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fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease

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Abstract

Objective—To determine whether *APOE* genotype influences brain response and whether nonverbal stimuli generate findings comparable with those of previous studies that used verbal stimuli. The relationship between *APOE* genotype and blood oxygenation level dependent (BOLD) brain response was examined during a picture-encoding task in nondemented older adults.

Methods—Twenty nondemented participants with normal episodic memory function were divided into two groups based on the presence (n = 10) or absence (n = 10) of the *APOE* ε4 allele. Picture learning was completed during functional MRI in a blocked design alternating between experimental (novel pictures) and control (repeated picture) conditions.

Results—Nondemented older adults with an *APOE* ε4 allele showed greater magnitude and extent of BOLD brain response during learning of new pictures relative to their matched ε3 counterparts. Different patterns and directions of association between hippocampal activity and learning and memory performance were also demonstrated.

Conclusions—The results suggest that brain response differences are not due to poorer general memory abilities, differential atrophy, or brain response during control conditions, but instead appear to be directly influenced by *APOE* genotype. Results are consistent with a compensatory hypothesis wherein older adults at genetic risk for Alzheimer disease by virtue of the *APOE* ε4 allele appear to require additional cognitive effort to achieve comparable performance levels on tests of episodic memory encoding.

Studies of nondemented older adults who later develop Alzheimer disease (AD) show a subtle decline in episodic memory prior to emergence of the obvious cognitive and behavioral changes required for a clinical diagnosis of the disease.[1-7] Often this decline in episodic memory is evident some years prior to the development of dementia and has been shown to predict the subsequent development of AD.[1-4,8,9] In addition, the ε4 allele of the gene coding for *APOE* is linked to an increased risk of developing late-onset AD.[10,11] There have been a variety of brain changes associated with the *APOE* ε4 allele in AD, including structural[12,13] and functional brain changes,[14] as well as subtle neuropsychologic deficits.[8,9,15] Further, studies suggest that the pathologic burden of AD may begin decades—not years—prior to the diagnosis of AD and may be influenced by one's *APOE* genotype.[16]

Given the increasing emergence of treatments for dementia, sensitive and reliable markers of incipient dementia are needed to enhance our ability to detect AD in its earliest stages when potential neuroprotective agents might be most effective.[17] fMRI offers considerable promise as a noninvasive technique for detection of early brain changes associated with an incipient

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dementia. fMRI study of episodic memory in at-risk older adults would have direct relevance to the early pathologic changes in medial temporal and prefrontal cortices in AD[18] and provide a useful assay of activity in susceptible brain regions during the preclinical period of AD.

Initial work[19] demonstrated an increase in the intensity and extent of brain activation in nondemented middle-aged and older adults with the *APOE* ε4 allele during verbal learning, suggesting a compensatory mechanism wherein *APOE* ε4 carriers utilize additional cognitive resources to bring memory-related performance to a normal level. However, differential atrophy or response to baseline conditions between genotype groups were not assessed, and *APOE* ε4 genotype and poorer memory function were confounded to some degree, thereby clouding the issue of whether the differential brain response was due to *APOE* genotype or simply due to poorer memory function. To determine the influence of the *APOE* ε4 allele in ostensibly healthy older adults with comparable episodic memory function, and to determine whether pictoral stimuli generate similar findings, we examined the relationship between *APOE* genotype and blood oxygen level dependent (BOLD) brain response during a picture-encoding task in nondemented older adults.

Methods

Participants

We studied 20 right-handed older adults from a larger pool of 80 volunteers participating in a longitudinal study of aging, all of whom were ostensibly healthy and living independently at the time of scanning. Participants were recruited through newspaper advertisements and community lectures (i.e., no clinic-based or medical referral sources) and selected without regard to ethnicity or race. Written informed consent was obtained from all participants. All participants were considered normal based on extensive medical, neurologic, laboratory, and neuropsychologic evaluations. Participants with a history of alcoholism, drug abuse, learning disability, neurologic, or psychiatric illness (including depression) are routinely excluded from the pool of normal control participants. No participant reported a significant level of depressive symptoms on the Geriatric Depression Scale (i.e., ≥10).[20] Thus, participants did not demonstrate deficits on cognitive screening or formal memory testing, nor did they demonstrate significant affective disturbance, functional impairments, or difficulties with activities of daily living (table 1).

