Published in final edited form as:

Neuropsychologia. 2011 July ; 49(9): 2448–2455. doi:10.1016/j.neuropsychologia.2011.04.022.

Reduced hippocampal activity during encoding in cognitively normal adults carrying the APOE ε4 allele

Maheen M. Adamson^{1,2}, J. Benjamin Hutchinson³, Amy Shelton⁴, Anthony D. Wagner³, and Joy L. Taylor^{1,2}

¹ Department of Veterans Affairs, Sierra-Pacific MIRECC and WRIISC Palo Alto, California ²

Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine,

Stanford, California ³ Psychology Department, Stanford University, Stanford, California ⁴

Department of Psychological and Brain Sciences, John Hopkins University, Baltimore, Maryland

Abstract

Apolipoprotein (APOE) ε4-related differences in memory performance have been detected before age 65. The hippocampus and the surrounding medial temporal lobe (MTL) structures are the first site affected by Alzheimer's disease (AD) and the MTL is the seat of episodic memory, including visuo-spatial memory. While reports of APOE ε4-related differences in these brain structures are not consistent in either cross-sectional or longitudinal structural and functional magnetic resonance imaging (fMRI) studies, there is increasing evidence that brain activity at baseline (defined as activity during fixation or rest) may differ in APOE ε4 carriers compared to non-carriers. In this fMRI study, cognitively normal APOE ε4 carriers and non-carriers engaged in a perspective-dependent spatial learning task (Shelton and Gabrieli, 2002) previously shown to activate MTL structures in older participants (Borghesani et al., 2008). A low-level, visually engaging dot-control task was used for comparison, in addition to fixation. APOE ε4 carriers showed less activation than non-carriers in the hippocampus proper during encoding. Specifically, when spatial encoding was contrasted against the dot-control task, encoding-related activation was significantly lower in carriers than non-carriers. By contrast, no ε4-related differences in the hippocampus were found when spatial encoding was compared with fixation. Lower activation, however, was not global since encoding-related activation in early visual cortex (left lingual gyrus) was not different between APOE ε4 carriers and non-carriers. The present data document APOE ε4-related differences in the hippocampus proper during encoding and underscore the role of low-level control contrasts for complex encoding tasks. These results have implications for fMRI studies that investigate the default-mode network (DMN) in middle-aged to older APOE ε4 carriers to help evaluate AD risk in this otherwise cognitively normal population.

Keywords

Medial Temporal Lobe; Hippocampus; Learning; Visuo-spatial; APOE ε4; Memory

CORRESPONDENCE: Maheen M. Adamson, Ph.D, Stanford/VA Aging Clinical Research Center, 3801 Miranda Avenue (151Y), Palo Alto, CA, 94304, Tel: (650) 493-5000 x62179, Fax: (650) 852-3297, madamson@stanford.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Carriers of Apolipoprotein (APOE) $\epsilon 4$ are at an increased risk of developing late onset Alzheimer's disease (AD) (Corder et al., 1993; Saunders et al., 1993; Tanzi and Bertram, 2001). Carrying at least one $\epsilon 4$ allele is a predictor of clinical progression from Mild Cognitive Impairment (MCI) to AD (de Leon et al., 2007; DeCarli et al., 2001; Landau et al., 2009; Petersen et al., 1995). In cognitively normal populations, APOE $\epsilon 4$ -related differences in neuropsychological task performance have been detected before age 65 (Adamson et al., 2010; Blair et al., 2005; Caselli et al., 2009; Kozauer et al., 2008;), although differences are typically modest (Small et al., 2004; Wisdom et al., 2011). The medial temporal lobe (MTL) is the seat of episodic memory (Eichenbaum, 2000; Schacter and Wagner, 1999; Squire et al., 2004), including visuo-spatial memory (Burgess et al., 2002), and the first site affected by AD (Braak and Braak, 1997). However, reports of APOE $\epsilon 4$ -related differences in brain structure, particularly in the MTL, are not consistent (Weirenga et al., 2007). This is especially the case in cross-sectional studies, which have alternately revealed smaller and no difference in hippocampal volumes in APOE $\epsilon 4$ carriers compared to non-carriers (reviewed in Adamson et al., 2010). While it is possible that the impact of APOE $\epsilon 4$ on hippocampal volume changes over time will turn out to be larger or more consistent than single-time point assessments, more timely methods of assessing early indications of AD pathology are needed. Functional magnetic resonance imaging (fMRI) studies frequently focus on MTL subregions to capture activation patterns that are predictive of subsequent clinically significant decline (Bookheimer et al., 2000) and predictive of progression from MCI to AD (Machulda et al., 2003). Studying APOE $\epsilon 4$ -related hippocampal and MTL cortical activity differences during an episodic memory task may prove promising for evaluating the risk of AD associated with APOE $\epsilon 4$ genotype in cognitively normal older adults.

Results from recent fMRI studies using episodic memory paradigms, however, have not been consistent in evaluating the APOE $\epsilon 4$ risk for AD in cognitively normal older adults (Cherbuin et al., 2007; Trachtenberg et al., 2010). Several studies followed the approach of measuring brain activity relative to fixation or rest periods. While an increase in MTL Blood Oxygen Level Dependent (BOLD) activity was reported in APOE $\epsilon 4$ carriers using word-pair (Bookheimer et al., 2000; Fleisher et al., 2005) and verbal paired-associate tasks (Han et al., 2007), a decrease was reported in APOE $\epsilon 4$ carriers during spatial learning (Borghesani et al., 2008) and semantic categorization (Lind et al., 2006). No APOE $\epsilon 4$ -related differences were reported during another paired-associate task (Bassett et al., 2006).

There is increasing evidence (Gusnard and Raichle, 2001; Stark and Squire, 2001) that 'baseline' fixation and rest conditions of functional imaging paradigms are associated with activation in the MTL. Studies that used rest or fixation conditions to examine the default mode network (which includes the MTL as a node) have reported abnormal activity in cognitively normal APOE $\epsilon 4$ carriers (Fleisher et al., 2009; Pihlajamaki and Sperling, 2009). Several fMRI studies examining possible APOE $\epsilon 4$ -related differences during episodic memory encoding avoided the baseline issue by using 'tighter' or 'higher-level' contrasts, such as comparisons between the encoding of novel versus familiar stimuli. Three of these studies found reduced MTL activation in $\epsilon 4$ carriers compared to non-carriers during encoding of novel versus familiar words or pictorial stimuli (Borghesani et al., 2008; Lind et al., 2006; Trivedi et al., 2006). Two other studies found that the direction (increase or decrease) of differences in activation between APOE $\epsilon 4$ carriers and non-carriers in MTL during encoding of novel versus familiar items also depends on family history of AD (Johnson et al., 2006) and laterality (Bondi et al., 2005).

Han et al. (2007), on the other hand, have argued that comparing two high-level contrasts, such as novel and familiar conditions, may both entail encoding in the MTL making it difficult to isolate encoding processes relative to the task at hand (see also Buckner et al., 2001). Despite this argument, using fixation as a low-level contrast is not an appropriate baseline state for assessing the underlying encoding processes involved in a complex cognitive task, because fixation has been repeatedly observed to activate the MTL (Stark and Squire, 2001). With these issues about high- versus low-level task contrasts in mind, the present study used a visually engaging dot-control task, in addition to fixation, to provide a low-level control that may provide a cleaner assessment of differences between healthy APOE $\epsilon 4$ carriers and non-carriers in MTL activation during encoding.

