4.6	0.003	0.997
RT hits remember	1609 ± 428	2142.2 ± 415	2163.7 ± 856.1	2.857	0.073
Know answers (hits–false alarms)	2.5 ± 4.0	3.4 ± 3.2	3.3 ± 5.9	0.121	0.887
RT hits know	2513.4 ± 823	2666.1 ± 594.9	2709.7 ± 538.3	0.248	0.782

Note: Values, means ± SD; reaction times (RTs) in milliseconds.
*Paired *t*-tests between runs per *APOE* group ($P < 0.05$).

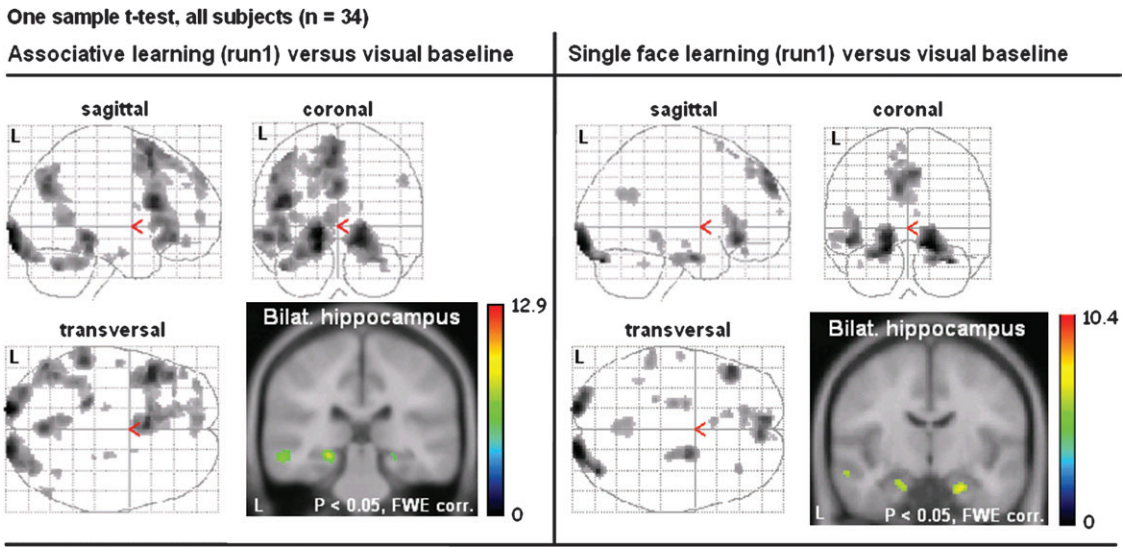

Figure 3. Learning-related brain activity in all 34 subjects (all *APOE* groups). Displayed are sagittal, coronal, and horizontal SPM2 through projections of brain regions that exhibited a significant activation during the first run of associative learning (left side) and the first run of single-face learning (right side), each compared with the visual baseline task. Bilateral hippocampal activity is displayed as color-coded statistical parametric *t*-map on Montreal Neurological Institute anatomical template.

Table 3
Brain activation differences between *APOE* groups during repeated learning and during retrieval

Brain region	Left/right	MNI coordinates (mm)			^kE	*F*	*t*
		x	*y*	*z*			
One-way ANOVA and post hoc *t*-tests							
Repeated associative learning (run 1 > run 3)							
APOE ε3/ε4 > ε2/ε3							
Hippocampus	R	30	−16	−16	8	7.66	
	R	30	−18	−16	182		4.29
	L	−22	−26	−12	9	7.07*	
	L	−22	−26	−12	15		4.01
Orbital gyrus	L	−24	28	−8	21	10.03	
	L	−24	30	−8	11		3.95
Post middle temporal area	L	−40	−54	4	71	14.67	
	L	−40	−54	4	232		6.34
APOE ε2/ε3 > ε3/ε4	No significant differences						
Repeated single-face learning (run 1 > run 3)							
APOE ε3/ε4 > ε2/ε3							
Hippocampus	L	−22	−28	−6	6	6.03*	
	L	−22	−28	−6	3		3.7
Middle frontal gyrus	L	−30	34	38	25	10.39	
	L	−30	34	38	73		5.14
APOE ε2/ε3 > ε3/ε4	No significant differences						
Associative retrieval > face recognition							
APOE ε3/ε4 > ε2/ε3	No significant differences						
APOE ε2/ε3 > ε3/ε4							
Hippocampus	R	36	−40	−4	13	8.85	
	R	34	−40	−6	16		4.01
Fusiform gyrus	L	−42	−36	−22	17	10.20	
	L	−44	−34	−24	4		3.68
Single-face retrieval > baseline							
APOE ε3/ε4 > ε2/ε3	No significant differences						
APOE ε2/ε3 > ε3/ε4							
Middle frontal gyrus	R	36	26	52	102	11.55	
	R	36	26	52	71		4.55
Superior frontal gyrus	R	6	40	54	1408	20.78	
	R	6	40	54	10		3.7
Precuneus	R	8	−48	50	10	7.66	
	R	8	−48	50	122		4.21