All 80 participants were genotyped for *APOE* allele type using a PCR-based method[11] (*APOE* ε4% = 25%). From the larger group 20 participants were then selected for scanning based on their demographic characteristics and *APOE* genotypes and divided into two groups on the basis of the presence (n = 10) or absence (n = 10) of the *APOE* ε4 allele. All non-ε4 participants were homozygous for the ε3 allele (ε3/ε3); two of the ε4 participants were homozygotes (ε4/ε4) and the remaining eight participants were ε3/ε4 heterozygotes. As shown in table 1, the two groups did not differ on the basis of mean age, education, sex distribution, or on global cognitive functioning (all p values > 0.45). Furthermore, on memory testing, the two groups did not differ on variables from either the Wechsler Memory Scale–Revised[21] or the California Verbal Learning Test (CVLT),[22] with the exception of the summary learning measure from the CVLT ($p = 0.04$) wherein the ε4 group outperformed the ε3 group. Nonetheless, both groups' mean scores were well within normal limits on this measure as well as on the other measures (see table 1).

Stimuli and procedure

A picture-encoding paradigm[23] was completed during scanning in a blocked design alternating between experimental and control conditions. In the experimental (“ENCODE”) condition, participants viewed and were asked to learn and remember 48 color photographs of indoor and

outdoor scenes presented one at a time. In the control condition ("REPEAT"), one color photograph of autumn leaves was used as a repeated picture. Each block consisted of six trials, comprising picture presentation (2,500 msec) and an intertrial interval (500 msec). A 3-second warning screen reminded participants which type of block was to follow. Thus, each block lasted 21 seconds. Additionally, four blocks of fixation baseline trials were presented ("FIXATE"), one in the beginning, two in the middle, and one at the end of the trial blocks. The pictoral stimuli were presented to the participants using an LCD projector, back-projected onto a screen at the participant's feet. In the scanner, participants pressed a button on each trial to indicate they were attending to the pictures. Motor responses were made using a fiber-optic button box and were recorded by the MicroExperimental Lab2 software package (Psychological Software Tools, Pittsburgh, PA). Approximately 10 minutes after imaging, all participants completed a two-choice recognition testing for the 48 photos.

Anatomic and functional whole-brain imaging

All scans were whole-brain acquisitions conducted with a 1.5 T GE imager. High-resolution T1-weighted anatomic images were collected with either an SPGR sequence (124 slices acquired in the sagittal plane; 1.2 mm slice thickness; 256 × 256 matrix; field of view [FOV] = 250 mm; resulting in a 1 mm^2 in-plane resolution) or a SPIRAL sequence (128 slices with 8 echoes; resolution was 1.25 mm in plane, and 1.33 to 1.42 mm through plane; 192 × 192 matrix using 16 spiral interleaves; FOV = 240 mm). Functional data from 156 whole brain images of BOLD signal intensity were acquired axially using a gradient-recalled echoplanar imaging (EPI) sequence. Seven-millimeter-thick slices sampled the entire brain (20 to 22 slices acquired in the axial plane; repetition time [TR] = 3,000 msec; echo time = 40 msec; flip angle = 90 degrees; 64 × 64 matrix; FOV = 240 mm; 3.75 mm^2 in-plane resolution).

Individual participant data analysis path

All analyses were conducted with Analysis of Functional NeuroImages (AFNI) software,[24] and all participant datasets were analyzed in the following scripted manner. A three-dimensional brick was created from the structural scan slices, and the three-dimensional bricks were warped into a standardized coordinate space (Talairach-Tournoux).[25] A three-dimensional brick of image data was also created for each TR down the time course of the EPI scanning sequence. Effects of small movements were minimized with the AFNI three-dimensional volume registration program and, very infrequently when excessive motion occurred, by inserting the mean value of adjacent repetitions in voxels with residual motion. A threshold value was used to exclude low intensity values generally located outside the brain.

The comparison of interest was the difference in activation levels while viewing new pictures vs a repeated picture (i.e., ENCODE – REPEAT). A predicted and shifted (up to 6 seconds) trapezoidal reference function was cross-correlated with the motion-corrected MR time course data in each voxel within the three-dimensional functional brick. Datasets were then resampled into 4 mm^3 voxels and written into Talairach-Tournoux space.[25] Finally, to reduce noise and account for correlations between adjacent voxels and variations in anatomy, functional datasets were blurred with a 7 mm FWHM kernel.