Recently, deIpoli and colleagues (2007) reported that atrophy in MTL regions involved in navigation – mainly the hippocampus, parahippocampus and retrosplenial cortex – is accompanied by navigation deficits in AD and MCI, suggesting that assessments of spatial memory can serve as an important marker for AD-related cognitive deficits. Topographic disorientation, or the feeling of being lost, is often reported as an early symptom of AD and worsens with disease progression (Pai and Jacobs, 2004). Two distinct methods – survey and route learning assays – have been previously employed to assess spatial learning and memory. Survey learning requires utilization of the relationships between landmarks and the environment, from a bird's eye view, resulting in acquisition of a global spatial representation. In contrast, route learning results in the building of a spatial representation from an egocentric ground-level perspective.

Extensive evidence implicates a putative 'spatial network', inclusive of the hippocampus, parahippocampal gyrus, posterior parietal, and retrosplenial regions, and interactions between these regions, in spatial learning (Moscovitch et al., 2006; Seltzer and Pandya, 1984; Suzuki and Amaral, 1994). For example, extant evidence suggests that the right hippocampus, parahippocampal gyrus, posterior parietal cortex, and anterior temporal cortex play an important role in creating allocentric cognitive maps (Burgess et al., 2002; Gorno-Tempini and Price, 2001; McNamara and Shelton, 2003). The hippocampus is also implicated in building "cognitive maps" during spatial learning from a route perspective, such that information about objects and their location in the local environment is updated as one moves through space (Shelton and Gabrieli, 2002; Shelton and McNamara, 2004). It is important to note that the true nature of egocentric and allocentric systems varies on other dimensions as well, including whether one is in the space or external to it, and whether the global structure is more readily available. Nevertheless, the putative 'spatial network' is active during environment encoding via perspective-dependent learning tasks, with a subset of regions being active both when stimuli are encoded from a survey perspective and from a route perspective (Shelton and Gabrieli, 2002; Shelton and McNamara, 2004).

Recently, Borghesani and colleagues (2008) utilized a perspective-dependent learning task (Shelton and Gabrieli, 2002) to explore APOE $\epsilon 4$ -related differences in brain activation during survey and route encoding. When compared with fixation, this study revealed reduced MTL activity during the encoding of both survey and route perspectives in APOE $\epsilon 4$ carriers. In addition, when compared with survey encoding, there was reduced MTL activity during route encoding in APOE $\epsilon 4$ carriers.

Building on these observations, the present study examined APOE $\epsilon 4$ -related differences in hippocampal activity during a perspective-dependent learning task in older adults. This task has previously shown to activate the MTL robustly in young (Shelton and Gabrieli, 2002; Shelton and Pippitt, 2007) and older (Borghesani et al., 2008) adults. In addition to fixation, we employed a low-level, visually engaging dot-control task for comparison with the route and survey encoding tasks. The hypotheses were:

1. APOE ϵ 4 carriers will show reduced activation, relative to non-carriers, in the hippocampus proper during encoding of route and survey perspectives compared to the dot-control task. This is based on previous findings suggesting that APOE ϵ 4 carriers may not activate hippocampus and the surrounding MTL structures to the extent that non-carriers do, perhaps due to functional and/or structural dysregulation that may indicate AD-related processes (Braak and Braak, 1997).
2. Additionally, APOE ϵ 4 carriers will show reduced activation, relative to non-carriers, in regions beyond the hippocampus proper that are involved in encoding (compared to the dot-control task). We focused on regions implicated in the default mode network (DMN), as reported in Pihlajamäki et al (2009).

2. Materials and methods

2.1. Participants

A total of 26 cognitively normal adults (4 women and 22 men) were enrolled. Out of these participants, data from 5 participants were excluded from analysis: 3 due to movement greater than 4 mm, 1 due to a software problem, and 1 due to problems with hippocampal structural segmentation. Therefore, data from 21 participants (3 women and 18 men) were analyzed. Ten of the 21 adults were APOE ϵ 3/4 carriers and the remaining 11 had the ϵ 3/3 genotype. See Table 1 for demographics according to APOE ϵ 4 status. All participants performed within normal limits on Rey AVLT delayed recall (range = 5 to 15/15 words recalled), Trail Making B (range = 32 to 107 sec) and FAS phonemic fluency tests (range = 23 to 54 words), based on published age-based norms (Geffen, 1995; Ivnik et al., 1992; 1996; Tombaugh et al., 1996; Tombaugh et al., 1996). Participants ranged in age from 54–73 years (mean = 63.75 ± 5.3). Only six participants were on hypertension medication.

These participants were selectively recruited from participants of the ongoing longitudinal Stanford/VA Aviation Study who had been previously genotyped for APOE. (Of 190 APOE-genotyped participants in the Aviation Study, 56.84% have the ϵ 3/3 genotype, 22.1% have the ϵ 3/4 genotype, 2.1% ϵ 4/4, and the remaining have one or two ϵ 2 alleles). Allele frequencies in the main aviator cohort were: ϵ 2 = 10.3%, ϵ 3 = 76.3% and ϵ 4 = 13.4%. These allele frequencies are typical for nondemented Caucasian populations (Farrer et al., 1997). Entry criteria for the longitudinal Aviation Study are: age between 40 and 69 years, current FAA medical certificate, and currently flying with at least 300 but no more than 15,000 hours of total flight time. The majority of Aviation Study participants are recreational pilots, although a minority are flight instructors, air transport pilots, or have had job duties that include aircraft piloting or mechanics (See Taylor et al. (2007) for additional details). Informed consent, approved by Stanford University and VA Palo Alto Health Care System Institutional Review Boards, was obtained from each participant.

2.2. Procedures

2.2.1. DNA acquisition and APOE genotyping—APOE genotyping was performed with genomic DNA extracted from samples of frozen whole blood, buccal mucosa, or saliva. For blood samples, we used the Gentra PureGene kit (Gentra Systems, Minneapolis, MN); for buccal mucosa samples we used the protocol of Richards et al. (1993); and for saliva, we extracted DNA from epithelial cells using the Oragene kit (DNA Genotek, Ottawa, ON). APOE genotyping was performed as previously described (Murphy et al., 1997). Two independent observers who were blind to participants' neuroimaging data determined APOE genotypes, and all staff involved in testing or neuroimaging analysis were blind to the participants' genotypes.

2.2.2. Experimental task—Participants underwent an fMRI scan while performing a perspective-dependent spatial learning task originally designed by Shelton and colleagues (Shelton and Gabrieli, 2002; Shelton and McNamara, 2004; Shelton and Pippitt, 2007). Essentially, movies of two environments (park and market) were presented during the encoding practice and the encoding fMRI scanning session (for details on the environments, see Shelton and Gabrieli, 2002). The route movies for each environment were created from the perspective of a 6-foot-tall observer walking through the environment. The survey movies were created from the perspective of an aerial observer (70 feet above ground level in virtual space), looking straight down with 20% of the environment visible at any moment (see Figure 1). Each participant viewed a route movie and a survey movie, with one complete viewing of each movie lasting 46 sec; thus, each participant saw the same two movies throughout the encoding (e.g., market-route and park-survey were repeatedly viewed by a participant). Across participants, the two environments were presented from the route or survey perspectives. A 20-sec long dot-control task, previously designed by Shelton and colleagues (unpublished), was presented along with the route and survey tasks in each block. During the dot-control task, nine consecutive red and blue dots were presented, one per 1 sec, on a noisy background (equal luminosity to the route and survey movies). The participants were instructed to indicate the color of the last dot by pressing a corresponding key on the button box.

