

Effect of Alzheimer Disease Risk on Brain Function During Self-appraisal in Healthy Middle-aged Adults

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Context: Asymptomatic middle-aged adult children of patients with Alzheimer disease (AD) recently were found to exhibit functional magnetic resonance imaging (fMRI) deficits in the mesial temporal lobe during an encoding task. Whether this effect will be observed on other fMRI tasks is yet unknown. This study examines the neural substrates of self-appraisal (SA) in persons at risk for AD. Accurate appraisal of deficits is a problem for many patients with AD, and prior fMRI studies of healthy young adults indicate that brain areas vulnerable to AD such as the anterior mesial temporal lobe and posterior cingulate are involved during SA tasks.

Objective: To determine whether parental family history of AD (hereafter referred to as FH) or presence of the $\epsilon 4$ allele of the apolipoprotein E gene (*APOE4*) exerts independent effects on brain function during SA.

Design: Cross-sectional factorial design in which *APOE4* status (present vs absent) was one factor and FH was the other. All participants received cognitive testing, genotyping, and an fMRI task that required subjective SA decisions regarding trait adjective words in comparison with semantic decisions about the same words.

Setting: An academic medical center with a research-dedicated 3.0-T MR imaging facility.

Participants: Cognitively normal middle-aged adults (n=110), 51 with an FH and 59 without an FH.

Main Outcome Measure: Blood oxygen-dependent contrast measured using T2*-weighted echo-planar imaging.

Results: Parental family history of AD and *APOE4* status interacted in the posterior cingulate and left superior and medial frontal regions. There were main effects of FH (FH negative > FH positive) in the left hippocampus and ventral posterior cingulate. There were no main effects of *APOE* genotype.

Conclusions: Our results suggest that FH may affect brain function during subjective SA in regions commonly affected by AD. Although the participants in this study were asymptomatic and middle-aged, the findings suggest that there may be subtle alterations in brain function attributable to AD risk factors.

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NEUROPATHOLOGICAL STUDIES¹⁻⁴ of persons at risk for Alzheimer disease (AD) suggest that AD may be preceded by a silent preclinical phase in which the brain incurs neuropathological change. Presence of the $\epsilon 4$ allele of the apolipoprotein E gene (*APOE4*) and parental family history of AD (hereafter referred to as FH)⁵ are risk factors for developing late-onset AD.⁶ Identifying initial brain changes in at-risk individuals using noninvasive functional imaging may help elucidate preclinical presence and progression of early AD.

Most prior functional magnetic resonance imaging (fMRI) studies⁷⁻¹⁵ in populations at risk for AD have focused on the hippocampus using episodic memory tasks that draw on encoding or retrieval pro-

cesses because memory symptoms are among the earliest to occur in AD. It has recently been shown that asymptomatic middle-aged adults (mean age, 55 years) who have a parent with AD exhibit reduced blood oxygenation level-dependent (BOLD) responses in the mesial and ventral temporal lobes during an encoding task,¹² and this effect was not explained by *APOE* genotype. The findings suggest that memory-related brain changes attributable to FH may be occurring in regions vulnerable to AD approximately 2 decades before the typical age at onset in sporadic AD.

Other early symptoms of AD may involve high-level executive functions such as metacognitive appraisal. Studies on executive functions have often operationalized the construct to the cognitive con-

Table 1. Demographic Neuropsychological and Performance Data for Each Group^a

Variable	Negative Family History		Positive Family History		P Value
	ε4 Negative (n = 47)	ε4 Positive (n = 12)	ε4 Negative (n = 24)	ε4 Positive (n = 27)	
Age, y	55.2 (6.3)	55.7 (5.8)	52.2 (6.6)	54.9 (6.0)	NS
Education, y	16.2 (2.6)	17.1 (2.2)	16.3 (2.5)	16.8 (2.3)	NS
Male to female sex ratio	9:38	7:5	11:13	13:14	<.001 ^b
Neuropsychological function					
Wide Range Achievement Test III–Reading	109.0 (8.3)	108.5 (7.6)	108.3 (8.9)	108.15 (7.6)	NS
Rey Auditory Verbal Learning Test					
1-5	50.2 (7.3)	49.1 (7.3)	51.7 (7.2)	47.3 (8.7)	NS
7	10.0 (2.6)	9.8 (2.3)	10.7 (3.0)	8.9 (2.9)	NS
Trail-Making Test					
A	27.0 (8.2)	31.5 (8.6)	24.9 (6.5)	29.5 (7.5)	.009 ^c
B	63.3 (21.4)	60.1 (21.5)	50.5 (13.3)	64.3 (20.8)	NS
Controlled Oral Word	43.6 (10.0)	48.2 (11.6)	43.0 (10.8)	44.6 (10.0)	NS
Boston Naming Test	57.3 (3.1)	57.7 (3.6)	57.5 (2.5)	57.5 (1.9)	NS
Center for Epidemiological Depression Scale	5.0 (5.8)	6.3 (5.1)	3.9 (4.0)	5.5 (5.6)	NS
Hemoglobin level, g/dL	13.87 (0.81)	14.00 (1.34)	14.00 (1.08)	14.12 (0.87)	NS
Systolic blood pressure, mm Hg	130.4 (16.3)	127.6 (17.0)	129.7 (14.9)	133.5 (15.9)	NS
Performance in the scanner					
Reaction time self-appraisal	1.58 (0.21)	1.61 (0.19)	1.60 (0.29)	1.62 (0.22)	NS
Reaction time semantic	1.69 (0.26)	1.77 (0.21)	1.70 (0.31)	1.74 (0.27)	NS

