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Altered medial temporal lobe responses during visuospatial encoding in healthy APOE*4 carriers

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Abstract

The apolipoprotein ε4 allele (APOE*4) is a major genetic risk factor for Alzheimer's disease (AD) and has been associated with altered cortical activation as assessed by functional neuroimaging in cognitively normal younger and older carriers. We chose to evaluate medial temporal lobe (MTL) activation during encoding and recognition using a perspective dependent (route or survey) visuospatial memory task by monitoring the blood-oxygen-level-dependent (BOLD) fMRI response in older, non-demented APOE*4 carriers (APOE*4+) and non-carriers (APOE*4−). During encoding, the APOE*4− group had greater average task-associated BOLD responses in ventral visual pathways, including the MTLs, as compared to the APOE*4+ group. Furthermore, MTL activation was greater during route encoding than survey encoding on average in APOE*4−, but not APOE*4 +, subjects. During recognition, both groups performed similarly and no BOLD signal differences were found. Finally, within-group analysis revealed MTL activation during encoding was correlated with recognition performance in APOE*4−, but not APOE*4+ subjects. Reduced task-associated MTL activation that does not correlate with either visuospatial perspective or task performance suggests that MTL dysregulation occurs prior to clinical symptoms of dementia in APOE*4 carriers.

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Disclosure statement

There are no actual or potential conflicts of interest for the authors that could have inappropriately influenced this work. Subjects were recruited in accordance with the University of Washington Internal Review Board (IRB) approved policies and procedures.

Keywords

Alzheimer; Apolipoprotein; Hippocampus; APOE*4; Perspective; Visuospatial learning; Encoding; Recognition; fMRI; Route; Survey

1. Introduction

Dementia occurs in 10–20% of the population over 65, with Alzheimer's disease (AD), the most common cause of dementia, affecting about 4 million Americans (60). Although cognitive impairment precedes overt AD it can have multiple non-AD etiologies including depression, vascular disease, poor medical health and other forms of dementia (34). Differentiating the multiple etiologies of mild cognitive problems remains clinically difficult and no current test can provide accurate prognostic information regarding the extent of memory impairment an individual may suffer (21). This is especially relevant in AD given that pathological changes may begin before cognitive decline (45) and new treatments are being sought to modify this process (70). Thus identifying individuals who harbor clinically undetectable AD pathology and the ability to monitor their response to treatment will be important for drug development and clinical care.

One approach to clarifying presymptomatic neurophysiologic changes in AD is to study those who are at increased risk of developing AD prior to their manifesting cognitive problems. Carriers of the APOE*4 allele (APOE*4+) have an increased risk of developing mild cognitive impairment (MCI) and AD (11,50,66) and appear to have increased pathologic burden (54, 67). Imaging with PET and SPECT lend support to the hypothesis that the APOE*4 allele worsens AD, with both increased (29,39) and decreased (17,35,39,51) resting metabolism being reported in demented APOE*4 carriers as compared to demented non-carriers. In MCI, carriers of the APOE*4 allele reduced metabolism in the parietal-temporal regions and medial parietal lobe, including the posterior cingulate and retrosplenial area (40), perhaps reflecting greater pathologic burden and worse prognosis for these patients (for review see (10,41)). PET and SPECT metabolic studies also reveal hypometabolism in younger (47,53) and older (48, 52,59) cognitively unimpaired APOE*4+ subjects. Studies with fMRI have been less consistent; both increased (3,19,26,62,71), decreased (36,61) and unchanged (1) BOLD responses have been reported in APOE*4+ subjects and no clear anatomic region is reliably affected. Furthermore, recent fMRI studies suggest that a family history of dementia may modulate the effects APOE*4 on brain activation (33) or more robustly impact brain activation than APOE genotype (1).

The medial temporal lobes (MTLs), including the hippocampus, are essential for visuospatial learning (6) and visuospatial abilities are compromised in pre-clinical AD (58). Likewise, neurofibrillary tangles characteristic of AD are initially found in the MTLs and then later spread dorsolaterally throughout the cortex (4). Although an increased rate of hippocampal volume loss has been found in non-demented APOE*4+ as compared to APOE*4− subjects (9) whether the MTLs in non-demented APOE*4+ subjects are dysfunctional remains unclear. Robust metabolic changes in MTLs of healthy APOE*4 carriers have not been found (14) or not reported alongside consistent metabolic changes in the parietal and retrosplenial regions (48). Several fMRI studies have reported increased MTL activation in cognitively normal APOE*4 carriers using word pair (3,19) or picture learning paradigms (2,33) while reduced MTL activation has also been reported (36,63). Thus the neurophysiologic significance of early volume loss and pathology in the MTLs of APOE*4 carriers remains to be clarified.

In this study we examined older, cognitively normal APOE*4+ and APOE*4− subjects while they engaged in a perspective dependent spatial memory task which has been shown to activate

the MTLs in young subjects (55,57). Separate encoding and recognition periods were evaluated to determine the extent that MTL activation is influenced by the APOE*4 allele and to explore if memory processing (encoding) and retrieval (recognition) are similarly affected. During encoding, subjects viewed animated movies of complex environments from either the route perspective, as if they were walking, or from a survey perspective, as if they were studying a map. During recognition still images of the previous viewed environments were judged as correct or rearranged. This task allows differences in brain activation during allocentric (survey, i.e., world centered) and egocentric (route, i.e., body-centered) encoding and recognition to be explored (42). The MTLs of young subjects during this task respond differently during route and survey encoding, with route encoding producing more robust MTL activation then survey encoding (55) and thus employing this paradigm allows us to explore the regulation of MTL activation during visuospatial memory tasks that vary only in perspective.

