

Memory Performance and fMRI Signal in Presymptomatic Familial Alzheimer's Disease

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Abstract: Rare autosomal dominant mutations result in familial Alzheimer's disease (FAD) with a relatively consistent age of onset within families. This provides an estimate of years until disease onset (relative age) in mutation carriers. Increased AD risk has been associated with differences in functional magnetic resonance imaging (fMRI) activity during memory tasks, but most of these studies have focused on possession of apolipoprotein E allele 4 (*APOE4*), a risk factor, but not causative variant, of late-onset AD. Evaluation of fMRI activity in presymptomatic FAD mutation carriers versus noncarriers provides insight into preclinical changes in those who will certainly develop AD in a prescribed period of time. Adults from FAD mutation-carrying families (nine mutation carriers, eight noncarriers) underwent fMRI scanning while performing a memory task. We examined fMRI signal differences between carriers and noncarriers, and how signal related to fMRI task performance within mutation status group, controlling for relative age and education. Mutation noncarriers had greater retrieval period activity than carriers in several AD-relevant regions, including the left hippocampus. Better performing noncarriers showed greater encoding period activity including in the parahippocampal gyrus. Poorer performing carriers showed greater retrieval period signal, including in the frontal and temporal lobes, suggesting underlying pathological processes. *Hum Brain Mapp* 34:3308–3319, 2013. © 2012 Wiley Periodicals, Inc.

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INTRODUCTION

Pathological brain changes occur many years before Alzheimer's disease (AD) is diagnosable through cognitive testing [Braak and Braak, 1991; Thal et al., 2002]. Neuroanatomical and neurophysiological differences in this early stage may be observed through functional and structural magnetic resonance imaging (fMRI and sMRI) in those with mild cognitive impairment (MCI) [Dickerson and Sperling, 2008; Frisoni et al., 2010], or an increased genetic risk for AD as determined either by possession of an apolipoprotein E ϵ 4 allele (*APOE4*) [Bookheimer and Burggren, 2009], or mutations that confer AD in an autosomal dominant manner [Quiroz et al., 2010; Ringman et al., 2007, 2011a].

There is no perfect predictor of late-onset AD, making incipient disease difficult to ascertain, except retrospectively. However, carriers of rare genetic mutations in the presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), and amyloid precursor protein (*APP*) genes inherit an early onset form of familial AD (FAD) in a fully penetrant autosomal dominant manner [Bertram and Tanzi, 2008]. In FAD, age of onset varies between families, but is typically similar within a family [Fox et al., 1997; Murrell et al., 2006], allowing the incipient AD stage to be estimated via "relative age." We used relative age (the number of years before median age of disease diagnosis in a family) as a surrogate for incipient disease stage in mutation carriers. This allows the earliest, preclinical stages of the disease (before massive structural damage to the brain has occurred) to be studied prospectively.

Many studies have found that adults with increased genetic risk for AD have greater [Bassett et al., 2006; Bondi et al., 2005; Bookheimer et al., 2000; Filippini et al., 2009; Han et al., 2007; Quiroz et al., 2010] or less [Bassett et al., 2006; Bondi et al., 2005; Johnson et al., 2006; Quiroz et al., 2010; Trivedi et al., 2006] regional fMRI activity during episodic memory tasks in the medial temporal lobe (MTL). In some cases, higher AD genetic risk was associated with both higher and lower fMRI signal in the same study depending on MTL subregion and brain hemisphere [Bondi et al., 2005; Quiroz et al., 2010]. Of the studies that found MTL effects, only one [Quiroz et al., 2010] measured genetic risk for AD using FAD mutations rather than either *APOE* genotype or a family history of late-onset AD. In that study, which used a novelty encoding task, mutation noncarriers showed more fMRI activity than carriers in some AD-related regions, such as the left parahippocampal gyrus and precuneus, while carriers showed more fMRI activity than noncarriers in other AD-related regions such as right posterior cingulate, inferior and superior pa-

rietal lobules, hippocampus, and dorsolateral prefrontal cortex [Quiroz et al., 2010]. The task that we employed was different from that used by the previous study, but we hypothesized based on their work and others, that we would find fMRI activity differences between mutation carriers and noncarriers in AD-related regions, especially the MTL.

AD risk conferred by *APOE4* may affect the brain via both common and distinct mechanisms as FAD mutations do. For instance, *PSEN1* and *APP* mutations generally increase beta amyloid ($A\beta$) production, its aggregation, or the proportion of $A\beta_{42}$ to $A\beta_{40}$ [Brouwers et al., 2008]. *APOE4* is also associated with greater $A\beta$ aggregation, as well as clearance, but may also result in different tau phosphorylation and aggregation, inflammation, and lipid metabolism [Verghese et al., 2011]. Here we investigated the understudied relationship between FAD mutations and functional brain activity in those with preclinical AD.

We also evaluated in which brain regions fMRI activity was best associated with task performance after controlling for relative age and education. Retrieval success for episodic memory tasks has been shown to associate with fMRI activity in the MTL, posterior midline, medial prefrontal cortex, and posterior parietal cortex [Heun et al., 2006; Huijbers et al., 2010; Tsukiura et al., 2011], all regions that are preferentially affected in AD. We hypothesized that those who perform better on our memory task would show greater fMRI signal in these regions versus those who perform worse, particularly in mutation carriers. Identifying ways in which the brain activity is modified in those having probable differences in amyloid processing, and clarifying which regions are most important to a cognitive task given possible early disease processes offers insight into integral disease processes and how they affect cognition. These insights may help guide future prevention and intervention efforts.