Group data analysis path

T-maps were created for each *APOE* genotype group to determine whether the mean intensity value difference between the new and repeated picture conditions in each voxel was different from zero. A between-group t-map was also generated to determine whether pattern of average intensity value differences between the picture conditions differed between the two *APOE* genotype groups. A cluster thresholding technique was used to determine which areas of activation on the t-maps were significant by thresholding at a p value of 0.025. The cluster size was predetermined as a region of at least 13 contiguous significant voxels (i.e., 832 mm^3

volume), which protected for a whole-brain p value of 0.05. This correction is appropriate to protect the hypothesis that when no activation is present anywhere within the brain a chance volume of activation will occur less than 2.5% of the time.

Search regions of interest (ROIs)

Encoding-related brain response was also examined within each group and compared between the two groups in each voxel of four bilateral search regions: hippocampus, parahippocampal gyrus, inferior prefrontal cortex (Brodmann's area [BA] 44/45), and fusiform gyrus. Search regions were selected from previous studies of novel picture encoding.[23,26-29] Coordinates for each search region, as well as its extent, were determined by Talairach Daemon software.[30] Search regions were used to mask each participant's three-dimensional dataset of fit coefficients. To examine group differences, we compared mean fit coefficient between groups in all voxels within each search region via independent-samples *t*-tests. Clusters of brain response were considered significantly different from zero within groups or significantly different between the two groups if they contained at least seven contiguous voxels, each with a $p < 0.025$ per voxel (i.e., 448 mm^3 volume). This threshold and cluster volume pairing was found to protect a search-region-wise $p = 0.059$ in a Monte Carlo simulation (AlphaSim, AFNI). Between-subject variability at each voxel within the search regions also was compared between groups via analysis of variance (ANOVA). We identified areas of significant BOLD response within each group by comparing fit coefficients of voxels within each search region to zero (single-sample *t*-test). For the statistical maps of brain response presented in the figures, the magnitude of between- or within-group effect was expressed as an effect size statistic (eta^2) and given a valence based on its direction (range = −1.0 to + 1.0).[26]

Post hoc analyses

Several post hoc analyses were conducted to aid interpretation of the observed group differences.[26,31] First, the contrast of ENCODE vs FIXATE was compared between groups in a control region (primary visual cortex, BA 17) in order to explore the specificity of observed differences to encoding-related brain regions and to address the potential concern that methodologic or broad physiologic factors influenced the between-group findings.[32] Second, the contrast of REPEAT vs FIXATE was compared between groups to explore whether there were significant baseline differences between genotype groups that could limit interpretation of our primary contrast (ENCODE vs REPEAT). Third, correlations between hippocampal brain response and recognition memory task performance were computed, as were correlations between hippocampal brain response and learning on the *CVLT*.

Finally, whole brain segmentation of same-session structural MRI scans was undertaken to address the potential concern that any observed differences between *APOE* genotype groups in brain response may have arisen from broad differences in cerebral atrophy.[33] Following bias correction,[34] each scan was processed with one or more of the following automated skull-stripping methods: FreeSurfer's Hybrid Watershed Algorithm,[35] Brain Extraction Tool,[36] and 3dIntracranial in AFNI.[24,37] All scans were then processed through ANFI's[24] 3dIntracranial program to remove remaining skull[37] and manually edited to remove residual non-brain material. Tissue segmentation was performed using TriComp, a locally developed set of programs designed to fit a three-compartment Gaussian mixture model to the signal intensity histogram of the skull stripped T1-weighted images. Means, SDs, and weights for gray matter, white matter, and CSF compartments were estimated using the downhill-simplex method to minimize the residual sum of squares.[38] Total intracranial volume was also derived, and thus proportions of each compartment were calculated.

Results

Behavioral data: Recognition memory for the novel pictures

There were no significant differences in performance between those with an *APOE* ε4 allele and those homozygous for the *APOE* ε3 allele on forced-choice recognition testing of the novel pictures (see table 1). Both groups averaged better than 70% accuracy for recognition of the pictures following their scanning session (*APOE* ε4 group = 79.2%, SD = 11.8; *APOE* ε3 group = 72.3, SD = 13.1, $p = 0.28$).

Functional MR imaging data: Brain response to the encoding task

Within-genotype group whole brain analysis: *APOE* ε4 group—In multiple brain regions, the *APOE* ε4 group showed significantly greater BOLD brain response while learning new pictures compared to viewing a repeated picture. The majority of these sites were located in large, bilateral regions of the occipital/fusiform gyri, although the areas of greater BOLD response were spread throughout multiple brain regions (e.g., precuneus, frontal, temporal, and cingulate gyri) in all four lobes of the cerebrum (see table 2 and figure 1A for details).