2. METHODS

2.1 Participants

The Human Subjects Institutional Review Board of the University of Washington approved this study and written informed consent was obtained. Subjects were recruited via posted flyers and print advertisements that sought older, healthy controls to be part of ongoing aging studies. Their initial evaluation included a thorough history and directed physical exam by a physician, screening cognitive testing, an EKG (when appropriate), and laboratory evaluation including a chemistry panel, compete blood count, thyroid stimulating hormone and B12 levels. Seven APOE*4+ (one 2/4, five 3/4 and one 4/4) and 7 APOE*4− (one 2/3 and six 3/3), with no history of altered social, occupational or cognitive function were recruited. Three APOE*4+ and two APOE*4− subjects had a positive family history for dementia as defined by a parent or sibling having been diagnosed with AD. The Mini Mental State Examination (MMSE) (20) and the logical memory subtest (or similar paragraph (12)) of Wechsler Memory Scale revised (WMS-III), were used to establish normal cognitive functioning for all subjects. In addition, 10 of the 14 subjects (5 APOE*4+ and 5 APOE*4−) completed the Mattis Dementia Rating Scale (DRS) (38); 4 subjects were not given the Mattis DRS secondary to our simplifying cognitive screening in these healthy, normally functioning adults. Exclusion criteria included a) neurologic or psychiatric disease b) alcohol or drug dependence c) unstable or clinically significant systemic medical problems d) visual or hearing deficits which would interfere with cognitive testing e) concurrent use of psychotropic medications including antidepressants, antipsychotics, benzodiazepines, narcotics, anticonvulsants, anti-Parkinsonian medications, cholinesterase inhibitors, glucocorticoids, sedating antihistamines, and CNS acting antihypertensives.

APOE genotyping was done at the Genotyping Core of the UW Alzheimer's Disease Research Center by Hha1 restriction digests of PCR amplified APOE fragments (30). Subjects were age matched and did not differ in their baseline cognitive testing or ability to perform the task (Table 1). Each subject's high resolution structural MRI scan was reviewed for unsuspected pathology. Two APOE*4+ subjects had mild pariventricular white matter (PWM) changes and either a right unilateral, or bilateral, subcaudal lacunae (<10 mm in diameter). One APOE*4− individual had mild PWM changes. Neither the PWM or the lacunae had obvious effects on the functional data from these subjects (data not shown).

2.2 Task procedure

Subjects underwent BOLD-fMRI imaging while performing an environmental memory task designed by Shelton and colleagues (55–57) modified for older individuals by using a single environment during both encoding and recognition portions and allowing subjects six seconds

(rather then three) to identify still images during recognition (details to follow). This task is composed of separate, sequentially presented encoding and recognition runs lasting 342 seconds and 472 seconds, respectively. To ensure that subjects were familiar with identifying objects from the route and survey perspective and understood the requirements of the task they completed practice session outside the MRI suite with an environment not subsequently used during the scanning session. All subjects demonstrated satisfactory understanding and performance of the task after this practice session. During the fMRI session verbal instructions were provided though headphones and visual stimuli through goggles connected via high-resolution fiber optic cables. Stimuli were presented using an Apple computer running PsyScope (psyscope.psy.cmu.edu).

2.2.1. Encoding task—During the encoding run subjects viewed animated movies of an environment (either a park or market) presented from both the route perspective, as if they were walking through it, and the survey perspective, as if flying over it. The environment was shown six times, 3x from the route and 3x from the survey perspective, in an alternating quasi-random order. The individual movies were 46 seconds long and were preceded by 2 seconds of fixation. Three, 18 second fixation blocks (crosshair) were intermixed in the sequence. The run was thus composed of 3 fixation blocks (18 seconds each) + 3 repetitions of the route perspective movie (46 + 2 seconds each) + 3 repetitions of the survey perspective movie (46 + 2 seconds each) in a quasi-random order for a total run time or 342 seconds (TR=2, 171 volumes). Immediately following encoding subjects were tested on their knowledge of the complex environment during the recognition run (see below). Subjects were informed that their memory for the environment would be subsequently tested but active responses were not required during encoding.

2.2.2 Recognition task—During the recognition run subjects viewed still images of the previously studied environment and determined if objects within the environment were; i) correctly positioned (previously seen items in appropriate environmental locations), ii) rearranged (previously seen items shuffled within the environment), or iii) they couldn't tell (don't know). A total of 64 images were presented; 32 from the route perspective (4 blocks of 8 images, each block preceded by 2 seconds of fixation) and 32 images from the survey perspective (4 blocks of 8 images, each block preceded by 2 seconds of fixation). Four, 18 second fixation blocks (crosshair) were intermixed in the sequence. The entire run was thus composed of 4 fixation blocks (18 seconds each) + 4 route perspective picture blocks (48 + 2 seconds each) + 4 survey perspective picture blocks (48 + 2 seconds each) in a quasi-random order for a total run time of 472 seconds (TR=2, 236 volumes). Following the fMRI session subjects were asked to draw the environment to ensure they had completed the task appropriately (data not scored).

2.3. Imaging and Analysis

2.3.1 BOLD imaging—Structural and functional MRI were performed on a 1.5 T MR imaging system (General Electric, Waukesha, WI). Coronal anatomic (TR/TE 200/2.2 msec) and functional (TR 2000/50 msec, flip angle 90°, 64 × 64 matrix, in plane resolution of 3.75 mm) images were collected using a two-dimensional gradient-echo echo-planar pulse sequence. Each volume consisted of 20 coronal slices spaced 5.5 mm apart (total anterior-posterior imaged area = 11 cm) to optimize the visualization of the MTL, thus the frontal and occipital poles were not included in the functional data set. Given this partial coverage of our functional images we refer to "whole image analysis" rather then "whole brain analysis" when performing group modeling.