MATERIALS AND METHODS

Subjects

Subjects were 17 first-degree relatives of *PSEN1* or *APP* mutation carriers (age 19–46; mean 32.2 years) (Table I). Eight mutation carriers had the *PS1A431E* mutation and one had the *APPV717I* mutation. Noncarriers were from families having the *PS1A431E* mutation (4), the *APPV717I* mutation (2), and the *PS1L235V* mutation (2). A χ^2 test showed that the mutation carriers were not different from the noncarriers ($P = 0.45$) in terms of how many were from an *APP* mutation- versus a *PSEN1* mutation-carrying

TABLE I. Demographic characteristics of subjects

	Mutation carriers	Mutation noncarriers
No. subjects	9	8
Age (yr) ^{a, b}	29.8 ± 5.6	35.0 ± 8.5
Relative age (yr) ^{a, b}	-14.0 ± 5.5	-11.5 ± 11.6
Males/females ^a	1/8	1/7
Family gene risk (<i>PSEN1/APP</i>) ^a	8/1	6/2
<i>APOE4</i> ^a	2	1
Education (yr) ^{a, b}	12.9 ± 3.1	12.5 ± 4.5
Mini-Mental State Exam (MMSE) ^a	28.8 ± 1.0	28.5 ± 1.3
Cognitive Abilities Screening Instrument (CASI) ^a	93.0 ± 4.0	92.3 ± 5.8
Word pair pretest score (out of 42) ^a	27.2 ± 12.2	24.9 ± 9.6
Word pair posttest score (out of 7) ^a	6.0 ± 1.4	5.9 ± 0.8

^aA two-tailed *t*-test did not show a significant difference between mutation carriers and noncarriers.

^bListed as mean ± standard deviation.

family. All participants underwent extensive clinical, cognitive, biochemical, and imaging evaluations. Genotyping of FAD mutations was performed at UCLA as described previously [Braskie et al., 2012]. No mutation carriers were demented or had mild cognitive impairment [Petersen, 2004], using criteria described previously in detail [Braskie et al., 2012]. Subjects were normotensive and had no history of head injury requiring hospitalization, or of drug or alcohol dependency. No subject was taking medications designed to improve cognition. We excluded subjects having fMRI scans with excessive motion (>2 mm) or severe artifacts, subjects whose normalized (*z* score) pretest score on the scanner task exceeded an arbitrary threshold of 1.25 points different from the normalized posttest score, and those for whom the full pretest data were not available. Subjects were selected from 27 young to middle-aged adults scanned while performing a verbal paired associates task. Of those, 10 were excluded: 6 for having technically inadequate scans, 1 for lacking a pretest, 2 for having a pretest not representative of posttest score, and 1 for far exceeding the characteristic age of the family's disease diagnosis.

Subjects were of Mexican descent, residing either in Mexico or the United States. All MRI scans took place at UCLA on a single scanner. All subjects spoke sufficient Spanish to perform Spanish language cognitive testing. A fluently bilingual psychometrician performed all neuropsychological assessments, all of which were available and validated in Spanish. All subjects (except for a single subject who had undergone previous clinical testing) and the psychometrician were blind to subjects' genetic status.

Seventeen of these subjects were part of a prior novelty encoding fMRI study examining the effect of *APOE* genotype and familial mutation in familial AD mutation carriers [Ringman et al., 2011a]. Sixteen were evaluated previously in an article that related estimated time until AD diagnosis to fMRI activity during a novelty encoding

task [Braskie et al., 2012]. Those studies did not include the current verbal paired associates task data, nor did they relate fMRI signal to task performance.

Study procedures were approved by the Institutional Review Boards at UCLA and the National Institute of Neurology and Neurosurgery in Mexico City. All subjects provided written, informed consent. Subjects were told that they would be tested for the FAD mutation for which they were at risk but in the context of the research protocol would not learn the result.

Imaging Procedures

Subjects underwent fMRI scanning (3T Siemens Allegra) using an echo-planar imaging scan sequence while performing a verbal paired associates task (30 -3.0/1.0 mm gap slices, aligned to the anterior-posterior commissure plane; 3.1 × 3.1 mm in-plane resolution; TR = 2,500 ms; TE = 35 ms; flip angle = 90°). For coregistration to the Montreal Neurological Institute (MNI) standard brain, we also acquired a T2-weighted matched bandwidth scan (TR = 5,000 ms; TE = 33 ms; 4 averages) and a whole brain axial T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) three-dimensional MRI sequence (1 mm slices/0 mm gap; TR = 1,900 ms; TE = 4.38 ms; TI = 1,100 ms; flip angle 15°; 1 × 1 mm in-plane resolution).

Memory Activation Task

During fMRI scanning, subjects performed a Spanish language version of a verbal paired associates task shown previously to be sensitive to genetic risk for AD [Bookheimer et al., 2000]. In this task, subjects learned pairs of words, and were asked to recall the second words in the pairs, given the first words as cues.

Behavioral data were derived from an alternative pretest version of the task, administered on a laptop computer before scanning. The total number of correct retrievals for each subject was summed across six trials to arrive at a total possible score of 42. To include only subjects whose pretest scores were good indicators of the posttest scores, we converted pretests and post-tests to *z* scores and excluded subjects for whom the absolute value of the difference was >1.25. Nineteen subjects who had usable scans were included in this calculation, and of those, two were excluded based on this criterion. The two subjects who exceeded this threshold had values of 2.3 (for someone who performed at the top of the lowest quartile on the pretest but got a 0 on the posttest, possibly indicating inattention to the task in the scanner) and 1.9 (for someone who was in the lowest quartile on the pretest, but got a perfect score on the posttest, possibly indicating an initial misunderstanding of pretest instructions). The next highest difference score was 1.1. Using two-tailed *t*-tests, the absolute value of the difference between pretest and post-test *z* scores was not significantly different between mutation

carriers and noncarriers either before excluding the two subjects who had above-threshold difference values ($P = 0.68$) or in our final subjects sample ($P = 0.33$).