As noted above, each participant was assigned to learn two environments, one as a route and one as a survey. Before scanning, participants viewed each environment and the dot-control task one time to familiarize themselves with tasks. During this initial viewing, the experimenter identified the landmarks in each environment by name as they were encountered. Participants were informed that they would not need to recall the landmark names per se, and thus their goal was to familiarize themselves with the location of the landmarks. Participants were asked to learn each environment as well as possible for a later memory test.

During the functional scan, route, survey and dot-control movies were repeated six times along with 10-sec blocks of fixation before each movie. Order for the movies was determined by using all possible orders of conditions (route, survey and dot-control) across the six counterbalanced repetitions, with the constraint that there be no direct repetitions of any condition. During fixation blocks, participants were instructed to fixate on a white cross displayed in the middle of a black screen. Participants were assigned to one of four versions of the experiment where a different order was used to counterbalance which environment and which perspective was seen first. By chance, seven of the 11 APOE $\epsilon 4$ carriers saw the route perspective first, and seven of the ten non-carriers saw survey first. After scanning, to assess memory for the two environments, participants were asked to first draw a map of each environment from memory, and then place labeled color forms for the objects on a board depicting each environment.

2.2.3. fMRI data acquisition—Whole-brain imaging data were acquired on a 3 Tesla MRI system (General Electric Medical Systems). The scan session began with an in-plane anatomical scan, followed by a series of five 1.5-min scans for a word-list learning task (data not reported here), followed by the 15-min functional scan for the perspective-dependent spatial learning task. T2-weighted spin-echo anatomical images were acquired in 30 contiguous 6-mm coronal slices [30 msec TE; 4000 msec reaction time (TR)]. Functional images were acquired in the same slices using a T2*-sensitive gradient echo spiral pulse sequence (Glover and Lai, 1998) (30 msec TE; 2000 msec TR; 77° flip angle; 22 cm field of view; 64 × 64 acquisition matrix).

2.2.4. Image processing—Image processing was performed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK). The first 4 volumes of each functional series were discarded to allow T1 equilibrium. All functional images were then corrected for participant motion. Each participant's structural images were coregistered to the mean functional image and segmented into gray matter, white matter and cerebrospinal fluid. Skull stripping was done using Brain Xtract tool in SPM99 on T1 images. The grey matter volume was normalized to the MNI grey matter template, and the normalization parameters were applied to all the structural and functional volumes. Functional images were spatially smoothed using a 8-mm FWHM Gaussian kernel.

Individual statistical models were constructed in SPM2 for each participant using the assumptions of a general linear model. Encoding phases of route, survey, and dot-control movies were modelled as blocks. Regressors were added to control for participant motion. Statistical contrasts were constructed to compare route vs dot-control, route vs. fixation, route vs. survey, survey vs. dot-control, survey vs. fixation, and dot-control vs. fixation. These contrasts were used to obtain participant-specific estimates for each effect that were then entered into a second-level analysis, with participant as a random effect. A one-sample *t*-test against a contrast value of zero was then performed at each voxel. Voxel-based group effects are first reported at $p < .001$, uncorrected and were considered significant if they a) exceeded a threshold of $p < .05$, False Discovery Rate (FDR) corrected, and b) consisted of five or more contiguous voxels.

To generate a hippocampal region-of-interest (ROI), an anatomical mask for the hippocampus was created using a high-resolution T1 structural MRI scan of each participant. These scans were acquired on a 1.5T GE scanner approximately 2 yrs previously as part of the Stanford/VA aviator MRI study (Adamson et al., 2010). The time lag between the structural and functional scans were not confounded with the overall BOLD response (for route: $r = -.26$; $p > .1$; survey: $r = -.09$; $p > .1$; dot-control: $r = .1$; $p > .1$) or with APOE $\epsilon 4$ status ($r = .06$; $p > .1$). Semi-automated hippocampal voluming was performed using a commercial high-dimensional brain-mapping tool (Medtronic Surgical Navigation Technologies, Louisville, CO; for details of these procedures, see (Csernansky et al., 2000; Hsu et al., 2002; Kramer et al., 2005)). Briefly, 22 control points were manually placed as local landmarks around each participant's hippocampus. These landmarks included one at the hippocampus head, one at the tail, and one each at the superior, inferior, medial and lateral boundaries of the hippocampus. Each participant's brain was matched to a template brain via fluid image transformation, and the pixels within the boundaries of the hippocampus were counted to estimate the volume. Experienced tracers confirmed the boundaries of the markings before computing the estimation of each final hippocampal volume.

This hippocampal anatomical mask was created for each participant and was co-registered with each participant's functional data. The parameter estimates were averaged across all voxels within each subjects' mask. Complementing the voxel-level analyses, the beta weights associated with particular contrasts were extracted from this hippocampal ROI. To compare the hippocampal activation with activity in a brain region not usually reported to be influenced by APOE $\epsilon 4$ status, a control ROI was chosen *a priori*. This region was defined anatomically in the visual cortex based on the anatomical region (left lingual gyrus/calcarine fissure (peak voxel at -6, -81, 0, BA 17/18)) that was activated in both route and survey conditions (compared to fixation) in the original study (Shelton & Gabrieli, 2002). The beta estimates for all voxels within a 6-mm radius of the maximum from these coordinates were extracted. The beta estimates from the hippocampal and visual cortex ROIs for the route, survey and the dot-control conditions were submitted to analysis of variance, using SPSS 18 (Chicago, IL), with factors of task condition and APOE status.

3. Results

3.1. Demographics

Table 1 summarizes characteristics of the 21 participants who were included in the study, separated by APOE $\epsilon 4$ carrier status. There were no significant differences between $\epsilon 4$ carriers and non-carriers in demographic characteristics, Rey AVLT delayed recall performance, Trails B, FAS phonemic fluency tests or hippocampal volumes (all p 's $> .1$).

3.2. Behavioral results

To assess participants' memory for the two environments, a point-rating scale was used to score the post-scan tasks of recognition (placement of landmark-labeled color forms) and recall (map drawings). Specifically, 1 point was given if the object placed or drawn was an object presented but was not in the correct location; 1 point was given if the object placed or drawn was incorrect but was placed in a location that previously contained an object; and, 2 points were given if the object placed or drawn was present and in the correct location. A summary score was calculated as the average number of points divided by the number of objects presented. Maximum possible score for recognition or recall was 2.

For recognition, there was no effect of Perspective ($F(1, 19) = 2.11, p > .1$), APOE Genotype ($F(1, 19) = 0.37, p > .1$), nor a Genotype $\times$ Perspective interaction ($F(1, 19) = 0.38, p > .1$). The total score for the color forms task for APOE $\epsilon 4$ carriers was 1.17 ± 0.37 (park survey = 1.46 ± 0.30 ; park route = 1.11 ± 0.42 ; market survey = 1.07 ± 0.39 ; market route = 1.04 ± 0.33) and for APOE $\epsilon 4$ non-carriers was 1.24 ± 0.26 (park survey = 1.41 ± 0.30 ; park route = 1.14 ± 0.30 ; market survey = 1.27 ± 0.11 ; market route = 1.11 ± 0.28). Similarly, for recall, there was no effect of Perspective ($F(1, 19) = 3.50, p > .1$), APOE Genotype ($F(1, 19) = 0.52, p > .1$) nor a Genotype $\times$ Perspective interaction ($F(1, 19) = 0.52, p > .1$). The total score for the map drawing task for APOE $\epsilon 4$ carriers was 0.64 ± 0.26 (park survey = 0.55 ± 0.23 ; park route = 0.99 ± 0.29 ; market survey = 0.52 ± 0.08 ; market route = 0.52 ± 0.27) and for APOE $\epsilon 4$ non-carriers was 0.72 ± 0.31 (park survey = 0.62 ± 0.22 ; park route = 0.88 ± 0.25 ; market survey = 0.62 ± 0.15 ; market route = 0.71 ± 0.50).