Abbreviation: NS, not significant.

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.0.

^aData are given as mean (SD) unless otherwise indicated.

^b χ^2 Statistic.

^cStatistically significant main effect of *APOE* genotype.

control processes that subservise executive function, including working memory, mental flexibility and speed, imperviousness to distraction, and inhibition of prepotent responses. These well-studied functions have generally been attributed to the dorsolateral prefrontal cortex.¹⁶ The metacognitive aspects of executive function are less well studied and include processes such as self-monitoring, planning prospective action, making inferential or subjective decisions, self-appraisal (SA) (the focus of the present study), and social tuning of one's behavior for adaptive functioning in the world of people (judgment).

Prior studies have implicated cortical midline structures, including the anterior medial prefrontal cortex and posterior cingulate for metacognitive processes,¹⁷⁻¹⁹ particularly the processes of self-regulation of affect, self-reflection on abilities and traits, self-monitoring of actions and bodily states, and social cognition such as making inferences about the mental states of others.²⁰ The hippocampus has also been implicated in cognitive SA.²¹ Neuroimaging studies of the posterior cingulate have found a decreased cerebral metabolic rate of glucose metabolism,²²⁻²⁴ cerebral atrophy,^{22,25} and amyloid binding^{22,26} in persons with AD. In 2 studies,^{4,24} subjects at risk for AD also exhibited reductions in cerebral metabolic rate of glucose in the posterior cingulate. Furthermore, "resting state" abnormalities in AD have been found in the posterior cingulate and medial frontal lobes, as well as the hippocampus.^{22,27,28}

No studies have yet examined metacognitive brain function in healthy persons at risk for AD, to our knowledge. This may be a useful avenue of study because patients with AD often exhibit deficits in metacognitive abilities²⁹ such as appreciating the extent or severity of their

deficits. The objective of the present study was to determine whether we could observe AD risk-associated differences in BOLD activity during a self-referential decision task that consistently evokes BOLD activity from the posterior cingulate, medial frontal lobe, and mesial temporal lobes across prior studies^{19,30-32} of healthy adults. We examined brain activation in 110 physically and cognitively asymptomatic middle-aged adults who differed in FH and *APOE4* status. A 2 × 2 factorial design was used to examine the relative contribution of *APOE* genotype and FH on the cerebral response. Based on prior findings, we expected that FH would have an effect on cerebral activation that was separable from *APOE* genotype in cortical midline brain regions and hippocampus.

METHODS

PARTICIPANTS

One hundred ten subjects underwent fMRI and cognitive testing (**Table 1**). Fifty-one (mean ± SD age, 53.6 ± 6.4 years) had at least 1 parent with AD (FH positive) and were recruited from the Wisconsin Registry for Alzheimer's Prevention,³³ a longitudinal registry of cognitively normal adults between the ages of 40 and 65 years (at enrollment) who have at least 1 parent with sporadic AD. To verify the diagnosis of AD in the parent, parental medical records were obtained and were reviewed by a multidisciplinary diagnostic consensus panel. Typically, the clinical workup and diagnosis in the parent were conducted at the University of Wisconsin Memory Clinics, and the adult children were then approached for participation. The mean age at symptom onset in the affected parent was 73 years. All subjects in the FH-positive group underwent baseline neuropsych-

chological evaluations and laboratory tests that included APOE genotyping using polymerase chain reaction and sequencing. Fifty-three percent (27 of 51) were $\epsilon 4/\epsilon 3$ positive ($\epsilon 3/\epsilon 3$, 24 subjects; $\epsilon 3/\epsilon 4$, 20 subjects; and $\epsilon 4/\epsilon 4$, 7 subjects).