Within-genotype group whole brain analysis: *APOE* ε3 group—Unlike the findings in those with an *APOE* ε4 allele, participants in the *APOE* ε3 group showed relatively fewer regions of greater BOLD brain response during the new vs repeated picture conditions. The majority of these regions also were located in bilateral occipital/fusiform cortices, left medial frontal and right inferior frontal gyri. In addition, the *APOE* ε3 group uniquely demonstrated greater encoding-related brain response in bilateral caudate nuclei, and left parahippocampal cortex and left hippocampus (see table 2 and figure 1B for details).

Between-genotype groups whole brain analysis—Individuals with an *APOE* ε4 allele showed greater differential BOLD brain response while encoding new pictures vs viewing a repeated picture in a number of brain regions (see table 3 and figure 2). Specifically, clusters (i.e., 13 contiguous significant voxels) of significantly greater BOLD response were observed in six regions, including bilateral fusiform gyri, right superior parietal cortex, left pyramis/uvula, left middle frontal gyrus, and the medial frontal gyrus (see table 3 and figure 2).

Search ROI analyses

Within the search regions examined, the between-subjects tests of encoding-related BOLD brain response were greater in the *APOE* ε4 group relative to the *APOE* ε3 group in left inferior frontal, bilateral fusiform, and right hippocampal and parahippocampal cortices. However, in clusters within the left hippocampus and parahippocampal cortex, the *APOE* ε3 group showed a larger positive response (i.e., greater signal intensity during novel pictures than during repeated pictures), whereas the *APOE* ε4 group showed either a small positive response or no difference in signal intensity between the two conditions (see table E-1 on the *Neurology* Web site at www.neurology.org).

Post hoc analyses

Control analyses—Analysis of the response of voxels within BA 17 revealed a strong positive bilateral response to the encoding condition compared with fixation for both *APOE* ε4 and ε3 groups, with no significant clusters of group difference observed within this search region. We also found no evidence for differentially lower BOLD response among the ε4 group in any of the six regions identified in table 3 to the repeat condition compared with fixation (data available upon request).

Correlations—Patterns of correlation between individual differences in encoding-related brain response and subsequent recognition memory performance were examined for the pictures as well as for word-list learning as indexed by the CVLT. Given the small sample sizes, each of the reported *r*-values below do not attain significance (all *p* values > 0.05). Rather, they are reported solely for descriptive purposes. In the left hippocampus, the *APOE* ε4 group demonstrated a positive correlation between the mean fit coefficient and recognition memory ($r = 0.57$), whereas the ε3 group did not ($r = 0.07$). However, an opposite pattern of correlation was observed for the right hippocampus (ε4: $r = 0.01$; ε3: $r = 0.33$). Contrasting findings were also demonstrated in the correlations between hippocampal fit coefficients and performance on the summary learning variable from the CVLT (List A Trials 1 to 5 Total Recall). Specifically, in the left hippocampus, the *APOE* ε4 group demonstrated little correlation between the mean fit coefficient and CVLT learning ($r = 0.02$), whereas the ε3 group evinced a relatively larger association ($r = 0.28$). However, an opposite pattern and direction of association was observed for the right hippocampus (ε4: $r = -0.46$; ε3: $r = 0.53$). A Fisher's z transformation of the difference between these two correlation coefficients was significant ($z_{diff} = 2.03$, $p < 0.05$). Given concerns over ROIs derived from standard space for structures as variable as the hippocampus (i.e., volumes derived from native space may be more appropriate), we also found comparable patterns of association when the most intense voxel located in hippocampal native space was used instead of the mean fit coefficient in standard space (e.g., right hippocampus: ε4: $r = -0.72$; ε3: $r = 0.13$).