2.3.2. Whole image analysis—Functional data were processed using tools from the FMRIB Software Library (www.fmrib.ox.ac.uk and (64)). Prior to automated procedures each

functional series was manually reviewed and aberrant volumes or extreme motion artifacts were removed. Motion correction (31), spatial smoothing with a 7mm at half-maximum Gaussian kernel and low pass and high pass (sigma = 150 sec) filtering were applied. The first 5 volumes of each functional series were discarded to allow T1 equilibrium and statistical analysis was carried out using a general linear model (GLM). Each subject's data was modeled two ways allowing for both task-fixation and route-survey contrasts could be explored. First, route and survey were each assigned their own explanatory variable (EVs) to compare task-associated activation with fixation. Second, the fixation volumes (27 from encoding and 36 from recognition) were removed from the data allowing a single EV to model the route-survey contrast. This approach was used given the imbalanced nature of our paradigm that included more task blocks then fixation blocks. Absolute motion varied from 0.1mm – 1.2 mm and relative motion varied between 0.04 mm – 0.22 mm.

Group comparisons were obtained by mapping each subjects EPI functional images onto their high resolution structural images using 7 DOF and into standard space (MNI152 brain) with a 12 DOF affine transformation (32). Group mixed effects analysis (72) was used and activated clusters were identified based on random field theory and cluster analysis which corrects for multiple comparisons. APOE genotype, task performance, age and the interaction of task performance x genotype were included as covariates in the general linear model (GLM). Both whole-group contrasts (n=14 subjects) and between-group contrasts (n=2 groups, seven subjects per group) were explored to determine whether age, genotype and/or performance could predict BOLD signal changes. Neither whole-group or within-group analysis revealed activation that was correlated with age at reported z-thresholds (data not shown).

2.3.3. ROI analysis—A MTL region of interest (MTLroi) was demarcated for each subject on their high-resolution structural image and used as a mask to determine average z-scores from the individual's functional scan. The MTLroi consisted of the hippocampus and parahippocampal gyrus anteriorly from the final section containing the inferior horn of the lateral ventricle, restricted laterally by the collateral sulcus and extending posteriorly until the disappearance of the corpus callosum. The posterior MTLroi included the isthmus connecting the parahippocampal and cingulate gyrus. Average MTLroi volume was 19.3 ± 2.0 cm^3 (ave. ± s.d.) in APOE*4− subjects and 18.8 ± 2.5 cm^3 in APOE*4+ subjects (n.s.). MTLroi statistics were performed using STATA™.

RESULTS

3.1. Activation during encoding

3.1.1. Whole image analysis—Viewing the environmental movies from either the route or survey perspective induced BOLD signal changes in the lingual and fusiform gyri, retrosplenial regions and MTLs in APOE*4− subjects (within-group contrasts, Fig. 1a). The route perspective further activated regions of the parietal (Fig. 1a, top) and frontal lobes (not shown) that are not activated during survey encoding (Fig. 1a, bottom). Visual inspection suggests that APOE*4+ subjects displayed less encoding task-associated activation as compared to APOE*4− subjects (Fig. 1b). In APOE*4+ subjects, both route and survey encoding activated the fusiform gyrus while deactivations in lateral temporal-parietal regions were found during survey encoding (Fig. 1b, bottom). No regions of deactivation were found in APOE*4− subjects. Between-group contrasts revealed significantly greater task-associated activation in APOE*4− subjects during both route and survey encoding in multiple posterior temporal, parietal and occipital regions including the MTL bilaterally (Fig. 2a).

Perspective-dependent MTL activation was determined by comparing BOLD responses during route and survey encoding within individual subjects (route-survey differential). Within the APOE*4− group, route encoding activated the bilateral MTLs, left frontal (BA 4 & 6) and right

temporal-parietal regions (BA 37, 39 & 40) more than survey encoding (Figure 3a), whereas survey encoding did not induce more activation than route encoding in any region. A route-survey differential was not found in the APOE*4+ group even when less stringent comparisons were performed (data not shown). Between-group contrasts of the route-survey differential in the MTL revealed a significant group difference, with APOE*4− subjects having a greater route-survey differential then APOE*4− subjects (data not shown, p = 0.009 (right MTL) and p = 0.037 (left MTL)).

3.1.2. ROI analysis of the MTLs—Given our a priori hypothesis that MTL activation would be modulated by the APOE*4 allele and our results from the whole image analysis we chose to further explore MTL activation through ROI analysis (MTLroi which included the entire anterior-posterior extent of the hippocampus and parahippocampal gyrus). Average task-associated and route-survey differential MTLroi z-scores were determined in each subject. Within the MTLroi, on average, APOE*4− subjects had greater task-associated activation then APOE*4+ subjects during both route encoding (APOE*4− 2.6 ± 1.6 and APOE*4+ 0.1 ± 1.5, p = 0.012 unpaired t-test) and survey encoding (APOE*4− 1.6 ±1.5 and APOE*4+ −0.4 ± 1.2, p = 0.023 unpaired t-test) (Fig. 2b). Likewise, the APOE*4− group, but not the APOE*4+ group, had a significant route-survey differential in the MTLroi during encoding (APOE*4− = 1.69 ± 1.22, APOE*4+ = 0.04 ± 1.04, p = 0.02 unpaired t-test). All 7 APOE*4− subjects had an average route-survey differential z-score of greater than 1.5, whereas none of the APOE*4 − subjects had an average MTLroi positive z-score of this magnitude (Figure 3b).