Note: Listed are regions with significant effects in both the 1-way ANOVA, which includes the 3 *APOE* groups, and the post hoc *t*-tests between *APOE ε3/ε4* and *ε2/ε3* carriers. *t* and *F*, values of peaks within significantly ($P < 0.001$) activated clusters of voxels; post, posterior; ^kE, cluster size (in voxels); MNI, Montreal Neurological Institute; mm, millimeters.
*$P < 0.005$.

carriers exhibited primarily decreases of brain activity from run 1 to run 3 (contrast run 1–run 3) (Fig. 6).

To determine whether the slope of learning-related brain activity changes measured over the 3 learning runs was related to retrieval success in each *APOE* group, we computed correlations between the signal change from learning run 1 to run 3 and the number of correctly remembered associations or faces (only remember responses for faces: hits–false alarms). The correlations between associative learning–related brain activity changes over learning runs and associative retrieval performance were positive (the more signal decrease during learning, the better the retrieval performance) for the *ε3/ε4* carriers but negative (the more signal increase during learning, the better retrieval performance) for the *ε2/ε3* carriers within the left hippocampus (*ε3/ε4*: $r = 0.75$; *ε2/ε3*: $r = -0.84$; Fig. 7 and Table 4) and many neocortical areas (Table 4) that were not always the same between *APOE* groups. A similar pattern of results was observed for the correlations between face learning–related brain activity changes over learning runs and face recognition accuracy (Table 5).

During retrieval, the *ε3/ε4* carriers exhibited less brain activity than the *ε2/ε3* carriers in spite of their equivalent retrieval success. The comparison of the retrieval of face–profession associations with the retrieval of single faces isolates brain activity underlying the retrieval of associations alone. In this comparison, the *ε3/ε4* carriers exhibited weaker activity increases compared with the *ε2/ε3* carriers within the right hippocampus and the left fusiform gyrus (Table 3). In the comparison of single-face retrieval with the visual baseline condition, the *ε3/ε4* carriers exhibited weaker activity increases compared with the *ε2/ε3* carriers within the right middle and superior frontal gyri and within the right precuneus (Table 3).

The working memory experiment yielded robust bilateral frontoparietal activation in each *APOE* group (Supplementary Fig. S1). Frontoparietal activity has typically been found in neuroimaging studies of working memory (for a review, see Baddeley 2003). A conjunction analysis confirmed that activity common to all 3 *APOE* groups was located in frontoparietal