During the scan, subjects encoded seven pairs of unrelated words presented aurally in Spanish (MacStim presentation software version 3.1; WhiteAnt Occasional Publishing). Each word pair was presented for 3.75 s, followed by 1.25 s after each pair during which no word was presented. Each 35 s encoding block was followed by a 35 s distracter task period during which a “+” and “o” were alternately presented. Subjects were to press a button when they saw the “+.” During the 35 s retrieval blocks, participants heard the first word of each pair, and during the following 1.25 s, they attempted to recall the second word silently. The scan began and ended with 35 s of blank screen. After the scan, subjects were verbally tested to assess learning of the stimuli.

Functional MRI Data Analysis

We used FSL 4.1.4 tools (FMRIBs Software Library; available at: www.fmrib.ox.ac.uk/fsl) to analyze the fMRI data. Removal of nonbrain material, motion correction, and coregistration to MPRAGE scans and a standard MNI template brain were performed as described previously [Braskie et al., 2012]. fMRI scans were processed with a high-pass temporal filter of 110 s (based on one complete task cycle) and spatial smoothing with a Gaussian kernel of 5 mm full width half maximum. Motion parameters were added to the model to reduce the effect of motion on the data.

We used FSLs FMRIBs Improved Linear Model (FILM) [Woolrich et al., 2001] to perform individual statistical analyses. For each subject, we contrasted fMRI activity that occurred while the subject attempted to learn or recall word pairs with fMRI activity while they performed the distracter task. Encoding versus distraction, and retrieval versus distraction will be called encoding and retrieval periods, respectively. All voxel-wise analyses (both individual and group comparisons) were performed using a threshold of $z > 2.3$, adjusted to $P < 0.05$ using Gaussian Random Field theory-based cluster thresholding to correct for multiple comparisons. We compared the fMRI activity for mutation carriers versus noncarriers during encoding and retrieval blocks using FSL tool FMRIBs Local Analysis of Mixed Effects (FLAME) [Beckmann et al., 2003], and controlled for age, pretest score, and education across all subjects. Here, we evaluated group differences in activity with any differences that might exist between groups for age, task performance, and education removed from the analysis. We therefore compared mutation carriers and noncarriers in one analysis while including these as covariates of no interest demeaned across all subjects.

We next evaluated where fMRI signal best described task performance (pretest score) after adjusting for relative age and education within both the mutation carrier and

noncarrier groups. This effectively identifies voxels in which performance (given education level, incipient disease stage, and age) was correlated with fMRI response. Relative age was calculated as actual age minus the median age of AD diagnosis in the subject’s family. The pretest scores across all subjects included in the study were significantly correlated with performance on the posttest ($r = 0.67$; $P = 0.003$), and thus, the pretest was a good indicator of task performance in the scanner. We used the pretest values rather than the post-test values as an indicator of task performance because the pretest scores spanned a wider range and had no obvious ceiling effect. For this analysis, mutation carriers and noncarriers were directly compared within the same design. Relative age and pretest scores were covariates of no interest that were demeaned within each group. Because we were not evaluating the effects of education within group, but rather wished to remove the effects of varying education across groups, years of education were included as a covariate of no interest demeaned across groups.

All voxel-wise analyses were performed using the statistical parametric mapping within the FSL software. We used multiple regression ($P < 0.05$) to perform additional tests in a region of interest (ROI) analyses of the MTL (hippocampus and parahippocampal gyrus [PHG]).

Region of Interest (ROI) Analyses

For our functional analyses, we used the Harvard-Oxford standard ROIs [Desikan et al., 2006] to delineate right and left hippocampus and PHG in MNI space. fMRI signal in the MTL is sensitive to AD-related differences during memory tasks [Dickerson et al., 2005; Hamalainen et al., 2007; Petrella et al., 2007; Remy et al., 2005]. Registration of whole brains to a template brain may not sufficiently align hippocampal subregions to detect functional differences across subjects. Thus, for each subject, we used FSL *featquery* to evaluate mean signal within right and left hippocampus ROIs during encoding and retrieval.

Because we found a significant relationship between pretest score and PHG fMRI activity in noncarriers, but not carriers, we also performed an ROI analysis to determine whether there was a trend toward significance in carriers. The ROI was limited to PHG voxels that were significantly associated with pretest score in the noncarriers after adjusting for relative age and education. We used FSLs *featquery* tool to determine each subject’s mean fMRI percent signal change in the ROI. We performed multiple regression on the mean values, adjusting for relative age and education.

Structural Analyses

Structural ROIs of right and left hippocampus were automatically created using FSL FIRST software, a subcortical brain segmentation program that uses Bayesian shape

and appearance models [Patenaude et al., 2007]. Hippocampal masks were created based on individual MPRAGE scans in native space and then manually refined as needed by a single trained reviewer blind to mutation group status. We obtained volumes for right and left hippocampus and intracranial volume (ICV; derived from the skull-stripped MPRAGE scans) using the *fslstats* function in FSL. To adjust for head size, we divided hippocampal volumes by ICV for each subject. We evaluated the hippocampal volumes in two ways. First, multiple regression evaluated whether hippocampal volumes as a percentage of ICV were different between groups, controlling for sex and age. Second, as an additional test to determine whether atrophy may be responsible for our fMRI group differences in the hippocampus, we correlated raw left hippocampal volume with the mean retrieval period fMRI activity in those hippocampal voxels that showed significant group differences.