3.2. Activation during recognition

Immediately following the encoding scan, subjects were imaged while identifying still images from the previously seen environments as correct or rearranged. Activation of the lingual and fusiform gyri, retrosplenial areas, and medial and dorsal prefrontal regions (BA 6, 8, 24 and 32) was apparent in both groups while making recognition judgments (data not shown). However, no significant activation differences were found between groups or within groups (i.e., the route-survey differential) even when the z-threshold was made less stringent. MTLroi analysis revealed that average z-scores within the MTLroi during recognition were less than during encoding but they did not differ for APOE*4− and APOE*4+ subjects during route image (APOE*4− 0.5 ± 1.5 and APOE*4+ 0.2 ± 2.4, n.s.) or survey image (APOE*4− 0.4 ± 1.9 and APOE*4+ 0.1 ± 3.2, n.s.) viewing.

3.3. Performance correlated activation

During recognition, APOE*4− and APOE*4+ subjects distinguished still images as previously seen vs. rearranged with similar efficacy (Table 1) and whole-group analysis showed that performance worsened with age ($F(1,12) = 8.55$, $p = 0.012$, $r^2=0.42$). A full ANOVA within the FSL environment was used to assess between-group differences in how task-associated activation during encoding and recognition predicted recognition performance (RP) (dependent variable = 3D task-associated activation maps; predictor variables = genotype, RP, age, RP*genotype). During route encoding we found a significant route-RP*genotype interaction in the left MTL (p=0.01) and a potential interaction in the posterior right parahippocampal region (p=0.08) (Figure 4a). ROI analysis of these combined clusters reveals that greater route-RP was associated with less task-associated MTL activation in APOE*4−, but not APOE*4+, subjects (Figure 4b). Average MTLroi z-scores are similarly correlated with route-RP with lower MTLroi task-associated activation predicting better route-RP in APOE*4 −, but not APOE*4+, subjects (data not shown; dependent variable = average MTLroi z-scores; predictor variables = genotype, route-RP, route-RP*genotype; $F(3,10)$, $p=0.01$, $r^2=0.65$)). Survey-RP was did not correlate with MTL activation in either genotype during encoding and no performance x activation interactions were identified for either genotype during the recognition period.

4. DISCUSSION

Using a visuospatial memory task we evaluated BOLD signal responses in cognitively normal APOE*4+ and APOE*4− subjects. During memory encoding there was robust task-associated activation of the MTL in APOE*4− subjects that varied with perspective and recognition performance. APOE*4+ subjects had minimal MTL task-associated activation that was not modulated by perspective or recognition performance. No significant APOE*4 effects were found during recognition. This suggests that the MTL/cortical systems are utilized differently or dysregulated in APOE*4 carriers during visuospatial memory encoding prior to their having visuospatial difficulties. Moreover, it appears the neural systems utilized during encoding are more affected by the APOE*4 allele than those used during recognition in this visuospatial memory task.

4.1 Altered brain activation in APOE*4 carriers

Prior studies have reported fMRI alterations in cognitively normal (2,7,19,33,36,61,71) or mildly impaired (3,15) APOE*4+ individuals. However, there is considerable variability in both the direction and pattern of the differences. Increased activation has been reported during verbal (3,19) and visual (2) learning paradigms while decreased activation has been found during a naming task (61) and a semantic judgment task (36). Furthermore, not all tasks result in consistently different BOLD responses in APOE*4+ and APOE*4− subjects (see (1) vs (3) (7). The extent of BOLD signal differences also varies. Both large regions of the cortex (3) and more selected regions (2,19,36,61) have been found to differ between APOE*4 carriers and non-carriers. The sundry cognitive protocols used, various analysis methods and heterogeneous subject populations complicates direct comparison of these reports. Not all APOE*4 carriers will develop dementia, thus it is not possible to estimate if/when a given APOE*4+ individual will develop cognitive symptoms. In fact, two recent reports have assessed very similar contrasts (novel vs. familiar words) and reported conflicting findings regarding MTL activation (19,36).

Our study contributes to previous work in several regards. First, it is the only study to use a complex visual environment to assess visuospatial learning. The MTLs are known to be involved in visuospatial tasks (6) and thus we chose our task to specifically evaluate this region. Second, we used whole image group analysis to establish the relative specificity of BOLD signal changes during our task to the MTLs and restricted our ROI analysis to this a priori identified ROI. Third, a single previous study (3) reported that APOE*4 mediated BOLD responses were similar during encoding and recall period, and in their analysis encoding and recall data were pooled in order to analyze overall task related activation independent of baseline. Our evaluation of encoding and recognition separately suggests that encoding may be more affected by the APOE*4 allele than recognition. Finally, the environmental memory paradigm was designed to evaluate the tight contrast between route and survey perspectives, a comparison not dependent on baseline activation. “Loose” contrasts compare dissimilar cognitive states, such as a demanding memory task vs. fixation, while “tight” contrasts compare highly similar conditions theoretically allowing for greater specificity when reporting activation differences (16). Designating loose and tight contrasts is somewhat arbitrary, but only two prior APOE*4 fMRI studies have clearly used tight contrasts (19,36).

4.2. MTL activation in APOE*4 carriers

On average, we found less task-associated activation of the MTLs in APOE*4 carriers than non-carriers. “Task-associated” activation is defined here as the loose contrast between the BOLD signal while looking at a cross-hair (rest) vs. the BOLD signal induced when viewing the route or survey movie. Reduced task-associated activation could reflect either an increased BOLD signal at rest, a decreased BOLD signal during the task, or a combination of both. The

baseline state is thought to be altered in AD (25,37) and thus we have chosen to use the term "task associated activation" rather than "total activation" to reflect our inability to actually compare blood flow in our subjects. Our APOE*4 carriers and non-carriers performed similarly during the task and during baseline neuropsychological testing implying that reduced task-associated activation in APOE*4+ subjects does not reflect ineffectual brain use, only altered/different regulation of cortical systems. Our paradigms contained more task volumes (144 for encoding and 200 for recognition) then fixation volumes (27 for encoding and 36 for recognition). This imbalanced design reduces our power to detect task-associated differences secondary to the comparatively high variance of the short fixation blocks. Thus although task-associated activation is reduced in APOE*4− subjects, the lack of any significant activation in visuospatial regions should be interpreted cautiously.