Fifty-nine participants (mean \pm SD age, 55.3 ± 6.2 years) with no FH (FH negative) were recruited from the community and were matched to the demographic characteristics of the FH-positive sample. Absence of FH was determined through self-report of the participant by telephone interview and by detailed medical history questionnaire. To be included in the FH-negative group, both parents had to survive to at least age 70 years (most were well beyond this age) and not have a diagnosis of dementia or exhibit frank symptoms of dementia of any kind. Twelve control subjects (20%) were $\epsilon 4$ positive ($\epsilon 3/\epsilon 4$, 11 subjects; and $\epsilon 4/\epsilon 4$, 1 subject), and 47 were $\epsilon 4$ negative (all $\epsilon 3/\epsilon 3$).

The demographics of the $\epsilon 4$ -positive and $\epsilon 4$ -negative subgroups are given in Table 1, along with neuropsychological and fMRI task performance. We only included participants who had the $\epsilon 4$ or $\epsilon 3$ allele of APOE (21 participants with $\epsilon 2$ alleles were excluded). This was done to control for potential heterogeneity among genotypes. The proportion of women in the cells differed; therefore, sex was used as a covariate in the fMRI data analysis. Exclusions for this imaging study included MR imaging scanner incompatibility, abnormal structural MR imaging or neuropsychological test results as part of study participation, or history of major psychiatric disease (eg, schizophrenia, substance dependence, and current or recent major depression) or major medical conditions (eg, type 1 diabetes mellitus, cancer requiring chemotherapy or radiation therapy, and neurological disorders, including prior head trauma with loss of consciousness). Most patients taking psychoactive drugs were excluded, although we allowed low-dose selective serotonin reuptake inhibitors if the patient had been stable for more than 3 months.

All subjects in the study received an additional fMRI task of episodic encoding that has been reported on previously.¹² Participation in this study was contingent on signed informed consent, and the study was conducted in accord with the Declaration of Helsinki.

fMRI TASK

The fMRI paradigm has been described in detail in prior studies of healthy young adults³⁰ and subjects with mild cognitive impairment (MCI).³⁴ Briefly, the task requires participants to make yes or no decisions based on individually presented trait adjectives across 2 conditions, referential SA and nonreferential affective or semantic decision (SEM). The same set of 30 adjectives was presented in the SA and SEM conditions in counterbalanced order. In the SA condition, participants decided whether or not adjectives described their personal traits and abilities, whereas in the SEM condition, they decided whether or not adjectives in the set were of positive valence. The first presentation of each adjective was counterbalanced across conditions such that novelty was not confounded with condition order. Two equivalent forms of the task were presented sequentially (counterbalanced), each using separate adjective sets. Within each task run, each of the 2 conditions was presented in 5 pseudorandomized cycles. Words were presented every 4 seconds (3 seconds on screen and a 1-second interstimulus interval) in blocks of 6 per condition.

IMAGING PROCEDURES

After higher-order shimming, T2*-weighted gradient-echo echo-planar images were obtained as follows: echo time, 30

milliseconds; repetition time (TR), 2000 milliseconds; flip angle, 90°; acquisition matrix, 64×64 voxels; and field of view, 240 mm. Thirty sagittal sections of the brain were acquired within the TR at each time point, with voxel resolution of $3.75 \times 3.75 \times 4$ mm and 1-mm skip between sections. In 4-minute and 8-second imaging trials, 124 time points were collected, of which 3 images acquired during the first 6 seconds were discarded (for a total of 242 reconstructed time points).

Residual magnetic field inhomogeneity resulting in regional distortions are common with echo-planar images. We corrected these by measuring 3-dimensional field maps across the brain (coplanar with the fMRI sections). This was accomplished by measuring the phase of non-echo-planar image gradient-echo images at 2 echo times (7 milliseconds and 10 milliseconds). The phase difference between the 2 echo images is proportional to the static field inhomogeneity.³⁵ The warp calculation and correction³⁶ were performed using the FMRIB Software Library version FSL3.2 (<http://www.fmrib.ox.ac.uk/fsl>). Anatomical T1-weighted volumes and T2-weighted axial sections were also acquired using parameters previously described.¹²

For anatomical imaging and voxel-based morphometry analysis, axial T1-weighted and T2-weighted images were acquired after the functional runs. A 3-dimensional inversion recovery-prepared fast gradient echo-pulse sequence provided high-resolution T1-weighted structural images with the following parameters: inversion time, 600 milliseconds, fast gradient echo-pulse readout with TR/echo time/flip angle, 9 milliseconds/1.8 milliseconds/20°; acquisition matrix, $256 \times 192 \times 124$ voxels (interpolated to $256 \times 256 \times 124$ voxels); field of view, 240 mm; section thickness, 1.2 mm (124 sections); and ± 160 -kHz receiver bandwidth.