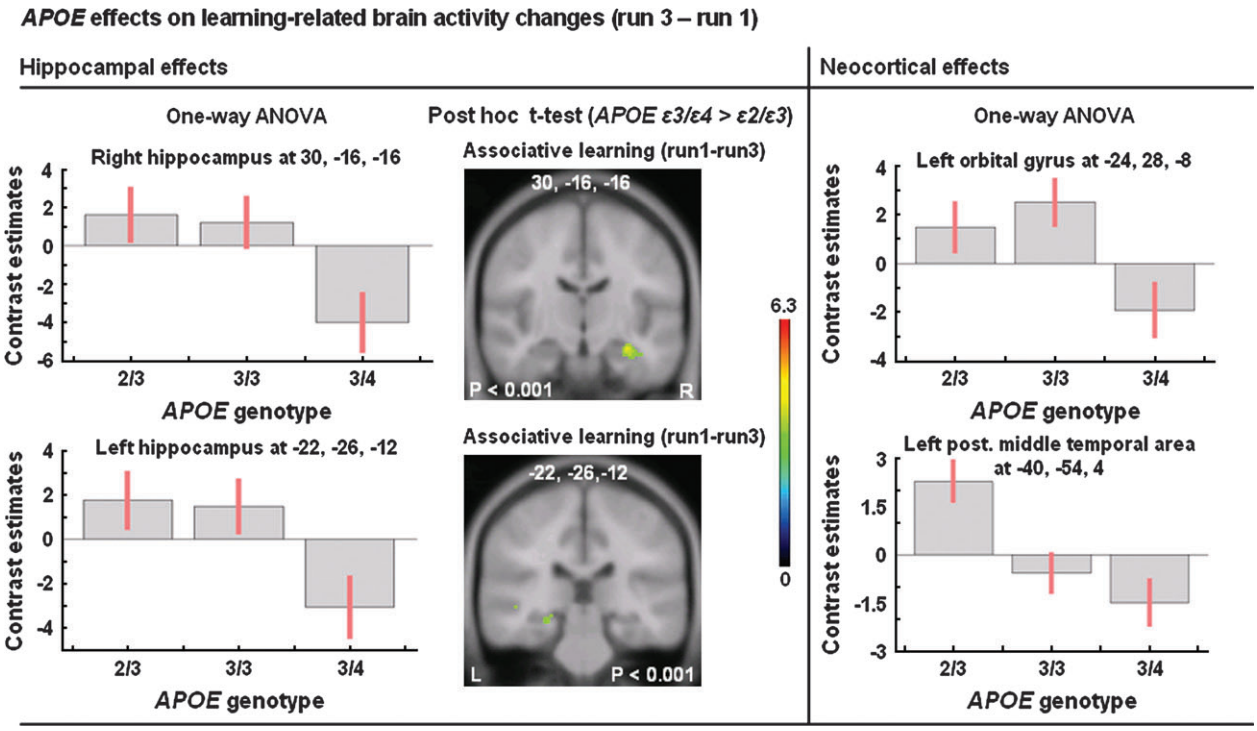

Figure 4. *APOE* effects on learning-related brain activity changes (run 3–run 1). Left panel: One-way ANOVA shows *APOE* effects on the right and left hippocampal signal changes over runs of associative learning (run 3–run 1). Columns indicate mean-corrected parameter estimates, bars depict standard error of mean parameter estimates. Post hoc 2-sample *t*-tests are showing larger right and left hippocampal signal decreases during associative learning from run 1 to run 3 in *APOE ε3/ε4* versus *APOE ε2/ε3* carriers. These results are displayed as color-coded statistical parametric *t*-maps on Montreal Neurological Institute anatomical template. Right panel: One-way ANOVA shows *APOE* effects on the activity change from run 1 to run 3 of associative learning (run 3–run 1) in the left orbital gyrus and a left posterior middle temporal area.

areas (Fig. S1 and Table S3). There were no significant MR signal differences between the *ε2/ε3* and the *ε3/ε4* carriers. Therefore, the above-reported brain activity differences between *APOE* groups during associative and single-face learning/retrieval were probably specific to episodic memory.

To determine whether *APOE* group differences in brain activity resulted from interindividual differences in the volume of gray or white brain matter, we performed volumetric analyses of the subjects' brain structures. Both automated whole brain gray and white matter segmentation (SPM2) (Ashburner and Friston 2000) and manual volume measurements of the hippocampal formation and the parahippocampal gyrus yielded comparable volumes between the 3 *APOE* groups (Supplementary Table S4).

Discussion

APOE4 is the major genetic risk factor for AD, whereas *APOE2* appears to confer a protective effect against AD. Although the frequency of the *APOE4* allele is low in humans, studies in primates suggest that *APOE4* is the ancestral allele (Finch and Sapolsky 1999). Its existence and further persistence in humans might be explained by an advantageous effect of *APOE4* in early adulthood. Here, we report an association of *APOE4* with better episodic memory performance and with smaller learning- and retrieval-related brain activity increases compared with *APOE2* and *APOE3* in young and healthy human subjects.

The direct comparison between *APOE* groups showed that, despite comparable starting levels of learning-related brain activity between *APOE* groups (Fig. 5), the *APOE ε3/ε4* carriers decreased their learning-related bilateral hippocampal, left orbital frontal, left middle frontal, and left middle temporal activities during the progressively deeper encoding of faces and associations over runs, whereas the *APOE ε2/ε3* carriers increased their learning-related activity in these regions (Fig. 4 and Table 3). This disparity in the learning-related brain activity slopes between groups was not related to differences in performance levels because all performance measures collected during the learning runs were statistically equal between the 3 *APOE* groups (Table 2). We therefore assume that the *APOE ε4* allele is associated with a more economic use of learning-related neural resources than the *APOE ε2* allele. Consequently, the *APOE ε4* allele and the *APOE ε2* allele do confer opposing effects not only on the development of AD in middle-aged individuals but also on the normal learning-related neurophysiology in young individuals. For patients with an amnestic mild cognitive impairment, that is, a transitional state between the cognitive changes of normal aging and AD (Petersen et al. 2001), Johnson et al. (2004) reported also significant differences in medial temporal activity slopes over repeated face learning compared with healthy subjects. Slopes were more negative in the controls than the patients. Furthermore, using hippocampal depth electrodes in patients with temporal lobe epilepsy, Grunwald et al. (1999) found that medial temporal N400 responses to items decreased with repetition in the intact hippocampus but not in the epileptic hippocampus. These data suggest that an economic use of learning-related neural resources characterizes a well functioning memory system.