We also calculated gray matter volumes within each brain. To do this, we first normalized each T1-weighted image to the MNI standard template brain using FSLs nonlinear image registration tool (FNIRT), and visually inspected the results. We then segmented each brain into gray and white matter and cerebrospinal fluid using FSLs automated segmentation tool (FAST) [Zhang et al., 2001]. Normalized gray matter volume for each individual was calculated using the *fslstats* tool.

To determine whether our fMRI group differences were above and beyond any contribution of gray matter or hippocampal atrophy, we performed two additional analyses. Total normalized gray matter volume and bilateral hippocampal volumes were in turn included as covariates of no interest in our fMRI analyses where we compared group activation differences during memory retrieval while controlling for age, pretest score, and education.

RESULTS

Mutation carriers were not different from noncarriers in terms of sex ($P = 0.93$), actual age ($P = 0.15$), relative age ($P = 0.57$), pretest score for the verbal paired associates task used in the scanner ($P = 0.67$), education ($P = 0.84$), or Mini-Mental State Exam (MMSE) score ($P = 0.62$) as determined using two-tailed unpaired *t*-tests (Table I).

The range of age of dementia diagnosis between families was relatively narrow: from 40 to 54 years old. Therefore, in all subjects, relative age was strongly correlated with chronological age ($r = 0.82$; $P = 0.000047$); voxel associations with relative age also reflected chronological age to some extent. In mutation carriers, relative age additionally reflects how close the subject is to exhibiting AD symptoms, with a less negative (higher) number indicating more imminent disease.

When all subjects were considered without regard for group, fMRI activity was greater during both encoding and retrieval versus distraction in frontal (especially in the

left hemisphere), parietal and temporal cortex and cerebellum, and additionally during retrieval versus distraction in occipital cortex, the cingulate gyrus, the insula, striatum, and thalamus (Table II).

When fMRI activity was compared between mutation carriers and noncarriers, controlling for age, scanner task pretest score, and education, noncarriers showed more signal during retrieval in several regions known to be affected in early AD: inferior parietal cortex, precuneus, posterior middle temporal gyrus, and hippocampus (Figs. 1 and 2). Additional differences were found in the insula, brainstem, and thalamus (Table III). After controlling for gray matter volume by including it as a covariate of no interest, noncarriers still showed more signal during memory retrieval in all four AD-related regions: inferior parietal cortex, precuneus, posterior middle temporal gyrus, and hippocampus. When average bilateral hippocampal volume as a percentage of ICV was included as a covariate of no interest, noncarriers still showed more signal during memory retrieval in all of those regions except for the hippocampus. Mutation carriers did not show greater fMRI signal than noncarriers in any region. There were no significant effects of group during encoding. As an additional test to determine whether our group differences were actually limited to the retrieval period or may simply be subthreshold during encoding, we performed the same comparison for an additional contrast: retrieval versus encoding. No voxels were significantly different between groups for this contrast.

To identify brain activity that is important for performance, within each group we also examined the relationship between fMRI activity and pretest score, controlling for relative age and education. We found that in noncarriers, increased fMRI activity during encoding was associated with higher memory pretest score in medial frontal and occipital cortex, temporal cortex (including in the bilateral PHG), insula, cerebellum, and brainstem (Table IV; Fig. 3). No voxels were significantly associated with pretest score in carriers during encoding. During retrieval, lower pretest scores for carriers were associated with greater fMRI activity in frontal and temporal cortex, anterior cingulate, and insula (Table IV, Fig. 4). fMRI activity was not significantly associated with lower scores in the noncarriers or with higher scores in the carriers.

We found that after controlling for relative age and education, mutation noncarriers (but not carriers) who showed greater voxel-wise encoding period fMRI activity in bilateral posterior parahippocampal gyrus performed better on the scanner task pretest. The peak activity was found in Brodmann area (BA) 19, but the region of significant activity included voxels in BA 35 (perirhinal cortex) and BA 36 (parahippocampal cortex). Because the MTL is a particular focus of studies that evaluate early AD-related fMRI changes [Dickerson et al., 2005; Johnson et al., 2006; Kircher et al., 2007], we additionally used an ROI approach to evaluate fMRI activity in the PHG. We evaluated whether PHG fMRI signal truly responded

TABLE II. Regions of greater fMRI response: Encoding or retrieval versus distraction—all subjects

	Laterality	Brodmann area	Peak MNI coordinates	Max. z score
Encoding				
Frontal lobe				
Precentral g.	R/L	4	-54, -10, 44	4.34
Superior frontal g.	L	8	-10, 22, 48	2.76
Medial frontal g.	R/L	6	-6, 6, 56	4.54
Medial frontal g.	L	32	-6, 14, 48	3.35
Middle frontal g.	L	46	-50, 24, 22	3.26
Inferior frontal g.	L	13	-44, 28, 2	4.45
Inferior frontal g.	L	47	-42, 32, -6	4.66
Parietal lobe				
Postcentral g.	R/L	2	-50, -20, 50	3.44
Superior parietal lobule	L	7	-36, -60, 52	3.24
Precuneus	L	39	-34, -66, 40	3.76
Inferior parietal lobule	R/L	40	40, -34, 52	3.85
Temporal lobe				
Superior temporal g.	R/L	21	-64, -16, -4	5.56
Superior temporal g.	R/L	22	-62, -8, 0	5.49
Superior temporal g.	R/L	41	-44, -32, 10	5.38
Superior temporal g.	R/L	42	-58, -24, 6	5.87
Cerebellum	L		-12, -50, -12	3.39
Retrieval				
Frontal lobe				
Precentral g.	R/L	6	56, -4, 40	3.84
Medial frontal g.	R/L	6	6, 6, 56	5.70
Medial frontal g.	R/L	32	-4, 10, 48	5.18
Inferior frontal g.	L	9	-58, 12, 26	4.36
Inferior frontal g.	L	46	-52, 30, 8	4.78
Parietal lobe				
Postcentral g.	R/L	3	48, -18, 64	3.06
Postcentral g.	R	5	42, -38, 64	3.40
Precuneus	L	7	-16, -78, 40	3.54
Inferior parietal lobule	R/L	40	42, -36, 52	3.77
Cingulate g.	R/L	32	-8, 26, 28	4.91
Insula	R/L	13	32, 18, 0	4.58
Temporal lobe				
Superior temporal g.	R/L	22	-64, -32, 6	5.24
Superior temporal g.	R/L	41	60, -22, 10	4.93
Superior temporal g.	R/L	42	66, -28, 8	4.97
Middle temporal g.	R/L	21	-52, -32, -2	3.94
Occipital lobe				
Cuneus	L	7	-4, -76, 34	3.30
Cuneus	L	18	-4, -76, 22	3.14
Cuneus	L	19	-8, -78, 40	2.88
Caudate	R/L		-12, -4, 14	5.16
Putamen	R/L		26, -4, 8	3.02
Thalamus	R/L		16, -22, 16	3.92
Cerebellum	R/L		32, -62, -28	4.60