Segmentation—Total intracranial volume, gray and white matter volumes, and CSF volume were analyzed in a series of four 2 × 2 ANOVAs (*APOE* genotype [ε4 vs ε3] by MRI scan type [SPGR vs SPIRAL sequence]). Results revealed main effects for scan type on two of the four brain volumes measured (total intracranial volume: $F(1,18) = 4.75$, $p = 0.05$; gray matter: $F < 1$, $p = 0.37$; white matter: $F(1,18) = 1.68$, $p = 0.21$; CSF: $F(1,18) = 21.58$, $p < 0.001$), but no main effects for *APOE* genotype on any of the four measures (total intracranial volume: $F(1,18) = 1.06$, $p = 0.32$; gray matter: $F < 1$, $p = 0.97$; white matter: $F < 1$, $p = 0.65$; CSF: $F(1,18) = 3.05$, $p = 0.10$), and no significant interactions between *APOE* genotype and scan type (all *F*s < 1, *p*s = 0.41 to 0.97). Overall, the two *APOE* genotype groups did not differ on any of the whole-brain segmentation measures, indicating comparable volumes of gray and white matter, CSF volumes, as well as proportion scores (see table E-2 on the *Neurology* Web site at www.neurology.org).

Discussion

In multiple brain regions, nondemented older adults with an *APOE* ε4 allele and normal learning and memory capabilities showed greater magnitude and extent of BOLD brain response during picture learning relative to their ε3 counterparts (e.g., bilateral fusiform and medial frontal gyri, left inferior and middle frontal, right superior parietal, and right hippocampal and parahippocampal cortices). In addition, the *APOE* ε4 group showed lower brain response in the left hippocampus, relative to the *APOE* ε3 group. Both groups were performing equally well across many learning and memory measures. Both groups demonstrated comparable volumes of gray and white matter and CSF, all of which were also quite consistent with gray, white, and CSF segmentation volumes of older adults reported by others,[39] thereby demonstrating the robustness of our segmentation procedures and comparability of our groups to other nondemented older adult samples. Also, we found no evidence for differentially lower BOLD response among the ε4 group in any of the six regions identified in the ENCODE vs REPEAT contrast (see table 3). Our ε4 and ε3 groups also showed a strong positive bilateral response to the encoding condition in primary visual cortex (BA 17)—an area whose contribution to the encoding task should not differ between groups. Thus, it appears that BOLD response differences in nondemented older adults are not accounted for by differential memory abilities, differential atrophy, baseline differences in the control (i.e.,

Repeat) condition, or broad physiologic differences per se, but instead appear to be more directly influenced by one's *APOE* genotype.

Results are consistent with a compensatory hypothesis wherein *APOE* ε4 persons appear to require additional cognitive effort to achieve the same level of performance. Indeed, several functional neuroimaging studies have shown that BOLD brain response associated with the performance of memory tasks is more diffuse in patients with early AD than in normal older individuals, suggesting the need to recruit areas outside of the usual structures that mediate memory.[40-42] It may be that, after an initial decline in memory proficiency following damage to MTL structures, patients in the preclinical stage of AD are able to effectively recruit compensatory brain resources (e.g., frontal and temporal cortical regions important for executive functions and semantic memory) to halt or slow further memory decline for a period of time. A similar compensatory response in certain brain-derived neurotrophic factors[43,44] or cholinergic activity[45] may also attenuate memory changes for a time. Given that adequate cholinergic activity and neurotrophic mechanisms are partly responsible for the maintenance of neuronal function and structural integrity, these findings suggest that, under conditions of progressive neurodegeneration, the MTL stimulates the overexpression of certain cholinergic and neurotrophic factors as a possible mechanism of compensation. As the disease progresses, however, each of these additional resources becomes compromised and the patient exhibits a period of rapid decline in episodic memory abilities.[15] Attendant declines in brain activity[42] and cholinergic activity[45] in these critical brain regions for episodic memory function would then be expected in clinically evident AD.

Several functional MRI studies are also consistent with the compensation hypothesis, although none specifically investigated the role of *APOE* genotype. Rombouts et al.[46] found increases in fusiform and frontal—but not MTL—activation during face encoding following rivastigmine administration. Machulda et al.[47] showed that MCI and AD patients had less MTL activation during encoding than normal subjects but similar activation on a sensory task. Grady et al.[41] also demonstrated that AD patients used additional neural resources in prefrontal and posterior cortices, presumably those mediating executive functions, when performing semantic and episodic memory tasks to compensate for losses attributable to the degenerative process of AD. Importantly, Grady et al. showed that activity in dorsolateral prefrontal and posterior cortical regions was correlated with better task performance. Finally, Daselaar et al.[48] utilized an event-related paradigm to investigate separately the contributions of encoding and retrieval to memory. Results demonstrated reductions in MTL activity alongside increases in brain activity in other regions in the subgroup with reduced memory performance, suggesting differences in retrieval strategy and compensation for the encoding deficit. Nevertheless, not all studies support conclusions consistent with increased brain response as compensation.[49]