The question arises whether the *APOE* differences in brain activity slopes reflect a differential neurophysiology underlying

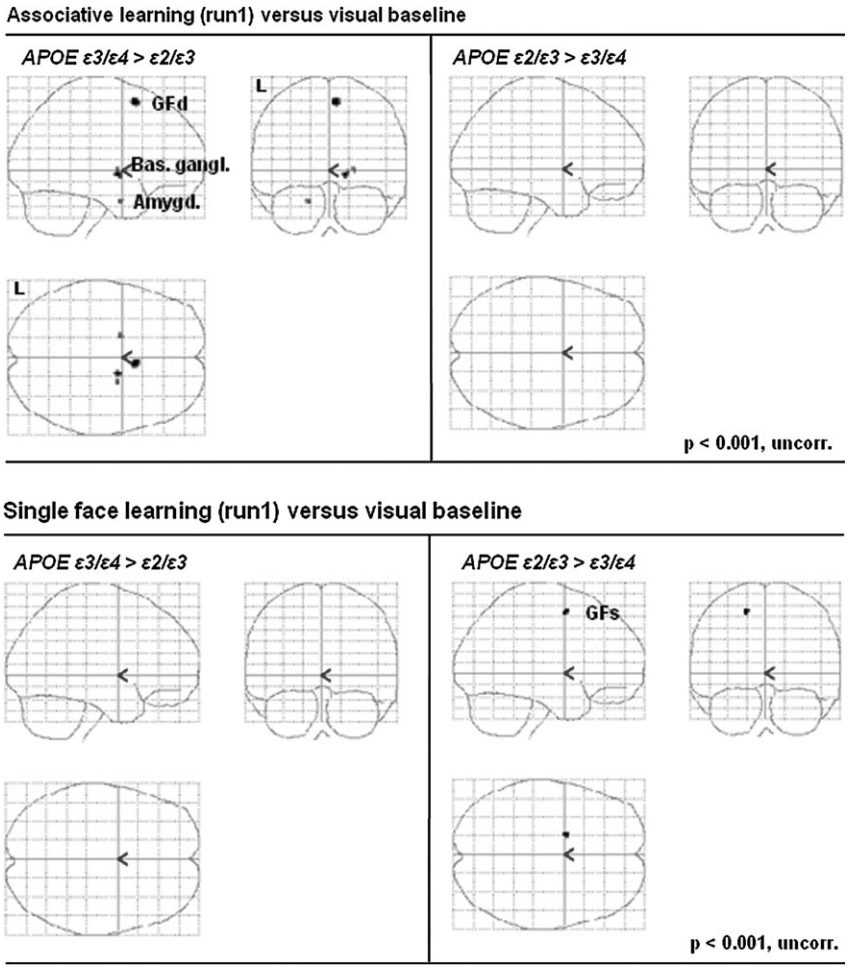

Figure 5. Comparisons between *APOE ε3/ε4* and *APOE ε2/ε3* carriers during the first associative learning run (upper panel) and during the first single-face learning run (lower panel), each versus the visual baseline task. Activity differences between *APOE* groups are shown as SPM2 through projections of brain regions in sagittal, coronal, and horizontal views. GFd, medial frontal gyrus; Bas. gangl., basal ganglia; Amygd., amygdala; GFs, superior frontal gyrus.

episodic memory or another form of memory that is simultaneously active during the learning runs. The repeated exposure to material does evoke retrieval (from previous exposure) and reencoding processes in the realm of not only episodic memory but also priming. Priming is a form of implicit/nondeclarative memory that involves a facilitation of the ability to identify, produce, or classify an item as a result of a previous encounter with that item or a related item (Schacter et al. 2004). Priming is often associated with accelerated information processing (shortening of response latencies) and decreasing neural activity over repeated exposures, as observed in our *APOE ε3/ε4* group. One could, therefore, speculate that the differential activity slopes over learning runs reflected priming more than episodic memory. We found that neither of the *APOE* groups exhibited a significant correlation of medial temporal activity slopes with the shortening of response latencies from run 1 to run 3. Instead, medial temporal (Fig. 7) and also neocortical activity slopes were correlated with retrieval success for both faces (Table 5) and face–profession associations (Table 4). Yet, the direction of these correlations appeared to distinguish the *ε3/ε4* carriers from the *ε2/ε3* carriers. Whereas correlations were positive (the more signal decrease over runs, the better retrieval performance) for the *ε3/ε4* carriers, they were negative (the more signal increase over runs, the better retrieval performance) for the *ε2/ε3* carriers. Thus, a large signal increase over learning runs denoted the good learners among the *APOE ε2/ε3* carriers, but a large signal decrease characterized the good learners among the *APOE ε3/ε4* carriers.