Maintained cognitive performance in the elderly has been associated with increased BOLD responses as compared to similarly performing younger subjects suggesting that compensation occurs in older, less efficient, brains (23). Likewise, greater activation in APOE*4+ subject groups has been observed (2,3,19) and suggested to reflect a compensatory response which burns out if dementia ensues (2). However, we found on average less, rather than more, task-associated activation in the MTL of APOE*4+ subjects, and no regions where APOE*4+ subjects had greater activation than APOE*4− subjects. Thus our findings do not support the hypothesis that there are region-specific compensatory increases in task-associated activation in cognitively normal APOE*4 carriers.

4.3 Perspective dependent MTL activation

Route perspective encoding led to greater MTL activation than survey encoding in APOE*4−, but not APOE*4+ subjects. The APOE*4− response is consistent with the original findings with this task in younger individuals (mean age 23) (55) and with greater inferior occipital gyral activation found when a scene is viewed from the ground/immersed-observer perspective versus the aerial/external-observer perspective (68). These results appear at odds with the long standing theory that allocentric memory is dependent on the hippocampus (42). However, the human hippocampus contains place responsive cells while the parahippocampal cortex contains objects responsive cells (18). The resolution and distortion of our fMRI data does not allow us to independently visualize these regions. Thus, we do not believe that greater activation of the MTLs during route encoding should be interpreted as suggesting that the MTLs are more important during egocentric than allocentric learning. Rather, greater cognitive demands of route perspective learning which requires binding of extrapersonal and intrapersonal information may have lead to greater MTL activation during egocentric encoding. Curiously, our subjects generally reported that the route perspective was more difficult to learn then the survey perspective (unquantified). Right frontal (~BA 4, 6) and left parietal (~BA 37, 39, 40) areas also appeared more active during route than survey encoding in APOE*4− subjects. Failure of prefrontal activation to increase with increasing task demands has been observed in APOE*4+ subjects (44) and thus the lack of a prefrontal route/survey differential may illustrate impaired prefrontal recruitment during difficult tasks in APOE*4− subjects.

Lack of perspective dependent MTL activation in APOE*4+ subjects could reflect neurophysiologic changes in several regions. Damage to the parietal cortex has been associated with problems in the egocentric reference frame and hemineglect (6), while MTL dysfunction severely compromises allocentric processes (27) and survey memory (6). Dorsal and medial parietal regions are hypometabolic in APOE*4 carriers (48), while the MTLs are the initial site of AD-like pathology (4) and thus dysfunction of either anatomical site could account for the lack of differential MTL route/survey activation. Alternatively, dedifferentiation of visuospatial information processing and activation of a more generalized network may be occurring in APOE*4+ subjects. Dedifferentiation of neural systems is thought to be one cause

of altered activation patterns in elderly subjects (46) and AD subjects activate cortical networks during easy tasks that are only activated by difficult tasks in control subjects (65). Furthermore, both visual processing (43) and the specificity of the dorsal-ventral visual pathways (8,22) can become less cortically distinct with aging. Thus either dysfunction of a single region or dedifferentiation of cortical networks could account for the lack of a route/survey MTL activation differential in APOE*4+ subjects.

4.4. Performance correlated MTL activation

Numerous studies have reported associations between brain activation and memory performance in the prefrontal, medial temporal and parietal lobes (for reviews see (49,69). Objects that are remembered are often associated with a greater BOLD signal than forgotten items (49). The block design of our experiment does not allow for the comparison of the BOLD signal during encoding (when viewing a specific object) and whether the position of that object is subsequently correctly recognized. However, we were still able to observe a relationship between MTL encoding activation and recognition performance in APOE*4− subjects, with better recognition performers having less MTL activation during encoding (Figure 4). This may reflect the greater efficiency of the MTL lobes in good route recognizers (for review, (28). Alternatively, good route-encoders could rely on other brain areas (i.e. right frontal or left parietal) when learning egocentric visuospatial material. This is in agreement with the hypothesis that parietal-based egocentric reference frame is converted into the medial temporal-based allocentric reference through a pathway that involves retrosplenial region (5), an area activated in APOE*4− than APOE*4+ subjects during both the route and survey encoding periods.

4.5 Family history and study limitations

Having a family history of dementia (FH+) has been reported to effect BOLD responses in both APOE carriers and non-carriers (1,33). Our study was not designed to address this issue and our subjects were not initially matched for this confound. Fortunately, our groups were relatively balanced with three of our APOE*4 carriers and two of our non-carriers being FH +. Direct contrasts of subjects with (n=5) and without (n=9) a FH+ (simple t-test) or inclusion of family history as a covariate in our group comparisons (full ANOVA) did not result in significant family history associated activation differences in any brain region (data not shown, low stringency contrast with z-threshold=2.0 and $p < 0.1$). The small number of individuals and unbalanced comparison reduce our power to detect an influence of FH and future studies will need to explore this issue. However, it does appear that APOE genotype influences the BOLD response more robustly than family history in our subjects and thus our primary comparison remains valid.

The small sample size of this study reduces our power to detect within-group and between-group differences (type II error) while increasing the likelihood of accepting false results (type I error) especially in our whole-brain analysis using FSL. For this reason we obtained the average z-scores from MTLroi to illustrate activation in individual subjects and to confirm our whole-brain results. Although average task-associated activation overlaps between groups (Figure 2b), within the MTL there is a non-overlapping distribution of route-survey differential z-scores (Figure 3b). Uncorrected p-values are reported for these z-score comparisons because we are essentially contrasting regions that had been previously found to be significantly different by our corrected, mixed-effects GLM analysis. Thus the simple t-tests of average z-scores within the MTLroi may be unnecessary, but informative.