3.3. fMRI results

3.3.1. Activation differences in the hippocampus—Our primary hypothesis was that APOE $\epsilon 4$ carriers will show reduced activation, relative to non-carriers, in the hippocampus during encoding of route and survey perspectives compared to dot-control. To test this, we analyzed the functional activity in an anatomically defined hippocampal ROI. Figure 2a illustrates the mean estimated BOLD response in $\epsilon 4$ carriers and non-carriers during the survey encoding, route encoding, and dot-control tasks (relative to fixation). To understand how the three task conditions and APOE status influenced hippocampal activation, we ran a mixed-model ANOVA, with task as a within-subject factor and genotype as a between-subjects factor. Two types of planned comparisons were used to examine differences among the three tasks and to parse task $\times$ APOE status interactions: 1) comparisons related to spatial encoding (average of route and survey vs. dot-control), and 2) comparisons related to the effect of perspective (route vs. survey).

Task-related activation differences: The main effect of task was significant ($F(2, 38) = 11.64, p < .001$). The first planned comparison revealed that the two spatial encoding tasks showed a trend for eliciting greater activation relative to the dot-control task ($F(1, 38) = 3.65, .05 < p < .1$). The second planned comparison revealed that the difference between the route and survey perspectives was numerically in the direction observed in previous studies (route $>$ survey), but it did not approach significance in this sample, ($F(1, 38) = 0.48, p > .1$; Figure 2a).

APOE ε4-related activation differences: There was no main effect of genotype ($F(1, 19) = .26, p > .1$). However, the hypothesized interaction between genotype and task was significant ($F(2, 38) = 5.29, p = .009$; Figure 2a). This interaction reflected reduced encoding-related activation (average of route and survey vs. dot-control) for the carriers compared to the non-carriers ($F(1, 38) = 19.2, p < .001$). In fact, in the carriers there was no significant difference between the route and survey tasks vs. dot-control ($t = 1.27, p > 0.1$), whereas in the non-carriers there was a significant increase in activation during route and survey vs. dot-control ($t = 4.76, p < 0.001$). When analysis was restricted to the contrast of the two spatial encoding tasks, there was no difference between ε4 carriers and non-carriers ($F(1, 38) = 0.01, p > .1$).

Since the same movies were repeatedly presented during the survey encoding, route encoding, and dot-control tasks, it is important to assess the effects of repetition on the BOLD response, i.e. repetition suppression during repeated presentations of the two experimental spatial encoding tasks (in contrast to the dot-control task)¹. To address this, we combined the beta estimates from the hippocampal ROI in the following manner: in each subject we collapsed the six dot-control task repetitions into pairs to provide three time points (Reps 1–2, Reps 3–4 and Reps 5–6). We then combined the beta estimates obtained during the repeated presentations of the spatial encoding tasks (survey and route) in the same manner. The end result was hippocampal beta estimates for each subject for multiple repetitions of the dot-control and the experimental spatial encoding tasks (see supplementary Figure S1a and S1b for an across subject average). There was no main effect of genotype or repetition ($p > .30$). There was a main effect of task, $F(1, 114) = 12.44, p < .001$. There was neither a Genotype $\times$ Repetition, Repetition $\times$ Task nor a Genotype $\times$ Repetition $\times$ Task interaction ($F_s < 1$). There was an overall Genotype $\times$ Task interaction, $F(1, 114) = 7.79, p < .01$, reflecting reduced encoding-related activation for the carriers compared to the non-carriers. Therefore, the APOE ε4 effect on hippocampal activity seemed to be present from the earliest presentations and maintained throughout.

To confirm that the reduced encoding-related activation (relative to dot-control) in APOE ε4 carriers did not reflect a global effect, we examined APOE ε4-related activity in left lingual gyrus/calcarine fissure of the visual cortex (BA 17/18; Figure 2b). In this *a priori* defined anatomical ROI, there was no main effect of genotype ($F(1, 19) = .43, p > .1$), nor an interaction between genotype and task ($F(2, 38) = .09, p > .1$). When the analysis was restricted to the two spatial learning conditions, there was no genotype $\times$ perspective interaction ($F(1, 38) = 0.01, p > .1$).

3.3.2 Activation differences in the whole brain—Our second hypothesis stated that APOE ε4 carriers will show reduced activation, relative to non-carriers, in regions beyond the hippocampus proper—includes components of the DMN—that are involved in effective encoding of route and survey perspectives compared to the dot-control task. The subsystems of the DMN include parts of the MTL, medial prefrontal cortex, posterior cingulate cortex, precuneus, and the medial, lateral and inferior parietal cortex (Pihlajamäki and Sperling, 2009). Therefore, in line with our hippocampal analysis above, we conducted whole brain (voxel-level) analyses, first examining task differences and then testing for interactions between task and APOE ε4 status (with task as a within-subject factor and genotype as a between-subjects factor).

Task-related activation differences: First, we looked for regions displaying greater activity for the two encoding perspectives relative to the dot control task. These regions included

¹We thank an anonymous reviewer for this suggestion.

bilateral middle temporal gyrus (BA 21), right posterior cingulate (BA 30/31), left superior parietal and precuneus (BA 7), left middle occipital gyrus (BA 19), right inferior frontal (BA 47), middle frontal (BA 9), superior frontal (BA 4), bilateral medial frontal gyrus (BA 11), and left postcentral gyrus (BA 5) in the uncorrected contrast ($p < .001$). The following regions survived correction at $p < .05$: left middle temporal gyrus (BA 21), right posterior cingulate (BA 30/31), left middle occipital gyrus (BA 19), right inferior frontal gyrus (BA 47), right middle frontal (BA 9), right superior frontal gyrus (BA 4), and bilateral medial frontal gyrus (BA 11). There was no significant difference between route and survey encoding at a statistical threshold of $p < .05$, corrected.

APOE $\epsilon 4$ -related activation differences: No regions in the brain demonstrated a significant interaction between genotype and spatial encoding perspective (route and survey). Similar to the hippocampal analysis described above, we then combined the data from the two perspectives and examined $\epsilon 4$ -related differences in BOLD response during spatial learning compared to the dot-control task. In the uncorrected contrast ($p < .001$), APOE $\epsilon 4$ carriers demonstrated reduced encoding-related activation relative to the non-carriers in left cingulate cortex (BA 24), right cingulate cortex (BA 30), right superior frontal gyrus (BA 4), left middle frontal gyrus (BA 9), right supramarginal gyrus (BA 40), left insular cortex (BA 13), left anterior prefrontal cortex (BA 10), left inferior frontal gyrus (BA 47), right parahippocampal gyrus (BA 34), left hippocampus, and right superior temporal gyrus (BA 22). (See supplementary Table S1 for uncorrected results at $p < .001$). None of these individual regions survived correction at $p < .05$. There were no areas that showed greater activation during spatial encoding vs. dot-control in $\epsilon 4$ carriers compared to non-carriers at either the uncorrected ($p < .001$) or corrected contrast, $p < .05$.

To explore how the two groups' BOLD activity varied during fixation and the dot-control task, we conducted a whole-brain analysis comparing BOLD activity during the dot-control task vs. fixation. When the dot-control task was directly compared to fixation, the mean BOLD response in $\epsilon 4$ carriers was greater than that in non-carriers in right supramarginal gyrus, supplementary motor area, and right dorsal anterior cingulate cortex. Similar to results above, this activation also did not survive correction ($p < .05$). Relative to $\epsilon 4$ carriers, non-carriers did not show a greater response during dot-control vs. fixation in any brain region (corrected at $p < .05$).