The inspection of brain activity slopes over learning runs within each *APOE* group (no direct comparison between groups) suggests reverse activity slopes in *APOE ε3/ε4* carriers versus *APOE ε2/ε3* carriers within the whole brain (Fig. 6). The *APOE ε3/ε4* group exhibited mostly negative activity slopes in many left and a few right prefrontal areas associated with executive functions (Collette et al. 2006) during both learning tasks, bilateral anterior superior temporal areas related to lexical–semantic processing (e.g., Bright et al. 2004) during associative learning, right middle temporal areas related to the processing of person semantics (Thompson et al. 2004) during single-face learning, and the right fusiform face area (Kanwisher et al. 1997) during single-face learning (Fig. 6). Activity slopes in several of these areas were positively correlated with retrieval success—the greater the activity decrease, the greater retrieval success (Tables 4 and 5). The *APOE ε3/ε4* group also exhibited a few spots of activity increases over learning runs within the inferior parietal lobule bilaterally, but these were not correlated with retrieval success. The activity slopes were primarily positive in the *APOE ε2/ε3* and the *APOE ε3/ε3* groups and

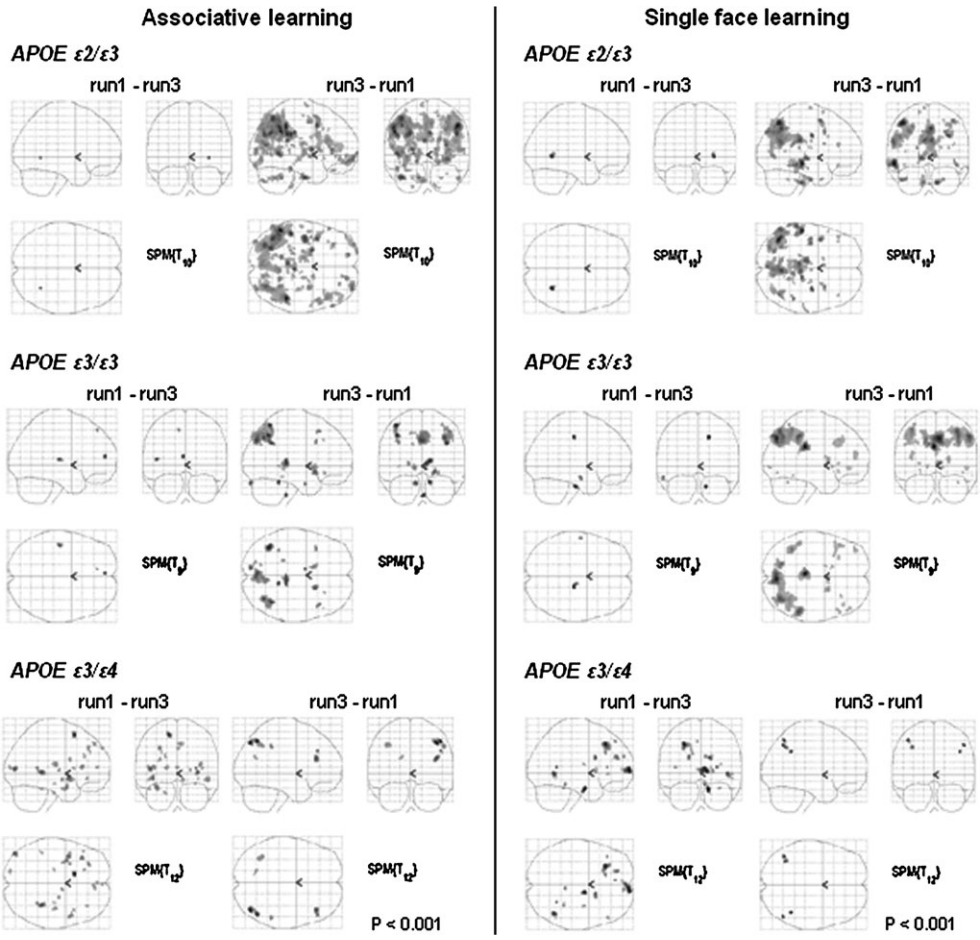

Figure 6. Brain activity differences between learning runs 1 and 3 per *APOE* group. Displayed are sagittal, coronal, and horizontal SPM2 through projections of brain regions that exhibited a significant signal decrease (run 1–run 3) or signal increase (run 3–run 1) during associative learning (left side) and single-face learning (right side).