A fast-recovery fast spin-echo 2-dimensional T2-weighted axial sequence was also acquired with the same start and stop locations as the T1-weighted images. The parameters were as follows: field of view, 240 mm; acquisition matrix, 256×256 voxels; TR, 9000 milliseconds; echo time, 93 milliseconds; and flip angle, 90°. Seventy sections were acquired; the section thickness was 1.7 mm with a 0.3-mm skip. An experienced neuroradiologist (H.A.R.) examined all of the images before the analysis for clinical evidence of any neurovascular disease or structural abnormality that would exclude the subjects from the analysis.

DATA ANALYSIS

Other preprocessing steps and statistical analysis were performed using Statistical Parametric Mapping SPM2 software (<http://www.fil.ion.ucl.ac.uk/spm>). The image time series was motion corrected, field map corrected as already described, normalized into the Montreal Neurological Institute standard space using the T2-weighted template provided through SPM2 (written out with $2 \times 2 \times 2$ -mm voxel resolution), and then smoothed with an 8-mm full-width-at-half-maximum gaussian kernel.

The time-series data for individual participants were analyzed using a boxcar model convolved with the canonical hemodynamic response function as implemented in SPM2.³⁷ The statistical model included high-frequency signal filtering (high-pass filter, 128 seconds) and the autoregressive(1) method of estimating temporal autocorrelation. The SA vs SEM contrast was computed for each participant and was entered into second-level analyses.

The mean effect of task (SA vs SEM), collapsed across groups, was first computed and thresholded at $P < .005$ uncorrected, which corresponded to $P_{\text{false discovery rate-corrected}} < .04$. This map was written out (**Figure 1** and **Table 2**) and was used to constrain the