Sample MNI coordinates reflect activation peaks for a region.

differently between groups during memory encoding or whether a subthreshold trend existed in mutation carriers. As determined in the voxel-wise analyses, after controlling for relative age and education in noncarriers, encoding period fMRI activity was greater with better task performance in bilateral PHG (R^2 [full model] = 0.89; P [full model] = 0.02; P [partial contribution of pretest] = 0.01).

Pretest score did not significantly relate to average fMRI activity in bilateral PHG in mutation carriers (R^2 [full model] = 0.73; P [full model] = 0.07; P [partial contribution of pretest] = 0.34). However, a strong trend toward greater fMRI activity in better performing subjects existed in the left PHG (R^2 [full model] = 0.76; P [full model] = 0.054; P [partial contribution of pretest] = 0.047), but not

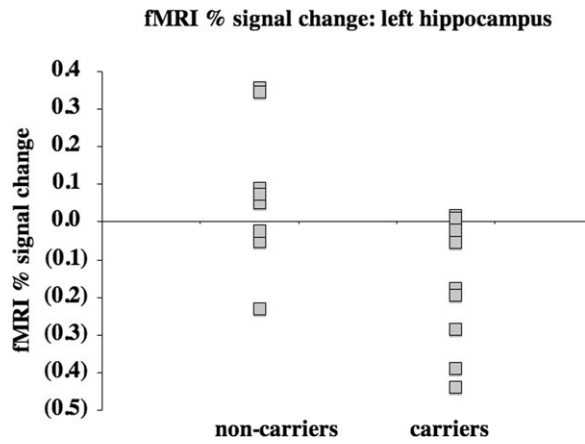


Figure 1.

After controlling for age, pretest score, and education across all subjects, percent signal change during memory retrieval was higher in mutation noncarriers versus carriers in the left hippocampus (R^2 [full model] = 0.69; P [full model] = 0.005; P [partial contribution of group] = 0.01).

the right PHG (R^2 [full model] = 0.65; P [full model] = 0.13; P [partial contribution of pretest] = 0.95).

We evaluated mean fMRI signal in bilateral hippocampus during encoding and retrieval using an ROI approach. During retrieval, when relative age, pretest scores, and education were controlled across all subjects, mutation carriers showed significantly less activity in bilateral hippocampus than non-carriers (R^2 [full model] = 0.62; P [full model] = 0.01; P [partial contribution of group] = 0.04). fMRI activity was not different between groups in bilateral hippocampus during encoding (R^2 [full model] = 0.31; P [full model] = 0.30). We then evaluated right and left hippocampus separately, controlling for relative age, pretest score, and education. During retrieval, mutation carriers showed significantly less fMRI activity in the left (R^2 [full model] = 0.69; P [full model] = 0.005; P [partial contribution of group] = 0.01), but not the right hippocampus (R^2 [full model] = 0.47; P [full model] = 0.09; P [partial contribution of group] = 0.22). However, after controlling for relative age and education during memory retrieval within each group, left hippocampal activity was not significantly associated with pretest score for carriers (R^2 [full model] = 0.57; P [full model] = 0.20) or noncarriers (R^2 [full model] = 0.57; P [full model] = 0.29). To evaluate the contribution of atrophy to our hippocampal group fMRI activity differences, we related the mean fMRI activity in significant left hippocampal voxels to the raw hippocampal volume values across all subjects. Raw left hippocampal volume was not significantly correlated with mean fMRI activity ($R^2 = 0.003$; $P = 0.85$). Right (R^2 [full model] = 0.17; P [full model] = 0.48), and left hippocampal volumes as a percentage of ICV were not significantly different between groups after adjusting for age and sex (R^2 [full model] = 0.21; P [full model] = 0.38).

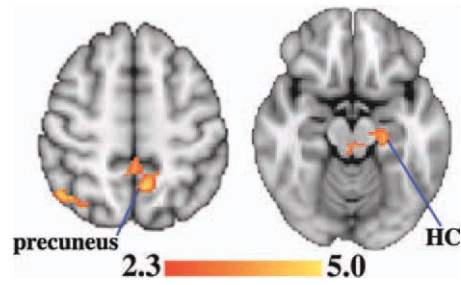


Figure 2.