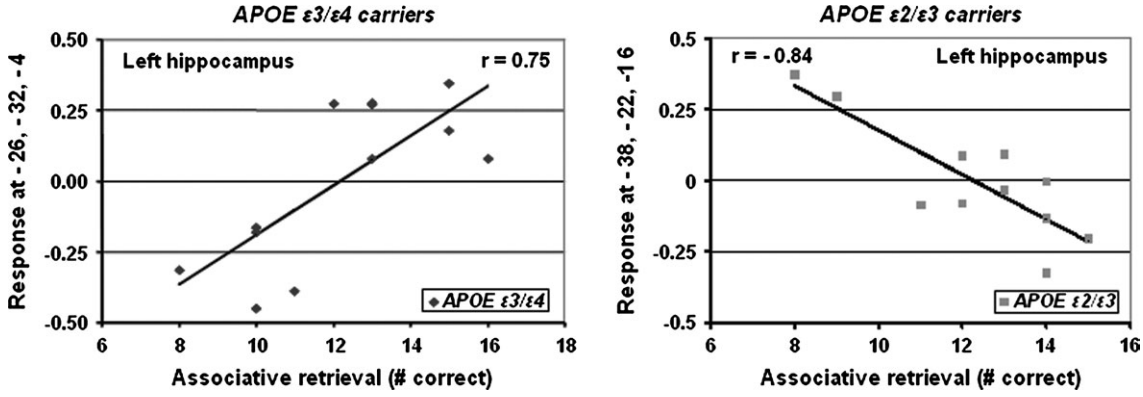

Figure 7. Simple regression between left hippocampal signal difference during associative learning (run 1–run 3) and associative retrieval performance computed for *APOE ε3/ε4* (left panel) and *APOE ε2/ε3* carriers (right panel). *Y* axis, beta values (SPM2) of the most active voxel in hippocampal activation cluster; *X* axis, number of correctly retrieved associations; black line, regression line.

were located in large parts of the parietal lobe bilaterally (Fig. 6) and might reflect an increase in the richness of imagery contents over learning runs (Mellet et al. 2000; Ganis et al. 2004; Sack et al. 2005) during the imagination task given for encoding. However, these parietal activity slopes were not correlated with retrieval success in either *APOE* group. Therefore, we assume that they were not directly relevant for memory storage. Whereas none of the other positive activity slopes in the *APOE ε3/ε3* group were correlated with retrieval success, the *APOE ε2/ε3* group exhibited further positive activity slopes in the frontal and temporal lobes that were correlated with retrieval success (Tables 4 and 5), suggesting that they were related to memory storage.

We also observed a more economic use of retrieval-related neural resources in the *APOE ε3/ε4* carriers versus the *APOE ε2/ε3* carriers. The *APOE ε3/ε4* carriers invested less neural

Table 4
Correlation between associative learning signal difference (run 1–run 3) and associative retrieval performance

Brain region	Left/right	MNI coordinates (mm)			*t*	*r*
		x	*y*	*z*		
Positive correlations						
APOE ε2/ε3						
Superior parietal lobule	L	−40	−40	64	6.36	0.90
APOE ε3/ε3						
Fusiform gyrus	L	−26	−82	−20	4.72	0.83
Inferior temporal gyrus	R	62	−48	−10	6.29	0.89
APOE ε3/ε4						
Hippocampus	L	−26	−32	−4	3.56*	0.75
Inferior frontal gyrus	R	40	42	−20	5.11	0.83
	R	42	24	−12	4.94	0.82
	L	−44	36	−20	4.88	0.82
Middle frontal gyrus	L	−34	32	44	7.39	0.91
	R	48	32	18	4.5	0.79
Superior frontal gyrus	R	20	−10	56	6.02	0.87
Paracentral lobule	R	6	−42	58	5.35	0.84
Precentral gyrus	L	−8	−24	64	4.55	0.80
Insula	R	30	−22	12	4.75	0.81
Putamen	L	−28	8	−4	5.27	0.84

Brain region	Left/right	MNI coordinates (mm)			*t*	*r*
		x	*y*	*z*		
Negative correlations						
APOE ε2/ε3						
Hippocampus	L	−38	−22	−16	4.57[a]	−0.84
Parahippocampal gyrus	L	−30	−14	−28	5.38	−0.87
Middle frontal gyrus	L	−32	42	38	5.39	−0.87
	R	26	6	54	4.87	−0.85
Superior frontal gyrus	R	26	62	24	7.54	−0.93
	L	−30	−8	62	5.69	−0.88
Orbital gyrus	L	−16	26	−18	5.37	−0.87
Cingulate gyrus	L	−8	−52	44	8.28	−0.94
	R	6	−32	36	5.44	−0.88
	L	−12	−46	34	4.88	−0.85
Middle temporal gyrus	L	−56	−56	8	6.86	−0.92
	R	44	−74	22	5.37	−0.87
Superior temporal gyrus	L	−60	−54	18	6.5	−0.91
	L	−58	−46	18	5.2	−0.87
Fusiform gyrus	L	−40	−86	8	5.73	−0.89
Lingual gyrus	L	−16	−90	−8	14.60	−0.98
	R	6	−66	2	4.98	−0.86
Middle occipital gyrus	L	−24	−90	28	5.32	−0.87
Basal ganglia	L	−20	16	−6	5.28	−0.87
Cerebellum	R	6	−58	−46	7.53	−0.93
APOE ε3/ε3						
Insula	L	−46	−14	10	5.21	−0.85
APOE ε3/ε4						
No significant correlations						