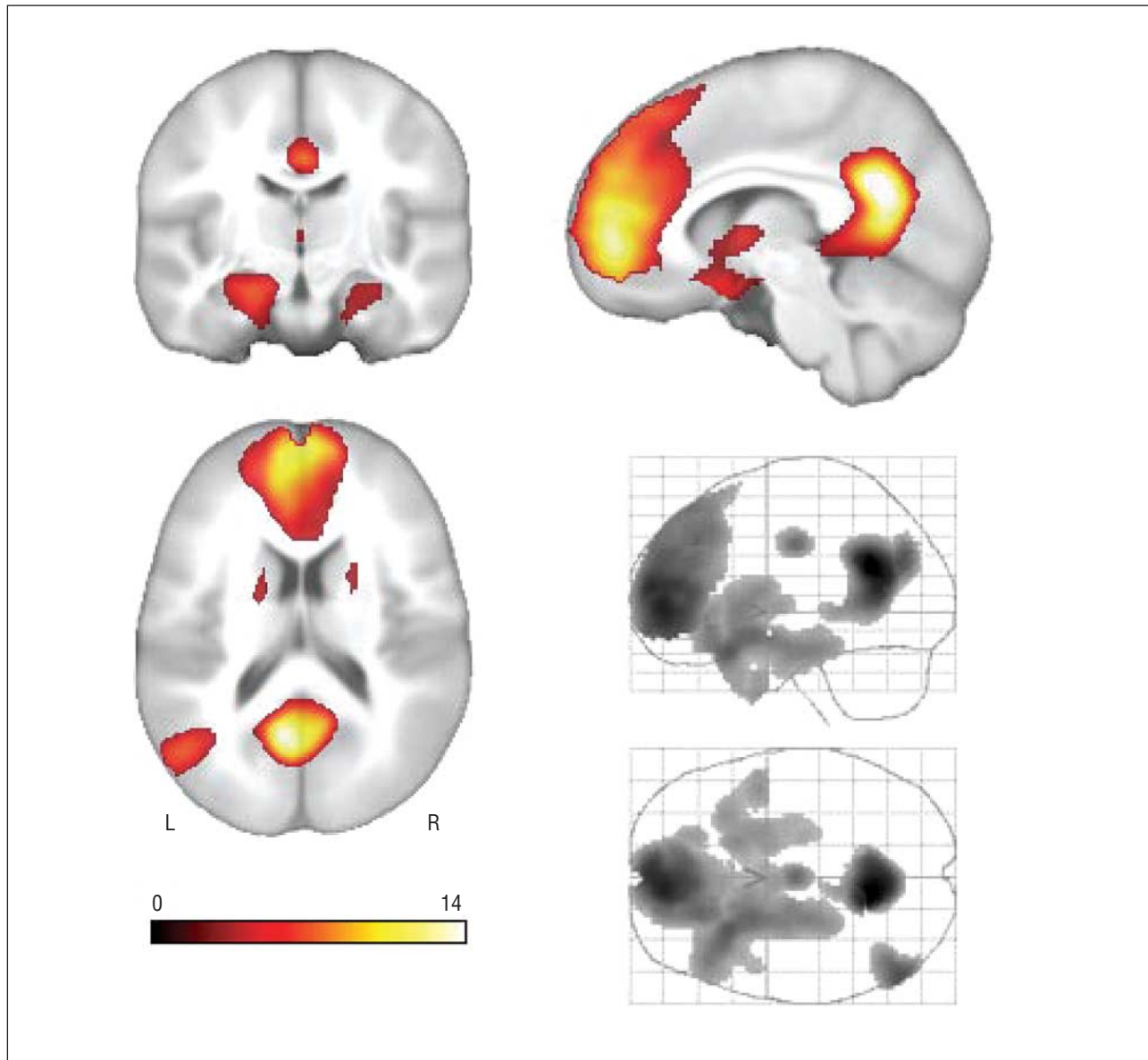


Figure 1. Main effect of task across all 110 cognitively normal participants. Orthographic coronal, sagittal, and axial views are shown, as well as lateral and transverse maximum-intensity projections of the result. Left is on the left. The map is thresholded at $P_{\text{false discovery rate}} < .05$, corresponding to $t > 2.57$. The main effect of task in this comparison was used to restrict inference on subsequent comparisons of risk status. See Table 2 for cluster locations and statistical details. L indicates left; R, right. The scale bar from 0 to 14 represents the value of the t statistic.

subsequent analyses of group differences to only those brain voxels that were relevant to the task. Using analysis of covariance (ANCOVA), a 2×2 factorial analysis was performed that examined between-group effects of FH, *APOE* genotype, and FH \times *APOE* genotype interaction. Sex was used as a covariate. This same design was applied to the demographic and neuropsychological data. For the fMRI factorial analyses, statistical significance was also assessed at a voxel-level threshold of $P < .005$ uncorrected.

For anatomical analyses, to determine whether group activation differences were due to anatomical differences in gray matter volume, we conducted voxel-based morphometry in the same search space and using the same model as the fMRI ANCOVA but with the additional covariate of total gray matter volume. The procedures have been described in detail elsewhere.^{12,38,39}

RESULTS

Demographic characteristics and task performance are given in Table 1. The χ^2 statistic indicated that the proportion of men and women differed in 1 group; therefore, sex was used as a covariate in subsequent behavioral and fMRI ANCOVAs. Factorial ANCOVA of demographic and neuropsychological variables indicated no FH \times *APOE* genotype interaction. Tests for main effects of *APOE* genotype and FH in these healthy asymptomatic subjects were also statistically nonsignificant except for Trail Making Test A, on which the $\epsilon 4$ -negative subjects performed 3.7 seconds faster than the $\epsilon 4$ -

positive subjects. There were no differences in the fMRI behavioral data with regard to reaction time and response bias. The fMRI findings follow.

EFFECT OF TASK

The mean response to the task (SA > SEM) is shown in Figure 1, with statistics and Montreal Neurological Institute locations given in Table 2. Active regions included 2 prominent midline clusters; the posterior cluster spans the ventral the posterior cingulate cortex, and the retrosplenial cortex.⁴⁰ The large anterior medial prefrontal cortex cluster spans the medial surface of the superior frontal gyrus and rostral anterior cingulate. Also, 2 large bilateral clusters were observed in the anterior mesial temporal lobe spanning the hippocampus and amygdala and extending contiguously to the ventral forebrain and basal ganglia and thalamus. All comparisons in the subsequent factorial ANCOVA analysis were constrained to only those regions that were active in Figure 1. This procedure reduced the search region to 9.3% of the original number of voxels in the common brain mask. This was implemented to reduce the potential vulnerability to false-positive errors and to ensure that subsequent results from group comparisons were interpretable with regard to the cognitive task.

EFFECT OF RISK FACTORS

Using factorial ANCOVA, an *F* test for FH × APOE genotype interaction yielded prefrontal clusters at voxel location -26, 36, 36 (*F* = 9.73, *P* = .002 uncorrected; 102 voxels) in the left superior frontal gyrus and at voxel location -10, 48, 2 (*F* = 9.71, *P* = .002 uncorrected; 26 voxels) in the left anterior cingulate. A third small cluster was found in the retrosplenial area of the posterior cingulate at voxel location 0, -50, 4 (*F* = 8.26, *P* = .005 uncorrected; 33 voxels). These clusters and associated plots of signal change are shown in **Figure 2**. Post hoc analyses were conducted, and statistically significant mean differences are indicated on the plots. Group differences were only statistically significant relative to the FH-negative ε4-positive group. The other 3 groups did not differ from each other.