After controlling for age, pretest score, and education across all subjects, fMRI signal during memory retrieval was greater in mutation noncarriers versus carriers in regions that are affected in AD. These regions included the precuneus and hippocampus. Significant voxels ($z \geq 2.3$; cluster thresholding corrected for multiple comparisons to adjust the image-wise threshold to $P < 0.05$) are highlighted to represent z scores. Coordinates for the axial direction in MNI space are 52 mm (left image) and -16 mm (right image). The brain is displayed in radiological convention (left = right). HC = hippocampus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

DISCUSSION

Despite similar cognitive abilities and task performance, during memory retrieval, FAD mutation carriers showed less fMRI activity than noncarriers in regions that included the left hippocampus (after controlling for age, pretest score, and education).

As we hypothesized, many of the regions in which we saw group differences—such as hippocampus, temporal cortex, precuneus, and inferior parietal lobule—show early structural changes in AD [Braak and Braak, 1991; Chetelat et al., 2010; McDonald et al., 2009]. When we controlled for total gray matter volumes by including them as a covariate of no interest, the variance in fMRI signal was

TABLE III. Regions in which fMRI response during memory retrieval is significantly greater in mutation noncarriers versus carriers after controlling for age, pretest scores, and education

	Laterality	Brodmann area	Peak MNI coordinates	Max. z score
Temporal lobe				
Middle temporal g.	R	19	40, -54 , 18	3.73
Hippocampus	L		-22 , -24 , -16	3.04
Parietal lobe				
Precuneus	RL	7	-8 , -56 , 50	3.53
Angular g.	R	39		
Supramarginal g.	R	40	46, -60 , 50	3.36
Insula	R	13	60, -30 , 22	3.14
Brain stem	RL		10, -28 , -12	3.13
Thalamus	R		24, -26 , 0	3.06

Sample MNI coordinates reflect activation peaks for a region.

TABLE IV. Regions in which fMRI response significantly correlates with pretest scores controlling for relative age and education

	Laterality	Brodmann area	Peak MNI coordinates	Max. z score
Encoding—noncarriers—greater fMRI signal with better pretest score				
Frontal lobe				
Inferior frontal g.	R	45	50, 20, 0	3.40
Inferior frontal g.	R	47	44, 20, -6	3.01
Temporal lobe				
Fusiform g.	RL	37	28, -44, -16	3.06
Parahippocampal g.	RL	19	22, -52, -6	3.39
Superior temporal g.	R	22	54, 18, -8	3.48
Occipital lobe				
Fusiform g.	RL	19	-26, -70, -6	2.93
Lateral occipital cortex	R	19	-48, -78, 0	3.36
Lingual g.	RL	18	16, -72, -4	3.29
Lingual g.	RL	19	18, -50, -4	3.36
Middle occipital cortex	L	19	-44, 76, 4	2.95
Insula	R	13	50, 16, 0	3.19
Cerebellum	RL		-12, -54, -6	3.34
Brainstem	RL		-16, -26, -4	2.58
Retrieval—carriers—greater fMRI activity with worse pretest score				
Frontal lobe				
Dorsolateral prefrontal cortex	R	9	52, 32, 30	3.34
Dorsolateral prefrontal cortex	R	46	48, 34, 14	3.41
Middle frontal g.	R	10	36, 44, 14	3.31
Paracentral lobule	RL	31	2, -8, 46	3.97
Superior frontal g.	R	6	10, 0, 66	3.68
Temporal lobe				
Middle temporal g.	RL	22	52, -48, 2	3.36
Superior temporal g.	RL	13	54, -18, 6	3.42
Superior temporal g.	L	21	-64, -8, -4	4.14
Superior temporal g.	RL	22	66, -38, 20	3.75
Superior temporal g.	RL	41	58, -22, 8	3.33
Superior temporal g.	RL	42	62, -32, 6	3.29
Transverse temporal g.	L	41	-38, -28, 12	3.13
Cingulate g.	RL	24	2, -14, 38	3.78
Insula	L	13	-44, -28, 20	3.15

Sample MNI coordinates reflect activation peaks for a region.

accounted for by group classification above and beyond any variance in gray matter volume in all four of these regions. We had similar results when we controlled for average bilateral hippocampal volume in the same way, but the difference in fMRI signal between the two groups was no longer statistically significant in the hippocampus, suggesting that hippocampal atrophy may contribute to the effect. However, hippocampal volume did not differ between groups and mean activity in significant voxels of the left hippocampus was not related to raw left hippocampal volumes, suggesting that atrophy is relatively unlikely to explain the entire effect. Damage to the entorhinal cortex—a region of very early AD pathology accumulation [Braak and Braak, 1991]—results in hypometabolism in most of these regions in nonhuman primates [Meguro et al., 1999], so our group differences may represent incipient AD processes. Group activity was significantly different only during retrieval, but when re-

trieval and encoding were contrasted, the groups did not differ, suggesting that similar, subthreshold effects may exist during encoding.

Presymptomatic mutation carriers showed less fMRI activity in the hippocampus versus noncarriers. Several previous fMRI studies of AD risk in cognitively intact adults found hippocampal differences associated with AD genetic risk [Bassett et al., 2006; Bondi et al., 2005; Bookheimer et al., 2000; Filippini et al., 2009; Han et al., 2007; Johnson et al., 2006; Quiroz et al., 2010; Trivedi et al., 2006]. In most of these studies, the focus was on greater MTL activity in higher risk adults, which most frequently occurred in the right hemisphere [Bassett et al., 2006; Bondi et al., 2005; Filippini et al., 2009; Han et al., 2007; Quiroz et al., 2010]. However, three of these studies also found, as we did, that lower AD risk related to greater left hippocampal and/or parahippocampal activity [Bassett et al., 2006; Bondi et al., 2005; Quiroz et al., 2010], and two additional