4. DISCUSSION

The present study investigated hippocampal activation in cognitively normal older adults as they engaged in a perspective-dependent learning task. Consistent with the primary hypothesis, APOE $\epsilon 4$ carriers showed less encoding-related activation in the hippocampus proper compared to non-carriers. That is, when the encoding of the two spatial perspectives was contrasted against the dot-control task the encoding-related activation was significantly lower in carriers than non-carriers. Lower activation, however, was not global as encoding-related activation was not different between APOE $\epsilon 4$ carriers and non-carriers in the bilateral middle occipital region. In addition, regions implicated in effective encoding across the whole brain (inclusive of neural components of the DMN) showed APOE $\epsilon 4$ -related differences during the perspective-dependent learning tasks as predicted. These neural differences were observed even though memory performance was comparable across carriers and non-carriers.

4.1. APOE $\epsilon 4$ and the Default Mode Network

The DMN is altered in cognitively normal older APOE $\epsilon 4$ carriers similar to MCI and AD patients (Filippini et al., 2009; Fleisher et al., 2009; Persson et al., 2008; Pihlajamaki et al., 2010; Pihlajamaki and Sperling, 2009; Rombouts et al., 2005). Lustig et al. (2003) reported

that while responses in medial parietal and posterior cingulate regions went from activation during a semantic judgment task to deactivation during fixation in young participants, these regions were consistently activated in older adults with AD. Pihlajamäki et al. (2009) provided evidence for the disruption of DMN along the continuum from normal aging to APOE $\epsilon 4$ carriers to MCI and then AD. Recently, Fleisher et al. (2009) reported no encoding-related activity differences in $\epsilon 4$ carriers compared to non-carriers during a novel face-name pair task. Encoding-associated deactivations in the medial and right lateral parietal cortex were greater in non-carriers, similar to findings in AD studies. Fleisher et al. (2009) also did a resting-state DMN analysis that revealed nine regions in lateral prefrontal, orbital frontal, temporal and parietal cortices that were different between $\epsilon 4$ carriers and non-carriers. The present study revealed APOE $\epsilon 4$ encoding-related differences ($\epsilon 4$ carriers < non-carriers, $p < .001$, uncorrected) in orbital frontal and temporal lobe areas. Caution must be taken as these areas did not survive a more conservative threshold. These areas, however, are argued to be components of the DMN, with recent data revealing that resting state activity in this region differs between carriers and non-carriers (Fleisher et al., 2009). In addition, a previous study also reported that the pattern of altered task-induced deactivations in APOE $\epsilon 4$ carriers is similar to the DMN (Persson et al., 2008).

It is possible that the $\epsilon 4$ -related difference in the present study is driven by preclinical atrophy in the hippocampus and surrounding areas. The underlying structural atrophy of these regions (hippocampal, surrounding MTL and orbital frontal cortex) may be the reason for the alteration in the DMN of $\epsilon 4$ carriers, MCI and AD as well as the reduction of encoding activity in APOE $\epsilon 4$ carriers compared to non-carriers in our study. Previous studies have shown that although elderly $\epsilon 4$ carriers show some atrophy in the MTL, there is no global brain atrophy (den Heijer et al., 2002; Geroldi et al., 1999; Soininen et al., 1995). Figure 2b provides evidence for this as it shows patterns of activity in the left lingual gyrus/calcarine fissure that differ from what is observed in the hippocampus, as there was neither a main effect of Genotype nor a Genotype $\times$ Task interaction.

4.2. Methodological considerations

A recent comprehensive review of studies investigating BOLD responses in APOE $\epsilon 4$ carriers during encoding reported that the data pertaining to the direction and location of the effect of APOE genotype on the BOLD response are inconsistent (Trachtenberg et al., 2010; Weirenga et al., 2007). Some of the reasons for these inconsistencies could be age differences in the participant population and methods for fMRI data analysis, including the use of high- versus low-level contrasts.

The present study methodologically differed from a recent, related study that reported reduced activation during both route and survey encoding in the MTL of older adult $\epsilon 4$ carriers (Borghesani et al., 2008). First, the participants in Borghesani et al. were, on average, older than our participants (mean ages of 72.4 vs. 63.8 yrs, respectively). Because the influences of APOE genotype on brain function may change with age (Alexander et al., 2007; Small et al., 2004), across-study differences may partially reflect age $\times$ genotype interactions. Future research is needed to determine whether and how the effects of genotype on spatial encoding processes change across the life span. Second, with regards to task-related differences, Borghesani and colleagues (2008) used a single environment for the two perspectives, such that participants may have used the two different perspectives to gather complementary information about the environment; that is, the learning effects during survey and route encoding were not independent. It is plausible to hypothesize that the processes engaged during survey or during route encoding will vary depending on whether an environment has or has not been previously encountered from the other perspective. Finally, the present study used a novel dot-control task as a low-level contrast (in addition to fixation), along with the high-level contrast of the two perspectives. Our data indicate that

the dot-control task does not activate the hippocampus in either gene group relative to the fixation baseline (see the negative BOLD response during dot-control; Figure 2a), suggesting that the processing demands for the dot-control task are less dependent on the hippocampus relative to the processes engaged during both fixation and during the two spatial encoding conditions. As such, the dot-control task may serve as a more effective baseline for detecting group differences in MTL-dependent spatial encoding processes, further underscoring the importance of the low-level control task when targeting complex encoding computations (Gusnard and Raichle, 2001; Stark and Squire, 2001) – specifically in cognitively normal young-old populations. Indeed, we observed an $\epsilon 4$ -related difference in encoding activation when compared to the dot-control task, but not when compared to the fixation baseline in our older participants. Collectively, while our data provide clear evidence of a reduction in encoding-related neural responses in $\epsilon 4$ -carriers, the methodological, including participants' age differences, between our experiment and that of Borghesani et al. (2008) complicate direct comparisons.

4.3. Task-related activation differences

Although the route vs. survey contrast did not reveal significant differences in functional activation in our study, the relative activity illustrated in Figure 2a shows that the difference between the route and survey perspectives is in the direction observed in previous studies (route > survey; Shelton and Gabrieli, 2002). The present study employed a stringent threshold at which no areas were differentially activated when route perspective was directly compared with survey perspective, regardless of genotype. When a less stringent threshold was adopted ($p < .01$, uncorrected), left insular cortex (BA 13), left middle temporal gyrus (BA 39), left superior frontal gyrus (BA 4), and left middle occipital gyrus (BA 19) were more active in route compared to survey perspective. Left superior frontal gyrus (BA 4), precentral gyrus (BA 3), and right middle frontal gyrus (BA 9) were more active in survey than route perspective.