With respect to fMRI studies of at-risk groups, contradictory findings across studies (e.g., decreased vs increased BOLD responses) may center on continued uncertainties regarding the mechanisms linking the hemodynamic response to its underlying neuroanatomy and neurophysiology. One particular concern centers on the notion that differences in the “resting state” will influence the amplitude of the BOLD response.[50] Such a possibility in AD has been demonstrated,[51] and a recent animal model using APP23 transgenic mice demonstrated amyloid plaques to have a direct effect on the hemodynamic response, due in part to compromised cerebrovascular reactivity.[52] Other human studies also demonstrate that the hemodynamic response itself changes in an age-related manner.[33,53] Thus, future efforts should incorporate other MR-based techniques (e.g., perfusion imaging, structural morphometry, cerebral blood volume mapping) to help parcellate the contributions of the neuroanatomic and neurophysiologic underpinnings to the BOLD signal.[54] Nonetheless, fMRI-based findings of possible brain compensation are analogous to neuropsychologic

demonstrations of non-episodic memory functions, such as semantic knowledge or visuospatial abilities, remaining intact early in the course of AD.[15]

In addition, the differing directions in brain response between the left and right MTLs as well as the differential patterns of association between hippocampal BOLD response and learning on the CVLT for the two groups also suggest possible compensatory brain activity. Prior work[55] with nondemented adults demonstrates a pattern of association evinced by the ε3 group in our study: a positive correlation between processing novel stimuli in the hippocampus and learning on the CVLT. Although the left hippocampus is generally engaged during encoding of new verbal information, the right hippocampus appears to become increasingly involved with higher CVLT performance.[55] This finding further suggests that successfully engaging the right as well as left hippocampus results in greater memory capacity. Again, our data from the ε3 group are in close accord with this pattern, but the ε4 group's negative correlation is in stark contrast to this expected association. Thus, the *APOE* ε4 group may be invoking bilateral MTL activation of brain resources in an aberrant manner as an attempt to facilitate performance while learning new material.[40]

Although the present results offer an interesting and plausible methodology for detection of incipient AD, the findings remain speculative given the small sample sizes and until longitudinal follow-up and clinical outcomes of the participants are gathered, which is under way. Furthermore, given the MTL's considerable structural and functional variability across individuals, ROI analyses may be better accomplished in native rather than standard space.[56] An additional unanswered question is whether the differential BOLD response demonstrated in *APOE* ε4 persons represents a predictor of AD development or a normal phenomenon present across the life span. Although our two groups did not demonstrate broad physiologic differences in our control region (i.e., BA 17–primary visual cortex), fMRI study of young- and middle-aged *APOE* ε4 and non-ε4 adults may be a more direct assessment of the potential for broad physiologic distinctions between *APOE* genotypes.[57]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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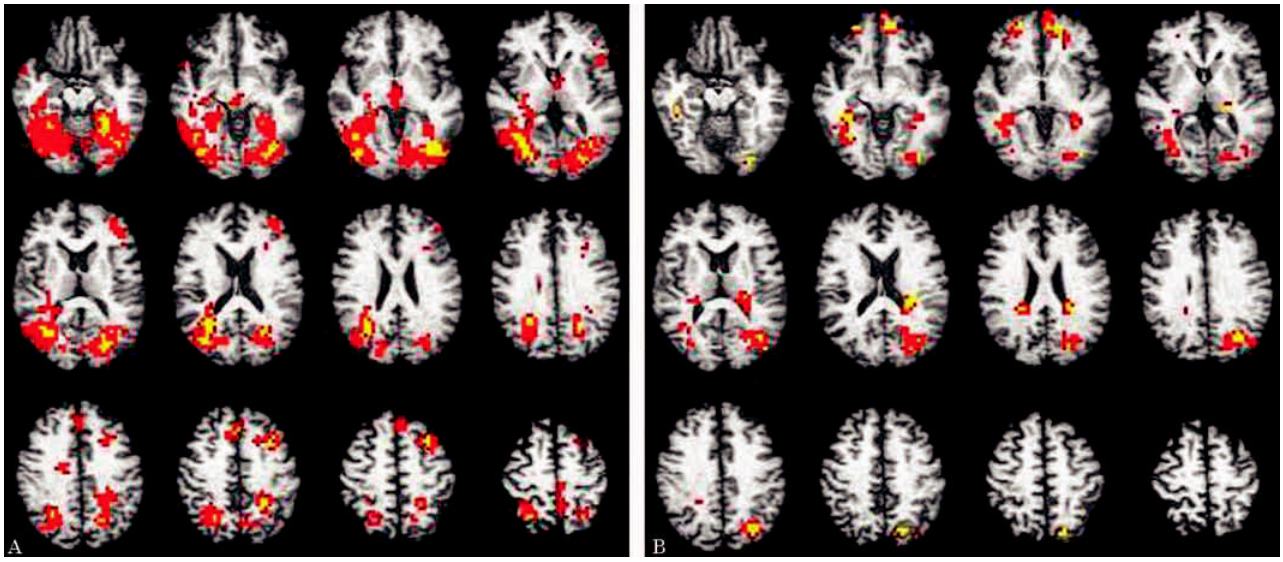