The main effects of FH and APOE genotype were tested next. Because main effects are not readily interpretable in the presence of interactions, voxels that were identified as statistically significant in the interaction map of Figure 2 were not considered in the analysis of main effects (this was achieved using the “mask with other contrasts” option in SPM2). The main effect of FH negative greater than FH positive was statistically significant in the left hippocampus (at voxel location -16, -22, -14; *t* = 4.05, *P* < .001 uncorrected; 233 voxels) and the left ventral posterior cingulate (at voxel location -14, -66, 20; *t* = 3.33, *P* = .001; 50 voxels). These results are shown in **Figure 3**. No statistically significant results were found in the reverse comparison (FH positive > FH negative). The effect of APOE genotype was tested using the contrast ε4 positive greater than ε4-negative (and its reverse). Statistically significant voxels in the interaction were

Table 2. Mean Effect of the Appraisal Task

No. of 2 × 2 × 2-mm Voxels	Voxel <i>t</i> Value ^a	Talairach Coordinates x, y, z ^b	Location
3649	15.92	-10, -54, 26	Posterior cingulate
10 149	13.17	-6, 54, 2	Anterior medial prefrontal cortex
742	9.86	-52, -70, 26	Left lateral parietal
8943	9.52	-28, 20, -22	Left posterior orbital
...	8.40	-22, 10, -14	Left nucleus accumbens
...	6.80	-22, -18, -22	Left hippocampus
...	6.82	-16, 14, 2	Left caudate
...	5.94	18, 16, 4	Right caudate
...	5.61	24, 6, -12	Right nucleus accumbens
...	5.25	32, 22, -24	Right lateral orbital
...	3.83	24, -10, -20	Right hippocampus
304	8.12	0, -10, 36	Midcingulate
87	6.49	28, -80, -40	Right cerebellum

Abbreviation: Ellipses, locations are submaxima to the cluster with 8943 voxels.

^aAll voxel-level *t* values are statistically significant at *P* < .005 uncorrected (critical *t* = 2.62), corresponding to *P*_{false discovery rate} < .04.

^bMontreal Neurological Institute standard space.

again excluded. The results revealed no statistically significant voxels in either contrast.

ANATOMICAL ANALYSIS

Using voxel-based morphometry, no group differences in gray matter volume were found. These results suggest that the fMRI findings were not attributable to atrophy.

COMMENT

This study examined the cerebral response during a meta-cognitive task, SA on trait adjectives. We used this task in persons at risk for AD because converging research has indicated that the regions normally responsive on this task seem to overlap with brain regions affected by AD.³⁰⁻³² Our analyses indicated differences in task-related activation associated with FH, as well as regions where APOE genotype and FH risk factors interacted. Parental family history of AD had the effect of diminishing the cerebral response in the ventral posterior cingulate and the left mesial temporal lobe. Although there were no main effects of APOE4 status, this risk factor interacted with FH in the left dorsolateral prefrontal cortex, anterior medial prefrontal cortex, and retrosplenial posterior cingulate; plots indicated that ε4 carriers who had no FH exhibited greater signal change to the task. The observed effects were not due to gray matter atrophy or global cognitive function.

The medial parietal cortex has been implicated in memory retrieval and recognition,^{22,41,42} as well as meta-cognitive appraisals.^{19,31,32,43-46} Several recent studies report medial parietal hypometabolism⁴⁷ or hypoperfusion⁴⁸ in individuals with MCI, a diagnosis that confers considerable risk for developing AD. Longitudinal stud-