Note: *t*, values of peaks within significantly ($P < 0.001$) activated clusters of voxels; *r*, correlation coefficient; MNI, Montreal Neurological Institute.
*$P < 0.005$.

resources into the retrieval process than the *APOE ε2/ε3* carriers within the right hippocampus and left fusiform gyrus during associative retrieval and within the right middle and superior frontal gyri and the right precuneus during face retrieval (Table 3); yet, the 2 groups achieved a comparable retrieval performance in these retrieval tasks (Table 2). This finding suggests that task demands were higher on the *APOE*2 than the *APOE*4 carriers—a finding that is intuitive given the better retrieval performance in the *APOE*4 carriers within the large and nonmatched sample of 340 subjects. Although we had matched participants of the fMRI study for memory performance, task demands might still have been higher on the *APOE*2 than the *APOE*4 carriers. It has been demonstrated for a variety of cognitive tasks that increasing task demands are associated with an increase in the spatial extent and the magnitude of brain activity in the task-specialized neural network (Just et al. 1996; Carpenter et al. 1999). Patients with an amnesic mild cognitive impairment exhibited larger memory-related activity enhancements within the medial temporal lobe (Dickerson et al. 2004) compared with healthy individuals. In addition, neuroimaging studies have shown that practice can lead to reductions in brain activation (Raichle et al. 1994; Simpson et al. 2001) and that brains of high performers or people with much practice work more efficiently (less activity with better task performance) than the brains of lower performers or people with less practice (Haier, Siegel, MacLachlan, et al. 1992; Haier, Siegel, Tang, et al. 1992; Neubauer et al. 2005). We conclude, therefore, that brain activity levels may be elevated in response to increasing task demands caused by either an objective increase in task difficulty or a subjective increase in task difficulty due to less practice or less favorable genetic or neurophysiological resources.

Our neuroimaging *APOE* groups were statistically equal in terms of neuropsychological test performance (Supplementary Table S2) and gray and white matter volumes (Supplementary Table S4)—particularly hippocampal and parahippocampal volumes. It is, therefore, unlikely that the performance and imaging results were biased by morphological or cognitive differences between *APOE* groups. Moreover, brain activity differences between *APOE* groups were found only for episodic memory, not for working memory. The *APOE ε2/ε3* and *APOE ε3/ε4* carriers differed neither in performance (Supplementary Table S1) nor in brain activity levels on the working memory task. It should be noted that the participants in these studies were well-educated (around 14 years of education) and scoring above average on the intelligence test (around 123 IQ points). Whether the reported *APOE* differences generalize

Table 5
Correlation between single-face–learning signal difference (run 1–run 3) and face recognition performance (for remember responses: hits–false alarms)

Brain region	Left/right	MNI coordinates (mm)			*t*	*r*
		x	*y*	*z*		
Positive correlations						
APOE ε2/ε3						
Medial frontal gyrus	L	−10	56	4	4.69	0.86
Fusiform gyrus	L	−38	−56	−26	6.23	0.91
APOE ε3/ε3						
Hippocampus	L	−36	−18	−18	4.15*	0.83
	R	22	−14	−14	4.15*	0.83
Parahippocampal gyrus	R	26	−42	−12	8.57	0.95
Fusiform gyrus	R	24	−64	−6	8.58	0.95
Inferior frontal gyrus	L	−46	26	26	10.11	0.96
	R	58	18	32	5.62	0.89
Middle frontal gyrus	L	−48	8	36	7.52	0.94
	L	−32	42	24	6.95	0.93
	R	44	44	24	6.3	0.91
Medial frontal gyrus	R	8	14	54	5.42	0.89
	L	−6	−4	58	5.19	0.88
Superior frontal gyrus	L	−16	12	64	4.87	0.86
Middle temporal gyrus	R	40	8	−36	6.61	0.92
	R	48	−4	−20	5.39	0.89
Superior temporal gyrus	R	64	−32	4	5.52	0.89
Inferior parietal lobule	R	58	−24	30	6.25	0.91
Inferior parietal lobule	L	−66	−24	26	5.15	0.88
Precentral gyrus	L	−14	−26	66	8.02	0.94
	R	58	−10	40	6.78	0.92
	R	32	−28	68	5.11	0.87
	L	−46	−12	54	5.06	0.87
Lingual gyrus	L	−8	−76	−4	7.42	0.93
	R	20	−94	−16	5.31	0.88
Superior parietal lobule	R	34	−80	42	5.86	0.90
Insula	R	34	−4	−6	5.54	0.89
Cerebellum	L	−6	−50	−12	8.21	0.95
APOE ε3/ε4						
Hippocampus	R	20	−16	−14	4.35*	0.81
Inferior frontal gyrus	L	−46	38	−12	4.7	0.83
Middle frontal gyrus	R	30	14	42	5.36	0.86
Superior frontal gyrus	L	−32	12	62	4.96	0.84
	R	30	12	58	4.81	0.84
	R	22	−12	74	4.72	0.83
	R	18	24	44	4.6	0.82
Cingulate gyrus	R	12	40	−10	4.83	0.84
	L	−14	−60	22	4.97	0.84
Middle temporal gyrus	L	−56	−14	−24	5.32	0.86
Superior temporal gyrus	R	44	−50	16	4.66	0.83
Inferior parietal lobule	L	−30	−66	36	8.58	0.94
	L	−34	−58	38	4.6	0.82
Cerebellum	R	4	−58	−32	4.75	0.83