There are a number of limitations to this study. First, the relatively small number of participants likely resulted in modest power to detect within and between group differences, and also contributed to an under representation of women. Note however, that a sample size smaller than the present study (combined $n = 14$ compared to combined $n = 21$) reported significant APOE $\epsilon 4$ related differences in the MTL earlier (Borghesani et al., 2008). Second, our fixation blocks lasted only 10 sec (total 18 fixation blocks), whereas the dot-control blocks were 20 sec long (total six blocks). While it is clear that the dot-control task resulted in reduced MTL activity relative to fixation, nevertheless the briefer durations of the fixation blocks may have resulted in there being partially colored by hemodynamic carryover, thus leading the fixation blocks to have less power as a baseline comparison to the perspective-dependent learning tasks. Third, while we note the relationship between the present effects and neural components of the putative DMN, we did not directly identify this network due to the limited amount of fixation data available. Future studies that use resting-state functional connectivity (fcMRI) measures to identify the DMN are necessary to more firmly establish the effects of $\epsilon 4$ -carrier status on activation in this network. Finally, the present study revealed matched memory performance in the carrier and non-carrier groups, and thus does not document a behavioral correlate of the observed functional differences in encoding-related neural responses. A recent study used the subsequent memory paradigm (Brewer et al., 1998; Paller and Wagner, 2002; Wagner et al., 1998) to identify differences in event-related BOLD activity between subsequently forgotten and remembered items and observed that neural processing differences between $\epsilon 4$ carriers and non-carriers were related to their ability to encode items into long term memory (Dennis et al., 2009). Future studies of the effects of APOE status on spatial encoding processes should be designed to

permit a linking of subsequent memory behavior to moment-to-moment measures of the BOLD response.

4.4. Conclusion

This study provides an additional viewpoint on APOE ϵ 4-related activation differences in the hippocampus proper during encoding of a previously established perspective-dependent learning paradigm. The current study used the dot-control task to effectively target APOE ϵ 4-related activity differences during the perspective-dependent learning tasks. Based on previous studies where DMN activity was reported to be disrupted in APOE ϵ 4 carriers, the present study further highlights the role of low-level control tasks to tease apart the influence of genetic susceptibilities on brain activity during learning. This approach, when coupled with resting-state fMRI analyses, may increase the chances of capturing clinically significant ϵ 4-related differences in middle aged to older population, and may yield better models to determine the influences of various moderators, like age, education, and general intelligence, on the neural substrates of episodic encoding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the Sierra-Pacific Mental Illness Research, Education, and Clinical Center (MIRECC), the War Related Illness and Injury Study Center (WRIISC), the Medical Research Service of the Department of Veterans Affairs, and by NIA grant R01 AG021632 (with Diversity Supplement to Dr. Adamson), NIH P30 AG 17824 and NIH R37 AG 12713, P41 RR023953 (PI: Weiner), and 2P41RR009784 (P.I. Glover). We thank Xiangyan Xu, Greer Murphy, Gary Glover, Anne Sawyer, Jerome Yesavage, Salla Rapakko, Vika Samarina, Mario Ortega, Michelle Farrell, and Quinn Kennedy. We also express appreciation to the aviator study participants for their time and interest in pursuit for answering intellectual questions.

References

- Adamson MM, Landy KM, Duong S, Fox-Bosetti S, Ashford JW, Murphy GM, Weiner M, Taylor JL. Apolipoprotein E epsilon4 influences on episodic recall and brain structures in aging pilots. *Neurobiol Aging*. 2010; 31:1059–1063. [PubMed: 18760504]
- Alexander DM, Williams LM, Gatt JM, Dobson-Stone C, Kuan SA, Todd EG, Schofield PR, Cooper NJ, Gordon E. The contribution of apolipoprotein E alleles on cognitive performance and dynamic neural activity over six decades. *Biol Psychol*. 2007; 75:229–238. [PubMed: 17433528]
- Bassett SS, Yousem DM, Cristinzio C, Kusevic I, Yassa MA, Caffo BS, Zeger SL. Familial risk for Alzheimer's disease alters fMRI activation patterns. *Brain*. 2006; 129:1229–1239. [PubMed: 16627465]
- Blair CK, Folsom AR, Knopman DS, Bray MS, Mosley TH, Boerwinkle E. APOE genotype and cognitive decline in a middle-aged cohort. *Neurology*. 2005; 64:268–276. [PubMed: 15668424]
- Bondi MW, Houston WS, Eyler LT, Brown GG. fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. *Neurology*. 2005; 64:501–508. [PubMed: 15699382]
- Bookheimer SY, Strojwas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziotta JC, Small GW. Patterns of brain activation in people at risk for Alzheimer's disease. *N Engl J Med*. 2000; 343:450–456. [PubMed: 10944562]
- Borghesani PR, Johnson LC, Shelton AL, Peskind ER, Aylward EH, Schellenberg GD, Cherrier MM. Altered medial temporal lobe responses during visuospatial encoding in healthy APOE*4 carriers. *Neurobiol Aging*. 2008; 29:981–991. [PubMed: 17350142]
- Braak H, Braak E. Diagnostic criteria for neuropathologic assessment of Alzheimer's disease. *Neurobiol Aging*. 1997; 18:S85–88. [PubMed: 9330992]

- Brewer JB, Zhao Z, Desmond JE, Glover GH, Gabrieli JD. Making memories: brain activity that predicts how well visual experience will be remembered. *Science*. 1998; 281:1185–1187. [PubMed: 9712581]
- Buckner RL, Wheeler ME, Sheridan MA. Encoding processes during retrieval tasks. *Journal of Cognitive Neuroscience*. 2001; 13:406–415. [PubMed: 11371316]
- Burgess N, Maguire EA, O'Keefe J. The human hippocampus and spatial and episodic memory. *Neuron*. 2002; 35:625–641. [PubMed: 12194864]
- Caselli RJ, Dueck AC, Osborne D, Sabbagh MN, Connor DJ, Ahern GL, Baxter LC, Rapcsak SZ, Shi J, Woodruff BK, Locke DE, Snyder CH, Alexander GE, Rademakers R, Reiman EM. Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. *N Engl J Med*. 2009; 361:255–263. [PubMed: 19605830]
- Cherbuin N, Leach LS, Christensen H, Anstey KJ. Neuroimaging and APOE Genotype: A Systematic Qualitative Review. *Dement Geriatr Cogn Disord*. 2007; 24:348–362. [PubMed: 17911980]
- Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993; 261:921–923. [PubMed: 8346443]
- Csernansky JG, Wang L, Joshi S, Miller JP, Gado M, Kido D, McKeel D, Morris JC, Miller MI. Early DAT is distinguished from aging by high-dimensional mapping of the hippocampus. *Dementia of the Alzheimer type*. *Neurology*. 2000; 55:1636–1643. [PubMed: 11113216]
- de Leon MJ, Mosconi L, Blennow K, DeSanti S, Zinkowski R, Mehta PD, Pratico D, Tsui W, Saint Louis LA, Sobanska L, Brys M, Li Y, Rich K, Rinne J, Rusinek H. Imaging and CSF studies in the preclinical diagnosis of Alzheimer's disease. *Ann N Y Acad Sci*. 2007; 1097:114–145. [PubMed: 17413016]
- DeCarli C, Miller BL, Swan GE, Reed T, Wolf PA, Carmelli D. Cerebrovascular and brain morphologic correlates of mild cognitive impairment in the National Heart, Lung, and Blood Institute Twin Study. *Arch Neurol*. 2001; 58:643–647. [PubMed: 11295996]
- deIpolyi AR, Rankin KP, Mucke L, Miller BL, Gorno-Tempini ML. Spatial cognition and the human navigation network in AD and MCI. *Neurology*. 2007; 69:986–997. [PubMed: 17785667]
- den Heijer T, Oudkerk M, Launer LJ, van Duijn CM, Hofman A, Breteler MM. Hippocampal, amygdalar, and global brain atrophy in different apolipoprotein E genotypes. *Neurology*. 2002; 59:746–748. [PubMed: 12221169]
- Dennis NA, Browndyke JN, Stokes J, Need A, Burke JR, Welsh-Bohmer KA, Cabeza R. Temporal lobe functional activity and connectivity in young adult APOE epsilon4 carriers. *Alzheimers Dement*. 2009
- Eichenbaum H. A cortical-hippocampal system for declarative memory. *Nat Rev Neurosci*. 2000; 1:41–50. [PubMed: 11252767]
- Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA*. 1997; 278:1349–1356. [PubMed: 9343467]
- Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, Matthews PM, Beckmann CF, Mackay CE. Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proc Natl Acad Sci U S A*. 2009; 106:7209–7214. [PubMed: 19357304]
- Fleisher A, Grundman M, Jack CR Jr, Petersen RC, Taylor C, Kim HT, Schiller DH, Bagwell V, Sencakova D, Weiner MF, DeCarli C, DeKosky ST, van Dyck CH, Thal LJ. Sex, apolipoprotein E epsilon 4 status, and hippocampal volume in mild cognitive impairment. *Arch Neurol*. 2005; 62:953–957. [PubMed: 15956166]
- Fleisher AS, Sherzai A, Taylor C, Langbaum JB, Chen K, Buxton RB. Resting-state BOLD networks versus task-associated functional MRI for distinguishing Alzheimer's disease risk groups. *Neuroimage*. 2009; 47:1678–1690. [PubMed: 19539034]
- Geffen, G. A compendium of neuropsychological tests: Administration, norms and commentary. 2. New York: Oxford University Press; 1995. Normative data for the Auditory Verbal Learning Test. Personal communication cited in Spreen and Strauss.