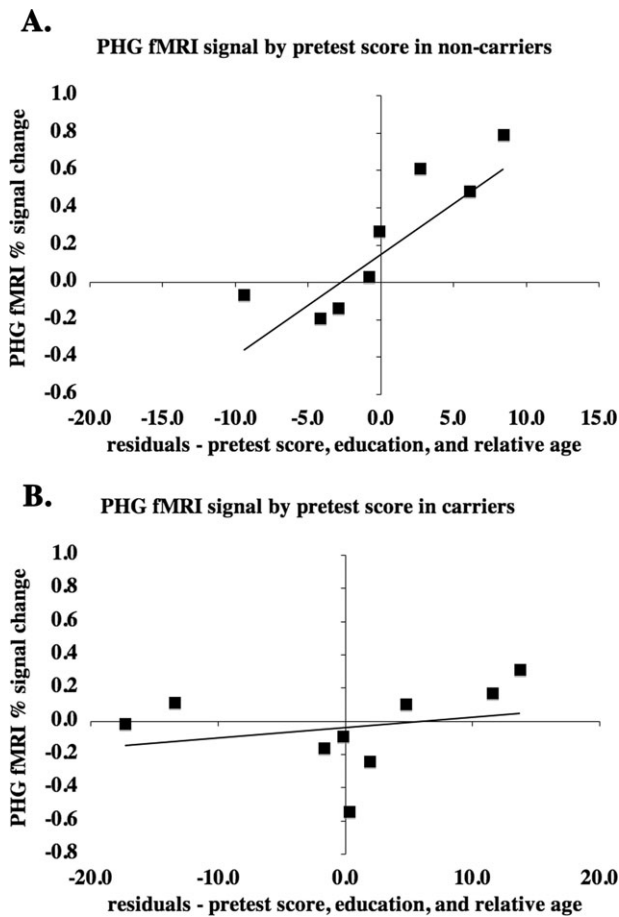


Figure 3.

After controlling for relative age and education within group, mutation noncarriers (**A**) with higher pretest scores showed significantly greater encoding period fMRI activity in bilateral PHG (R^2 [full model] = 0.89; P [full model] = 0.02; P [partial contribution of pretest] = 0.01). Mutation carriers (**B**) did not show a significant relationship between pretest score and average fMRI activity in bilateral PHC (R^2 [full model] = 0.73; P [full model] = 0.07; P [partial contribution of pretest] = 0.34), although a strong trend toward significance existed in left PHG.

studies found that lower risk adults had greater activity in the right [Trivedi et al., 2006] or bilateral [Johnson et al., 2006] hippocampus.

In a prior novelty encoding study, we found no group hippocampal differences in an overlapping sample of FAD mutation carriers [Braskie et al., 2012; Ringman et al., 2011a], even when those subjects [Braskie et al., 2012] were reanalyzed to control for age and education across all subjects (R^2 [full model] = 0.05; P [full model] = 0.78). In our current intentional encoding and retrieval task, we found that FAD mutation carriers showed less fMRI activity in the left hippocampus (during retrieval only) than our noncarriers. Our prior novelty task used incidental

rather than intentional encoding, and there was no memory recall component. It is possible that this recall task is more sensitive to mutation status differences in a small sample. The only previous AD risk study that we know of that separately evaluated where low AD risk was associated with higher fMRI during memory recall (rather than recognition), likewise found higher fMRI signal in low risk adults in the left MTL [Bassett et al., 2006]. Alternatively, our results may arise from resting state metabolism differences; the novelty encoding task, whose baseline activity involves viewing repeated pictures, may be less sensitive to such differences than the word pair task, which uses a simple reaction task as a baseline. However, preclinical FAD mutations are associated with reduced hippocampal resting state metabolism relative to controls [Mosconi et al., 2006], which would more likely result in greater task-induced fMRI hippocampal activity rather than the lower activity we saw here in carriers. Therefore, this explanation is less likely.

Within each group, we examined how fMRI activity related to memory pretest score, controlling for relative age and education. In mutation noncarriers, relative age closely reflects chronological age, while in carriers, it represents both chronological age and nearness to disease symptoms. This analysis demonstrates how fMRI activity relates to task performance given age, incipient disease stage, and level of education. During encoding, better performing mutation noncarriers, but not carriers, showed greater fMRI signal in several frontal, occipital, and temporal regions including bilateral PHG (Table IV) after

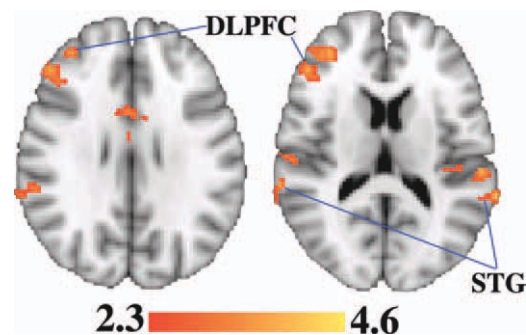


Figure 4.