Brain region	Left/right	MNI coordinates (mm)			*t*	*r*
		x	*y*	*z*		
Negative correlations						
APOE ε2/ε3						
Amygdala	L	−18	0	−26	8.14	0.94
Inferior frontal gyrus	R	36	30	−16	8.04	0.94
	L	−36	34	−4	5.32	0.88
Middle frontal gyrus	R	30	52	−8	5.43	0.89
	R	18	60	−8	5.77	0.90
Superior frontal gyrus	R	24	56	34	6.76	0.92
	L	−22	62	28	5.62	0.89
Precentral gyrus	R	46	4	38	4.82	0.86
Lingual gyrus	L	−4	−86	−10	5.27	0.88
	R	6	−88	−2	4.76	0.86
APOE ε3/ε3						
No significant correlations						
APOE ε3/ε4						
No significant correlations						

Note: *t*, values of peaks within significantly ($P < 0.001$) activated clusters of voxels; *r*, correlation coefficient. MNI, Montreal Neurological Institute.
*$P < 0.005$.

to average functioning individuals must be examined in future studies.

The economic use of neural resources in *APOE4* carriers concurs with advantageous effects of the *APOE4* allele on the normal neurophysiological functioning in young animals. Hippocampal LTP was enhanced at a younger age in knock-in mice lacking mouse *APOE*, but instead expressing human *APOE4* (Kitamura et al. 2004). This LTP enhancement was age dependent and disappeared in adult knock-in mice. Moreover, *APOE4*, but not *APOE3*, stimulated the transcriptional activity of CREB by activating the ERK cascade in rat primary hippocampal neurons (Ohkubo et al. 2001). The influence of *APOE4* on this memory-related pathway may provide an explanation for the beneficial effect of *APOE4* on human memory in young adults. On the other hand, there is evidence that *APOE4* alters intracellular calcium homeostasis, which might ultimately lead to neuronal damage (Qiu et al. 2003). One may speculate that a sustained *APOE4*-related neuronal calcium increase, which is related to improved memory performance at a young age, finally induces age-associated neuronal damage. Alternatively, the *APOE4*-associated cognitive impairment and abnormal brain activity/metabolism found in middle-aged and older subjects

might be a consequence of the continuous deposition of amyloid plaques and neurofibrillary tangles, which are associated with dysfunction, deafferentation, and degeneration of neurons in the long course of AD. The deposition of amyloid plaques and neurofibrillary tangles has been related to the presence of the *APOE4* allele (Ghebremedhin et al. 1998, 2001; Bennett et al. 2003, 2005; Tiraboschi et al. 2004; Thal et al. 2005). Importantly, these neuropathological changes precede the clinical diagnosis of AD by 30–50 years (Ohm et al. 1995; Braak H and Braak E 1996; Delacourte et al. 1999). A single copy of the *APOE4* allele in middle-aged and older persons with normal memory performance was associated with lowered parietal and temporal lobe metabolism, which predicted cognitive and metabolic decline after 2 years of longitudinal follow-up (Small et al. 2000; de Leon et al. 2001). Moreover, older *APOE4* carriers, compared with *APOE3* carriers, exhibited increases in brain activity in response to verbal (Bookheimer et al. 2000) and picture (Bondi et al. 2005) learning, presumably to compensate for AD-related preclinical neuropathology. Indeed, the greater their brain activity increase was, the greater was their memory decline during the following 2 years (Bookheimer et al. 2000). We assume that brain activity abnormalities in middle-aged and older *APOE4* carriers reflect ongoing pathophysiological processes of AD. Because of the long preclinical course of AD, a direct effect of the *APOE* isoforms on the normal memory-related neurophysiology, independently of pathological deposits, can only be studied in subjects as young as those included in the present study.

In conclusion, we suggest that the *APOE4* allele is associated with positive effects on episodic memory in young, healthy individuals. Its association with cognitive impairment and abnormal brain activity later in life is probably mediated by AD-related preclinical neuropathology. Future studies need to address a potential link between the *APOE4* allele's beneficial effects on normal memory and its role as a risk factor for AD.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Notes

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