Figure 1.

Magnitude and direction of brain response to the task overlaid onto axial slices of a representative anatomic image in Talairach space (slices span from 12 inferior to 54 superior in 6 mm increments). Activations shown include voxels significant at $p < 0.025$ *that are contained within a cluster of 13 or more voxels. Color scale represents effect sizes for the within-subjects difference between conditions (ENCODE vs REPEAT) as measured by eta*^{2} *(red voxels:* $0.50 < \eta^2 \leq 0.75$*; yellow voxels:* $0.76 < \eta^2$ *&* 1.0 *[*η^2 *indexes the effect size for the magnitude of the difference between the observed response and 0]). See also table 2 for areas of significant activation. (A)* APOE ε*4 participants. (B)* APOE ε*3 participants.*

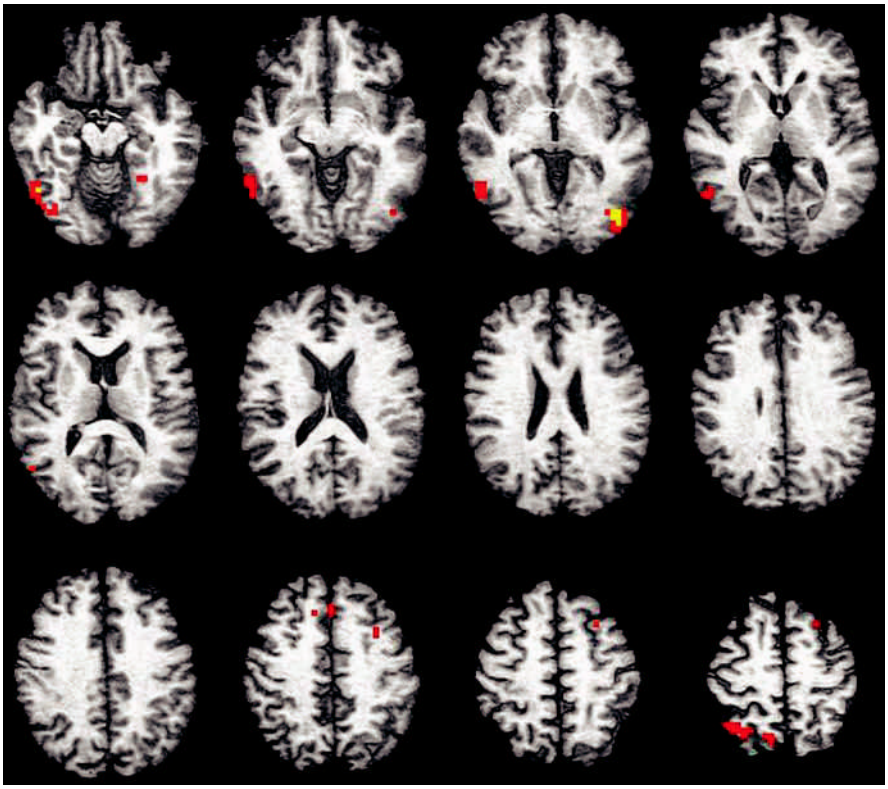

Figure 2.