- Geroldi C, Pihlajamaki M, Laakso MP, DeCarli C, Beltramello A, Bianchetti A, Soininen H, Trabucchi M, Frisoni GB. APOE-epsilon4 is associated with less frontal and more medial temporal lobe atrophy in AD. *Neurology*. 1999; 53:1825–1832. [PubMed: 10563634]
- Glover GH, Lai S. Self-navigated spiral fMRI: interleaved versus single-shot. *Magn Reson Med*. 1998; 39:361–368. [PubMed: 9498591]
- Gorno-Tempini ML, Price CJ. Identification of famous faces and buildings: a functional neuroimaging study of semantically unique items. *Brain*. 2001; 124:2087–2097. [PubMed: 11571224]
- Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci*. 2001; 2:685–694. [PubMed: 11584306]
- Han SD, Houston WS, Jak AJ, Eyler LT, Nagel BJ, Fleisher AS, Brown GG, Corey-Bloom J, Salmon DP, Thal LJ, Bondi MW. Verbal paired-associate learning by APOE genotype in non-demented older adults: fMRI evidence of a right hemispheric compensatory response. *Neurobiol Aging*. 2007; 28:238–247. [PubMed: 16434125]
- Hsu YY, Schuff N, Du AT, Mark K, Zhu X, Hardin D, Weiner MW. Comparison of automated and manual MRI volumetry of hippocampus in normal aging and dementia. *J Magn Reson Imaging*. 2002; 16:305–310. [PubMed: 12205587]
- Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC, Kokmen E, Kurland LT. Mayo's older Americans normative studies: Update AVLT norms for ages 56 to 97. *Clinical Neuropsychologist*. 1992; 6:83–104.
- Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC. Neuropsychological Tests' Norms above age 55: COWAT, MAE, BNT Token, WRAT-R Reading, AMNART, STROOP, TNT and JLO. *Clinical Neuropsychologist*. 1996; 10:262–278.
- Johnson SC, Schmitz TW, Moritz CH, Meyerand ME, Rowley HA, Alexander AL, Hansen KW, Gleason CE, Carlsson CM, Ries ML, Asthana S, Chen K, Reiman EM, Alexander GE. Activation of brain regions vulnerable to Alzheimer's disease: the effect of mild cognitive impairment. *Neurobiol Aging*. 2006; 27:1604–1612. [PubMed: 16226349]
- Kozauer NA, Mielke MM, Chan GK, Rebok GW, Lyketsos CG. Apolipoprotein E genotype and lifetime cognitive decline. *Int Psychogeriatr*. 2008; 20:109–123. [PubMed: 17711604]
- Kramer JH, Rosen HJ, Du AT, Schuff N, Hollnagel C, Weiner MW, Miller BL, Delis DC. Dissociations in hippocampal and frontal contributions to episodic memory performance. *Neuropsychology*. 2005; 19:799–805. [PubMed: 16351355]
- Landau SM, Harvey D, Madison CM, Koeppe RA, Reiman EM, Foster NL, Weiner MW, Jagust WJ. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiol Aging*. 2009
- Lind J, Larsson A, Persson J, Ingvar M, Nilsson LG, Backman L, Adolfsson R, Cruts M, Sleegers K, Van Broeckhoven C, Nyberg L. Reduced hippocampal volume in non-demented carriers of the apolipoprotein E epsilon4: relation to chronological age and recognition memory. *Neurosci Lett*. 2006; 396:23–27. [PubMed: 16406347]
- Lustig C, Snyder AZ, Bhakta M, O'Brien KC, McAvoy M, Raichle ME, Morris JC, Buckner RL. Functional deactivations: change with age and dementia of the Alzheimer type. *Proc Natl Acad Sci U S A*. 2003; 100:14504–14509. [PubMed: 14608034]
- Machulda MM, Ward HA, Borowski B, Gunter JL, Cha RH, O'Brien PC, Petersen RC, Boeve BF, Knopman D, Tang-Wai DF, Ivnik RJ, Smith GE, Tangalos EG, Jack CR Jr. Comparison of memory fMRI response among normal, MCI, and Alzheimer's patients. *Neurology*. 2003; 61:500–506. [PubMed: 12939424]
- McNamara TP, Shelton AL. Cognitive maps and the hippocampus. *Trends in Cognitive Sciences*. 2003; 7:333–335. [PubMed: 12907223]
- Moscovitch M, Nadel L, Winocur G, Gilboa A, Rosenbaum RS. The cognitive neuroscience of remote episodic, semantic and spatial memory. *Curr Opin Neurobiol*. 2006; 16:179–190. [PubMed: 16564688]
- Murphy GM Jr, Taylor J, Kraemer HC, Yesavage J, Tinklenberg JR. No association between apolipoprotein E epsilon 4 allele and rate of decline in Alzheimer's disease. *Am J Psychiatry*. 1997; 154:603–608. [PubMed: 9137113]