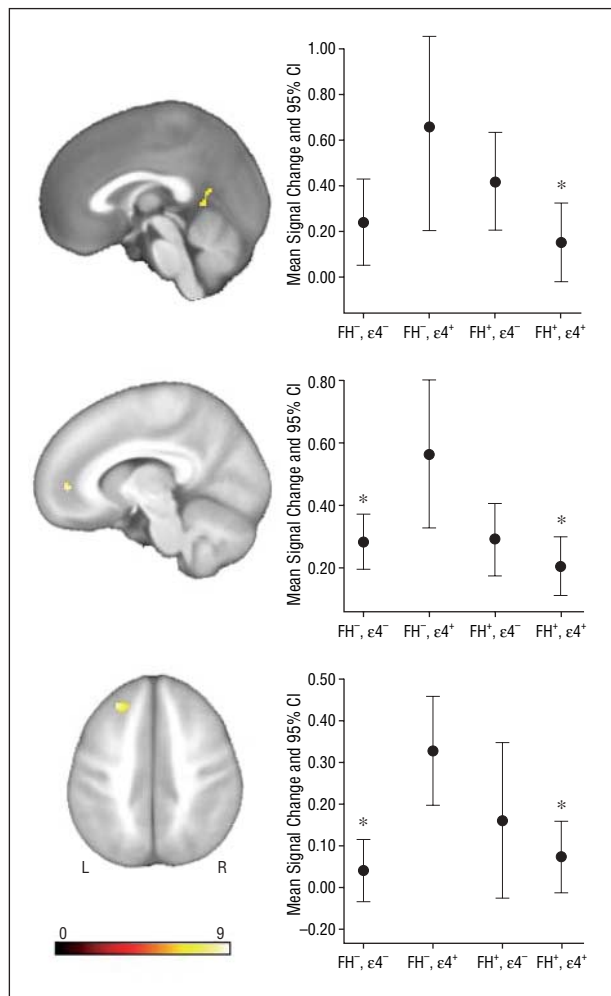


Figure 2. The interaction between first-degree family history of AD (hereafter referred to as FH) and *APOE4* ($\epsilon 4$) status. The 3 clusters that reached statistical significance are shown in sagittal and axial views. The corresponding plots depict the means for the 4 groups (error bars indicate 95% confidence intervals [CIs]) derived from the first eigenvariate of each subject across the entire cluster. *The mean differed statistically significantly from the FH-negative (FH-) $\epsilon 4$ -positive ($\epsilon 4^+$) group ($P < .005$). The scale bar from 0 to 9 represents the value of the F statistic for the interaction. FH⁺ indicates FH-positive group; $\epsilon 4^-$, $\epsilon 4$ negative.

ies⁴⁹⁻⁵¹ also indicate that posterior cingulate metabolism and regional blood flow discriminate between individuals with MCI who soon develop AD and patients with MCI who remain stable. Reiman and colleagues^{4,24} found that the medial parietal lobe, including the posterior cingulate cortex and precuneus, was hypometabolic for glucose in cognitively normal *APOE4* carriers relative to non-carriers (the effect of FH was not tested in these earlier studies). The medial parietal findings observed in the present study during a cognitive challenge seem to be generally consistent with these prior results and suggest that this region may be beginning to exhibit dysfunction in these asymptomatic middle-aged adults at risk for AD. As further evidence of this possibility, Ries et al³⁴ studied amnesic patients with MCI using the same paradigm reported herein and ratings of anosognosia. A statistically significant positive correlation was found between insight and activation; subjects with MCI who exhibit diminished insight for their cognitive impair-

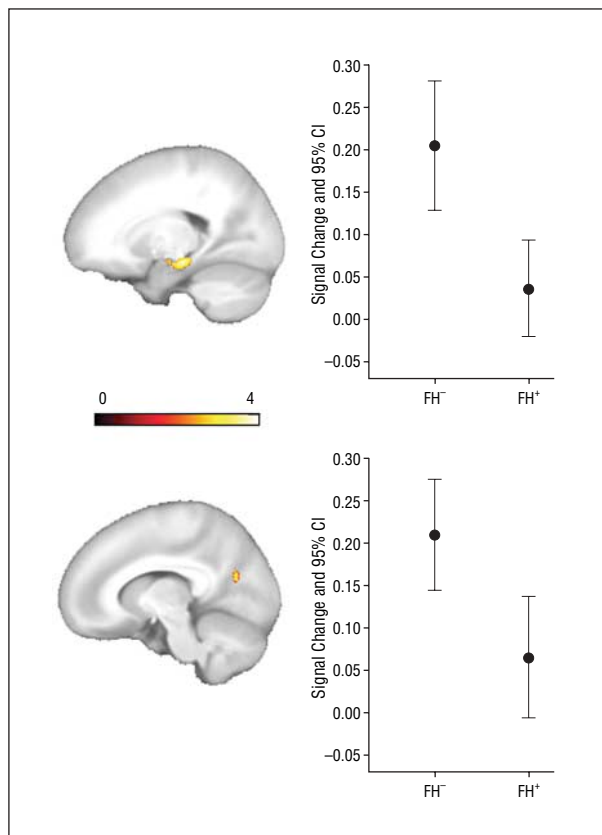


Figure 3. Statistical parametric map of the main effect of first-degree family history of AD (hereafter referred to as FH). The figure shows regions where the FH-negative (FH-) groups activate more on average than the FH-positive (FH⁺) groups. Select brain sections are shown (left is on the left) depicting the result in the posterior cingulate and subiculum with corresponding plots of the mean signal change derived from the first eigenvariate across the cluster (error bars indicate 95% confidence intervals [CIs]). The scale bar from 0 to 4 represents the value of the t statistic.

ment also exhibit diminished responses in the posterior cingulate and mesial frontal lobe. The data by Ries et al³⁴ and the findings in the present study suggest that risk factors for AD are affecting systems supporting metacognition, which may eventually become part of the symptom picture of AD.