4.6 Summary

In summary, we found that the APOE*4 allele modulates MTL activation in cognitively normal older subjects. Task-associated, perspective dependent and performance correlated BOLD

signal changes in the MTLs were all different on average in APOE*4 carriers and non-carriers. Reports of altered visuospatial abilities in cognitively normal middle-aged APOE*4 carriers (24) and brain metabolic changes in young APOE*4 carriers (47,53) raise the possibility that neurophysiologic alterations seen in APOE*4 carriers could reflect a "trait" rather than a "state". This raises the question of whether altered BOLD responses in these older APOE*4+ subjects represents a pre-dementia state or reflects a life-long difference in neuronal activation or neurovascular coupling. Neurovascular coupling is affected by aging and disease (13) and whether AD or the APOE*4 allele affects the process remains unknown. Future fMRI studies could address this issue by quantifying BOLD signal changes in younger APOE*4+ populations.

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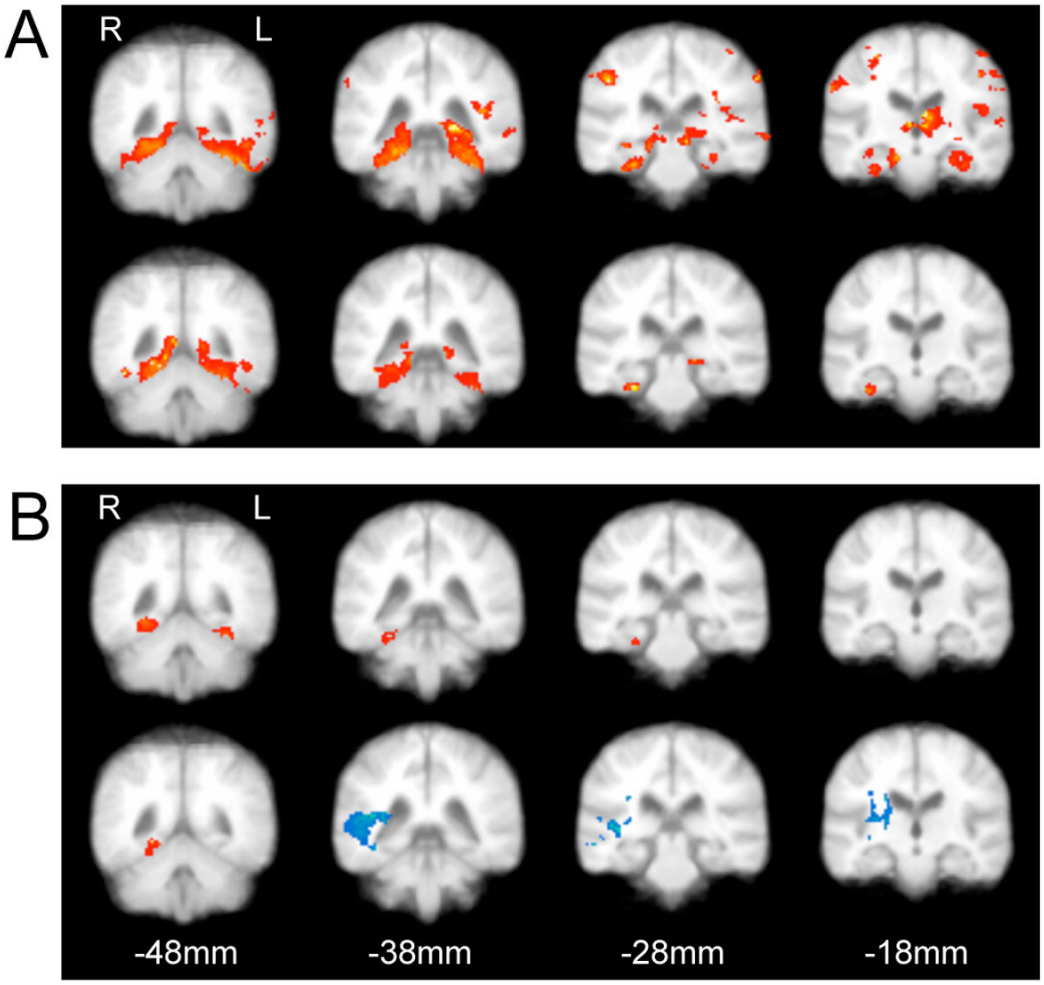

Figure 1.
Cortical activation during route and survey encoding contrasted with fixation. (a) APOE*4− subjects displayed robust activation of MTLs, ventral occipital regons areas and prefrontal cortex (not shown) during both route (upper) and survey (lower) encoding. (b) APOE*4+ subjects had less overall task associated activation during encoding which statistically was limited to the fusiform gyrus during route (upper) and survey (lower) encoding. An area of deactivation (blue) in the temporal/parietal regions was evident during survey encoding. Within-group contrasts with z-threshold = 2.7 and $p < 0.01$ (n=7 per group).