- Pai MC, Jacobs WJ. Topographical disorientation in community-residing patients with Alzheimer's disease. *Int J Geriatr Psychiatry*. 2004; 19:250–255. [PubMed: 15027040]
- Paller KA, Wagner AD. Observing the transformation of experience into memory. *Trends in Cognitive Sciences*. 2002; 6:93–102. [PubMed: 15866193]
- Persson J, Lind J, Larsson A, Ingvar M, Slegers K, Van Broeckhoven C, Adolfsson R, Nilsson LG, Nyberg L. Altered deactivation in individuals with genetic risk for Alzheimer's disease. *Neuropsychologia*. 2008; 46:1679–1687. [PubMed: 18346764]
- Petersen RC, Smith GE, Ivnik RJ, Tangalos EG, Schaid DJ, Thibodeau SN, Kokmen E, Waring SC, Kurland LT. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. *JAMA*. 1995; 273:1274–1278. [PubMed: 7646655]
- Pihlajamaki M, KOK, Bertram L, Tanzi RE, Dickerson BC, Blacker D, Albert MS, Sperling RA. Evidence of altered posteromedial cortical fMRI activity in subjects at risk for Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2010; 24:28–36. [PubMed: 19571734]
- Pihlajamaki M, Sperling RA. Functional MRI assessment of task-induced deactivation of the default mode network in Alzheimer's disease and at-risk older individuals. *Behav Neurol*. 2009; 21:77–91. [PubMed: 19847047]
- Richards B, Skoletsky J, Shuber AP, Balfour R, Stern RC, Dorkin HL, Parad RB, Witt D, Klinger KW. Multiplex PCR amplification from the CFTR gene using DNA prepared from buccal brushes/swabs. *Hum Mol Genet*. 1993; 2:159–163. [PubMed: 7684637]
- Rombouts SA, Barkhof F, Goekoop R, Stam CJ, Scheltens P. Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. *Hum Brain Mapp*. 2005; 26:231–239. [PubMed: 15954139]
- Saunders AM, Schmeider K, Breitner JC, Benson MD, Brown WT, Goldfarb L, Goldgaber D, Manwaring MG, Szymanski MH, McCown N, et al. Apolipoprotein E epsilon 4 allele distributions in late-onset Alzheimer's disease and in other amyloid-forming diseases. *Lancet*. 1993; 342:710–711. [PubMed: 8103823]
- Schacter DL, Wagner AD. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus*. 1999; 9:7–24. [PubMed: 10088896]
- Seltzer B, Pandya DN. Further observations on parieto-temporal connections in the rhesus monkey. *Exp Brain Res*. 1984; 55:301–312. [PubMed: 6745368]
- Shelton AL, Gabrieli JD. Neural correlates of encoding space from route and survey perspectives. *J Neurosci*. 2002; 22:2711–2717. [PubMed: 11923436]
- Shelton AL, McNamara TP. Orientation and perspective dependence in route and survey learning. *J Exp Psychol Learn Mem Cogn*. 2004; 30:158–170. [PubMed: 14736304]
- Shelton AL, Pippitt HA. Fixed versus dynamic orientations in environmental learning from ground-level and aerial perspectives. *Psychol Res*. 2007; 71:333–346. [PubMed: 16957953]
- Small BJ, Rosnick CB, Fratiglioni L, Backman L. Apolipoprotein E and cognitive performance: a meta-analysis. *Psychol Aging*. 2004; 19:592–600. [PubMed: 15584785]
- Soininen H, Partanen K, Pitkanen A, Hallikainen M, Hanninen T, Helisalmi S, Mannermaa A, Ryyanen M, Koivisto K, Riekkinen P Sr. Decreased hippocampal volume asymmetry on MRIs in nondemented elderly subjects carrying the apolipoprotein E epsilon 4 allele. *Neurology*. 1995; 45:391–392. [PubMed: 7854548]
- Squire LR, Stark CE, Clark RE. The medial temporal lobe. *Annu Rev Neurosci*. 2004; 27:279–306. [PubMed: 15217334]
- Stark CE, Squire LR. When zero is not zero: the problem of ambiguous baseline conditions in fMRI. *Proc Natl Acad Sci U S A*. 2001; 98:12760–12766. [PubMed: 11592989]
- Suzuki WA, Amaral DG. Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. *J Comp Neurol*. 1994; 350:497–533. [PubMed: 7890828]
- Tanzi RE, Bertram L. New frontiers in Alzheimer's disease genetics. *Neuron*. 2001; 32:181–184. [PubMed: 11683989]
- Tombaugh, TN.; Kozak, J.; Rees, L. A compendium of neuropsychological tests: Administration, norms and commentary. 2. New York: Oxford University Press; 1996. Normative Data for the controlled oral word association test. Personal communication cited in Spreen and Strauss.

- Tombaugh, TN.; Rees, L.; McIntyre, N. A compendium of neuropsychological tests: Administration, norms and commentary. 2. New York: Oxford University Press; 1998. Normative data for the Trail Making Test. Personal communication cited in Spreen and Strauss.
- Trachtenberg AJ, Filippini N, Mackay CE. The effects of APOE-epsilon4 on the BOLD response. *Neurobiol Aging*. 2010
- Trivedi MA, Schmitz TW, Ries ML, Torgerson BM, Sager MA, Hermann BP, Asthana S, Johnson SC. Reduced hippocampal activation during episodic encoding in middle-aged individuals at genetic risk of Alzheimer's disease: a cross-sectional study. *BMC Med*. 2006; 4:1. [PubMed: 16412236]
- Wagner AD, Schacter DL, Rotte M, Koutstaal W, Maril A, Dale AM, Rosen BR, Buckner RL. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science*. 1998; 281:1188–1191. [PubMed: 9712582]
- Wierenga CE, Bondi MW. Use of functional Magnetic Resonance Imaging in the early identification of Alzheimer's disease. *Neuropsychol Rev*. 2007; 17:127–143. [PubMed: 17476598]
- Wisdom NM, Callahan JL, Hawkins KA. The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. *Neurobiol Aging*. 2011; 32:63–74. [PubMed: 19285755]

Figure 1.

The initial block of the perspective dependent encoding task. The initial fixation lasted 8 seconds in the beginning of the first block, followed by a fixation (10sec) and an environment cue (park or market). Block order was determined by using all orders of the movies (route, survey, and dot-control) repeated six times, with the constraint that no condition was repeated directly. During each scan, one environment was shown in the route perspective while the other was shown in the survey perspective. Two different orders were used to counterbalance which environment was seen first as route or survey.

Figure 2.

Figure 2a. ROI analysis: Hippocampus estimated BOLD response: The mean estimated Blood Oxygen Level Dependent (BOLD) response in APOE $\epsilon 4$ carriers and non-carriers during the survey encoding, route encoding, and dot-control tasks in bilateral hippocampus. Error bars designate standard error.

Figure 2b ROI analysis: Estimated BOLD Response: The mean estimated Blood Oxygen Level Dependent (BOLD) response in APOE $\epsilon 4$ carriers and non-carriers during the survey encoding, route encoding, and dot-control tasks in the Left lingual gyrus/calcarine fissure (BA 17/18). Error bars designate standard error.

Table 1Demographic characteristics of the 21 participants by APOE $\epsilon 4$

	APOE $\epsilon 4$ non-carriers $n = 11$	APOE $\epsilon 4$ carriers $n = 10$
Age, y, mean $\pm$ SD	64.0 $\pm$ 5.1 (range = 56–73)	63.5 $\pm$ 5.5 (range = 54–70)
Education, y, mean $\pm$ SD ¹	16.7 $\pm$ 1.1	17.6 $\pm$ 2.1
Number White, non- Hispanic	9	9
Number Men	8	10
Rey AVLT delayed, mean $\pm$ SD Percentile range	10.4 $\pm$ 3.0 (14.5 – 99.0)	9.7 $\pm$ 3.0 (18.0 – 99.0)
Phonemic Fluency, mean $\pm$ SD Percentile range ²	37.8 $\pm$ 9.2 (9.5 – 85.0)	40.8 $\pm$ 10.9 (9.5 – 75.0)
Trails B, mean $\pm$ SD Percentile range	56.1 $\pm$ 23.2 (14.5 – 99.0)	64.7 $\pm$ 14.6 (34.5 – 92.0)
Hippocampal Volume (cc) ³	5.3 $\pm$ 0.6	5.1 $\pm$ 0.5
Number hypertension medication use ever	3	3
Number family history of dementia	3	6

¹ Education years greater than 20 years were truncated to 20 years² Phonemic fluency test (FAS) where participants are asked to generate as many words as possible that start with a specific letter of the alphabet in 60 seconds. A total score for 3 letters (FAS) is calculated.³ Hippocampal volume is residualized on Total Intracranial Volume (TIV) and then converted back to cc's for clarity.