Areas of the left medial temporal lobe were also differentially active in FH-negative subjects on this task. In a young adult sample, it was recently shown that this region of the hippocampus exhibits task-dependent functional connectivity with the anterior medial prefrontal cortex on this same task.³⁰ The hippocampus and subiculum are densely connected to the medial frontal lobe in rhesus monkeys.^{52,53} Phillips et al²¹ include the hippocampus in the dorsal axis of an emotion appraisal model (also involving the dorsomedial and dorsolateral frontal lobe) that receives biasing self-relevant input from ventral structures, including the amygdala, nucleus accumbens, and ventral medial frontal lobe.¹⁷ Amyloid burden in the mesial temporal lobe has been found to be related to the degree of anosognosia in patients with AD.⁵⁴ The role of the hippocampus in affective and cognitive appraisal and how this might relate to the symptom picture of AD is not completely understood and is deserving of much more study.

In this sample, *APOE4* status and FH interacted (Figure 2), but there were no *APOE4* main effects. The interaction was largely due to the finding that $\epsilon 4$ -positive subjects but not FH-negative subjects exhibited the greatest activation. An intriguing study by Mondadori et al⁵⁵ points out several salutary effects of *APOE4* status on the brain in early life, and they present fMRI results of a memory encoding task indicating that young adult $\epsilon 3/\epsilon 4$ carriers exhibit hippocampal learning-related signal adaptation but that young noncarriers do not. There is still much to learn about the effect of *APOE4* status across the life span, but in the context of the recent literature and the findings in the present study, it is likely that interactions are occurring between *APOE4* status and age or other AD risk factors that manifest as a putative salutary effect early in life but as a deleterious effect later in life.

The results herein are consistent with those of a prior study¹² of an episodic encoding task among most of these same subjects in which a robust effect of FH in the hippocampus and ventral temporal lobes during object encoding was found. That prior study also found that the FH-negative $\epsilon 4$ -positive group again exhibited the greatest cerebral response in the hippocampus, while FH-positive $\epsilon 4$ -positive subjects had the least. A similar finding was observed when subjects possessing the $\epsilon 2$ allele were removed.¹⁵

At least 2 other recent studies have reported FH effects. In a behavioral experiment of odor identification, it was found that siblings of patients with AD exhibited reduced accuracy relative to control subjects. This effect was more pronounced in siblings who were *APOE4* positive.⁵⁶ Using fMRI, Bassett et al⁷ examined FH and *APOE* genotype in a large sample ($n=195$) and found that FH affected brain activation during a paired-associate encoding task but that *APOE* genotype did not.

There remains a fundamental issue regarding fMRI group differences in cognitively normal vs at-risk or cognitively impaired populations. Some studies have reported risk-associated^{8,57-59} and disease-associated^{10,60} increases in cerebral activity, while other studies report decreases in cerebral response with increased risk^{12,14,55} or cognitive impairment.^{13,61-63} Although there are many sources of noise and variability using fMRI, some possible reasons for these study differences are the following: (1) Increased task difficulty has the effect of increasing fMRI activation.^{64,65} (2) Regarding the choice of comparison condition from which BOLD signal change is measured, it has been shown that a resting low-level baseline (such as rest or crosshair fixation) and an active cognitively challenging baseline produce different results.^{66,67} (3) Finally, the choice of analysis methods and statistical model (eg, spatially normalizing to a standard space vs native space⁶⁸ or counting of suprathreshold voxels within a region vs statistical parametric mapping) may cause difference results.¹⁰ Given the variability across studies, researchers who develop fMRI tasks for use in clinical and at-risk populations should adopt a task-specific psychometric approach to measuring brain activation. Such an approach might include parametrically varying difficulty, comparison with normative data,⁵⁵ and characterization of tasks across larger samples and across a

range of demographics (eg, age) and clinical parameters (eg, genes and cognitive status⁶¹).

In conclusion, these data suggest that FH may affect brain function many years before typical disease onset. The genetic and environmental factors that embody FH are still largely unknown, and further study is required. Our results highlight the idea that factors beyond *APOE* genotype contribute to AD and should be included when possible in studies of AD risk. Although memory dysfunction is a core feature of AD and is typically one of the first noticeable symptoms, these findings using a self-referential decision task suggest that brain areas underlying metacognitive functions may also show compromise in persons at risk and may correspond, in part, to the metacognitive deficits that are observed in symptomatic AD.

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