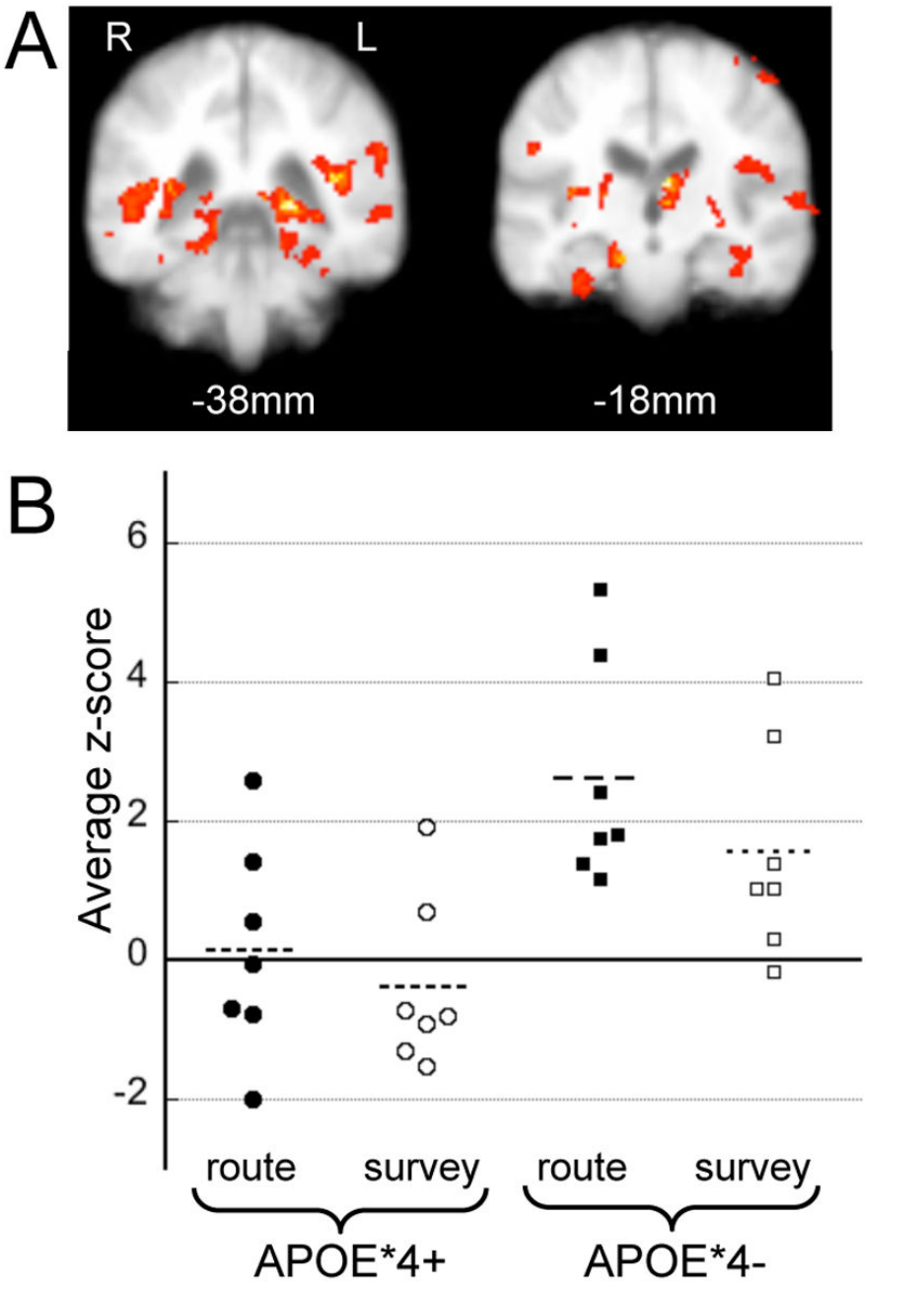

Figure 2.
Regions of greater activation in APOE*4− than APOE*4+ subjects during encoding. (a) Regions where APOE*4− subjects had greater BOLD signal during either route or survey encoding include the posterior (left) and anterior (right) MTLs and areas around the occipital-temporal-parietal junction. Between-group contrasts with z-threshold = 2.5 and $p < 0.01$ (n=14). (b) Average z-scores for individual subjects in the MTLroi during route (filled symbols:●,■) and survey (open symbols: ○, □) encoding. APOE*4− subjects (■, □) and APOE*4+ subjects (●, ○).