After controlling for relative age and education within each group, fMRI signal during memory retrieval was higher in mutation carriers having lower memory pretest scores. Highlighted regions include the dorsolateral prefrontal cortex (DLPFC) and superior temporal gyrus (STG), both of which were previously implicated in APOE4-related fMRI differences using a similar task [Bookheimer et al., 2000]. Significant voxels ($z \geq 2.3$; cluster thresholding corrected for multiple comparisons to adjust the image-wise threshold to $P < 0.05$) are highlighted to represent z scores. Coordinates for the axial direction in MNI space are 14 mm (left image) and 28 mm (right image). The brain is displayed in radiological convention (left = right). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

adjusting for relative age and education. A correlation between memory performance and MTL activity only in those having relatively lower AD risk is not without precedent [Trivedi et al., 2006]. To identify possible subthreshold effects, we further performed ROI analysis in both carriers and noncarriers on significant PHG voxels (Fig. 3). PHG activity was not significantly correlated with pretest score in mutation carriers, but there was a strong trend toward a positive relationship between the two in left PHG only. Therefore, noncarriers engaged PHG in both hemispheres to successfully perform the task, but in carriers, who may have more MTL pathology, this relationship was disrupted, particularly in the right hemisphere. Right MTL has previously been identified as a site of early AD genetic risk differences in fMRI signal during memory tasks [Bassett et al., 2006; Bondi et al., 2005; Filippini et al., 2009; Han et al., 2007]. Although there were no significant performance differences between groups, it is possible that the mutation carriers already have mild, preclinical memory deficits not detectable by our task. A task that evaluates reaction time as well as correctness of response in a challenging task may be useful to highlight cognitive differences between mutation carriers and noncarriers in future studies.

In contrast with our hypothesis, in mutation carriers, memory performance was worse in those who showed greater retrieval period fMRI activity in several regions, including dorsolateral prefrontal (DLPFC) and superior temporal gyrus (STG) (Table IV). It is possible that detrimental processes were affecting these regions in some mutation carriers, interfering with the subjects' ability to perform the task and increasing relative fMRI signal beyond an optimal level. Examples of processes that result in greater fMRI activity in high-risk subjects who perform worse may include inflammation, dedifferentiation (a decreased specificity of regional recruitment) [Li and Lindenberger, 1999; Logan et al., 2002], or an excitotoxic response to nearby amyloid pathology [Sperling et al., 2010]. The concept of intermediate levels of fMRI activity being needed to optimally perform a memory task has been explored previously [Liu et al., 2010].

Decreased cerebrospinal fluid (CSF) levels of $A\beta_{42}$, and increased levels of total τ and phosphorylated τ_{181} are associated with incipient [Mattsson et al., 2009] and established [Andreasen et al., 2001] AD. Prior research has shown that in an FAD mutation carrier, cerebrospinal fluid levels of $A\beta_{42}$, total τ and phosphorylated τ_{181} were already changing between 17 and 22 years before the average age of AD diagnosis in the patient's family [Ringman et al., 2011b]. Mutation carriers in our study were between 22 and 5 years younger than the median age of AD diagnosis in their families (mean relative age of 14), suggesting that most of these subjects were likely to already have initial AD changes underway at the time of our study. The regions affected here were both implicated previously in *APOE4*-related fMRI differences using a similar task [Bookheimer et al., 2000], suggesting that activity there

was relevant to the task and varied with AD risk. Our DLPFC results were limited to the right hemisphere, consistent with the hemispheric encoding/retrieval asymmetry (HERA) model [Tulving et al., 1994], in which right PFC is more engaged than left during episodic memory retrieval.

Our results may be influenced by blood perfusion or resting metabolism, both of which influence fMRI signal and may differ in presymptomatic FAD mutation carriers [Johnson et al., 2001; Kennedy et al., 1995; Mosconi et al., 2006; Scholl et al., 2011]. A prior study of late-onset AD risk found increased resting-state perfusion and (during memory encoding) lower fractional BOLD and perfusion in the MTL of *APOE4* carriers [Fleisher et al., 2009]. Future studies in FAD mutation carriers that examine such factors alongside task-related fMRI would be useful in determining their contributions to fMRI signal variations. We are limited by our small sample size, which may unduly increase the effects of random variations in the population. Therefore, our results must be seen as merely suggestive. Verifying these results in a larger sample would aid in interpreting these data. Additionally, despite our efforts to recruit similar numbers of male and female subjects, our sample was ~88% female. Mutation carriers and noncarriers had a similar percentage of male subjects. Future studies having more male subjects would be useful in determining the extent to which our results are generalizable to samples more representative of the population.

The generalizability of our results to late-onset AD is uncertain. Similar retrospective studies that control for relative age in older adults who later develop AD may be useful in determining how fMRI signal relates to cognitive performance. Comparing amyloid deposition (determined through positron emission tomography) with performance and fMRI signal in studies of those at risk for late-onset AD also may address this question. Different genetic risk factors, including those that cause FAD may affect fMRI signal in the brain in varying ways and through different mechanisms. In the current study, we have examined genetic risk from three different FAD mutations as one entity. We have also compared our results with results from previous articles whose focus was late-onset AD risk, primarily *APOE4*. We do so because although genetic risk factors may be manifested differently through fMRI signal, there are also similarities among these risk factors. For instance, *APP* and *PSEN1* mutation carriers and *APOE4* carriers are all likely to have increased total $A\beta$ or proportion of $A\beta_{42}$ to $A\beta_{40}$ in the brain with respect to noncarriers, regardless of whether this is due to increased production, aggregation, or decreased clearance [Brouwers et al., 2008; Verghese et al., 2011]. A focus on the similarities, rather than the differences between how these variants affect brain structure and function may improve the generalizability of results, and also may help identify which gene effects on the brain have the greatest impact on cognition and disease onset or progression.

CONCLUSION

Presymptomatic FAD mutation carriers showed less retrieval period fMRI signal than noncarriers in several AD-related regions (after adjusting for age, memory test score, and education). During memory encoding, greater fMRI signal in several regions, including bilateral PHG, related to better memory performance in mutation noncarriers. There was also a strong trend toward left PHG only relating to memory performance in mutation carriers, suggesting a disruption of this relationship in the right PHG. Greater fMRI activity was not anywhere correlated with better memory performance in mutation carriers. However, in some regions, including DLPFC and STG, greater retrieval period activity was associated with worse memory performance, suggesting that these regions are both important to performance and disrupted in mutation carriers, possibly by incipient AD-related processes.

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