Clusters of significant difference between APOE ε*4 and* ε*3 participants for encoding-related brain response overlaid on a representative anatomic image in Talairach (1988) space (slices span from 12 inferior to 54 superior in 6 mm increments). Activations shown include voxels significant at* $p < 0.025$ *that are contained within a cluster of 13 or more voxels. Color scale represents effect sizes for the* ε*4 –* ε*3 difference in fit coefficient as measured by eta*^{2} *(signed to reflect the direction of the contrast) (red voxels:* $0.50 < \eta^2 \leq 0.75$*; yellow voxels:* $0.76 < \eta^2 < 1.0$*).*

Table 1

Demographic, global cognitive, and learning and memory characteristics of the APOE *ε4 and ε3 groups*

Variables	*APOE* ε4, n = 10	*APOE* ε3, n = 10	*p* Value
Demographics			
Age, y	76.2 (4.8)	75.7 (5.8)	0.84
Education, y	14.9 (2.5)	15.3 (2.1)	0.70
Women/men	6/4	5/5	0.65
Global cognition			
DRS total (144 points possible)	140.6 (2.2)	141.3 (1.9)	0.45
Learning and memory			
DRS memory subscale	24.4 (0.7)	24.4 (0.7)	0.89
WMS-R immediate recall	25.9 (7.2)	24.6 (3.9)	0.62
WMS-R delayed recall	22.8 (7.9)	19.6 (5.3)	0.31
CVLT List 1–5 total recall	53.8 (6.1)	44.4 (11.6)	0.04
CVLT long delay free recall	11.5 (2.6)	9.4 (4.0)	0.18
CVLT recognition memory, %	94.7 (3.7)	89.6 (8.2)	0.09
Post-MRI recognition memory accuracy for the pictures, %	79.2 (11.8)	72.3 (13.1)	0.28

Values are mean (SD).

DRS = Dementia Rating Scale[58]; WMS-R = Wechsler Memory Scale-Revised[21]; CVLT = California Verbal Learning Test.[22]

Table 2

Areas of significantly greater brain response during encoding of novel vs repeated pictures in nondemented older adults

Brain region	Subregion	Volume, mm^3	Coordinates* of maximum intensity voxel	Eta^2 for encode vs repeat
APOE ε4 group				
R fusiform gyrus	BA 19	119,552	38R, 65P, 8I	0.93
L precuneus	BA 7	10,368	2L, 69P, 40S	0.83
L superior frontal gyrus	L middle frontal gyrus	5,248	30L, 11A, 48S	0.94
L middle frontal gyrus	BA 46	3,008	46L, 35A, 16S	0.70
R medial frontal gyrus	BA 8/R cingulate gyrus	2,944	2R, 27A, 40S	0.71
R red nucleus	R thalamus	2,816	2R, 25P, 4I	0.74
L paracentral lobule/BA 6	BA 4	2,816	2L, 33P, 60S	0.67
R superior temporal gyrus	BA 21	1,216	54R, 7A, 12I	0.56
R cingulate gyrus	BA 24	960	10R, 17P, 36S	0.56
APOE ε3 group				
L middle occipital gyrus	BA 18	14,016	26L, 81P, 0I	0.81
R middle occipital gyrus	BA 19	6,656	30R, 65P, 4S	0.76
L caudate tail	L cingulate gyrus	3,712	22L, 41P, 20S	0.74
L medial frontal gyrus	BA 10/L superior frontal gyrus	3,200	2L, 67A, 4I	0.79
R inferior frontal gyrus	BA 46	1,408	38R, 35A, 4S	0.70
R cingulate gyrus	R posterior cingulate	1,088	14R, 41P, 24S	0.68
L caudate	L parahippocampal gyrus/L hippocampus	1,024	34L, 37P, 0I	0.71
R caudate	R caudate tail	896	22R, 33P, 16S	0.64

BA = Brodmann area; P = posterior; I = inferior; S = superior; A = anterior.

*From Talairach and Tournoux.[25]

Table 3

Whole brain analysis regions of significantly greater brain response in APOE ε*4 vs* APOE ε*3 groups during novel picture encoding*

Brain region	Sub region	Volume, mm^3	Coordinates* of maximum intensity voxel	Eta^2 for ε4 vs ε3
L fusiform gyrus	BA 37	7,552	46L, 53P, 20I	0.59
R fusiform gyrus	BA 19	5,440	34R, 69P, 16I	0.52
R superior parietal lobule	BA 7	2,496	6R, 65P, 56S	0.42
L pyramis/uvula	Cerebellum	1,216	6L, 69P, 24I	0.38
L middle frontal gyrus	BA 6	1,088	26L, 11A, 56S	0.33
Medial frontal gyrus	BA 8	960	2R, 27A, 40S	0.37

BA = Brodmann area; P = posterior; I = inferior; S = superior; A = anterior.

*From Talairach and Tournoux.[25]