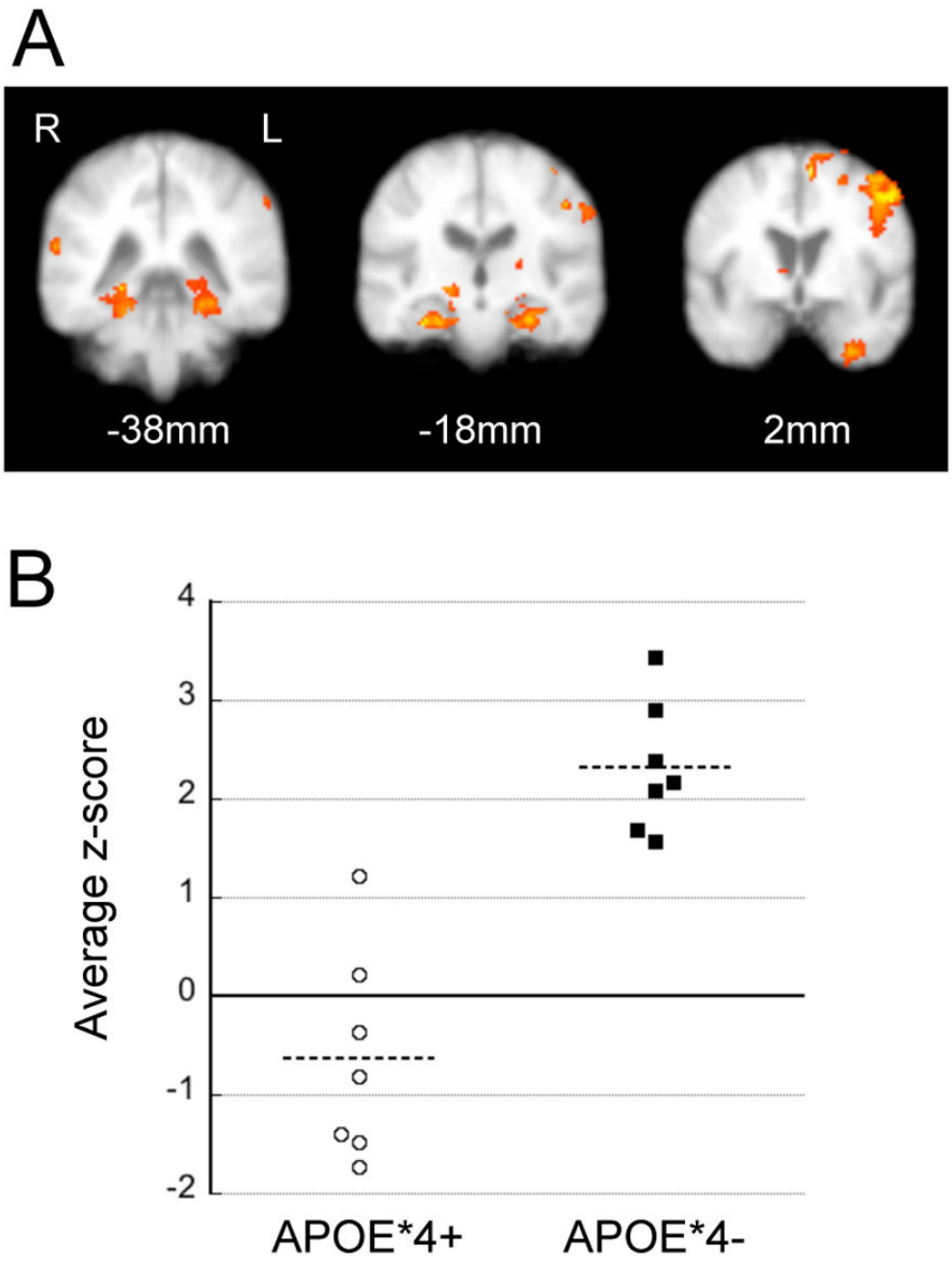

Figure 3.

Route/survey activation differential in APOE*4− subjects. (a) Regions of greater activation during route than survey encoding in APOE*4− subjects include the MTLs bilaterally, the left frontal and the right parietal cortex. Within-group contrasts with z-threshold = 2.5 and $p < 0.01$ (n=7). (b) Average route/survey differential z-scores in individual subjects within the MTLroi. APOE*4− subjects (■) and APOE*4+ subjects (○).

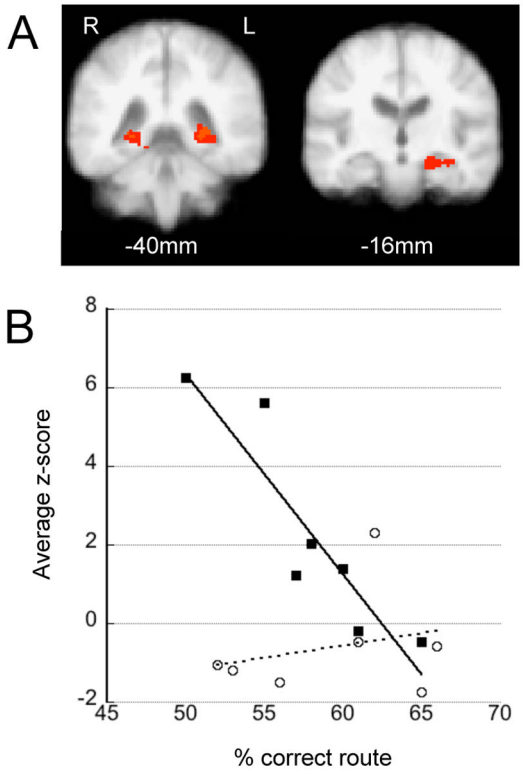

Figure 4.

Performance correlated activation in the MTLs during encoding. (a) Areas where there is a genotype x performance interaction in the left (p=0.01) and posterior right (p=0.08) MTLs during route encoding. Z-threshold = 2.3. (b) Average z-scores within these areas (combined) during route encoding correlate with performance in APOE*4− but not APOE*4+ subjects. APOE*4− subjects (■) and APOE*4+ subjects (○).

Table 1

Cognitive screening and recognition performance

	APOE*4− (n=7)	APOE*4+ (n=7)
Age	73.3 ± 7.4	72.4 ± 7.1
MMSE	29.1 ± 1.7	28.1 ± 1.6
Paragraph memory		
-immediate	14.6 ± 4.3	10.4 ± 4.4
-delayed	11.9 ± 6.4	9.3 ± 4.5
Mattis DRS*		
Total Score	137.0 ± 2.3	139.6 ± 3.1
Subscores		
attention	35.8 ± 1.8	36.2 ± 0.8
initiation	35.8 ± 0.8	36.2 ± 1.1
construction	5.8 ± 0.4	5.6 ± 0.9
conceptualization	37.6 ± 2.2	38.6 ± 0.9
memory	22.4 ± 0.5	23.0 ± 1.0
visual memory	4.0 ± 0.0	3.8 ± 0.4
Correct route (%)	57.9 ± 4.3	59.1 ± 5.1
Correct survey (%)	62.9 ± 13.1	60.5 ± 10.9
“Don’t know” route (%)	10.7 ± 7.3	5.4 ± 4.6
“Don’t know” survey (%)	9.8 ± 9.1	9.8 ± 6.8

Performance on all cognitive screening tests were within the normal range for both groups and all differences between groups are not significant ($p > 0.05$). The correct route (%) and correct survey (%) during recognition are significantly different from chance (50%) $p < 0.05$ for both genotypes. All values are means ± standard deviation. Mini-Mental Status Exam (MMSE).

* Data from 5 APOE*4− and 5 APOE*4+ subjects.