Published in final edited form as:
Arch Gen Psychiatry. 2007 October ; 64(10): 1163–1171. doi:10.1001/archpsyc.64.10.1163.

Effect of Alzheimer Disease Risk on Brain Function During Self-Appraisal in Healthy Middle-Aged Adults

Sterling C. Johnson, PhD[1,2], **Michele L. Ries, PhD**[1,2], **Timothy M. Hess, MS**[1,2], **Cynthia M. Carlsson, MD**[1,2], **Carey E. Gleason, PhD**[1,2], **Andrew L. Alexander, PhD**[2], **Howard A. Rowley, MD**[2], **Sanjay Asthana, MD**[1,2], and **Mark A. Sager, MD**[2]

1*Wm S. Middleton Memorial VA Hospital—Madison, Madison WI 53705*

2*University of Wisconsin—Madison, Madison WI 53705*

Abstract

Context—Recently asymptomatic middle-aged adult children of patients with Alzheimer Disease (AD) were found to exhibit fMRI deficits in the mesial temporal lobe during an encoding task. Whether this effect will be observed on other fMRI tasks is not yet known. This study examines the neural substrates of self-appraisal in people at risk for AD. Accurate appraisal of deficits is a problem for many AD patients, and prior fMRI studies of healthy young adults indicates that brain areas vulnerable to AD such as the anterior mesial temporal lobe and posterior cingulate are involved during self appraisal tasks.

Objective—To determine whether parental family history of AD (FH) or the ε4 allele of the Apolipoprotein E gene (APOE4) exert independent effects on brain function during self-appraisal.

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

Setting—An academic medical center with a research-dedicated 3.0 Tesla MRI facility.

Participants—Cognitively normal middle-aged adults (N=110): 51 +FH; 59 −FH.

Outcome measure—Blood oxygen-dependent contrast measured with T2* weighted echo-planar imaging.

Results—FH and APOE4 status interacted in the posterior cingulate as well as left superior and medial frontal regions. There were main effects of FH (−FH > +FH) in left hippocampus, and ventral posterior cingulate. There were no main effects of APOE.

Conclusion—These results suggest that a parental history of AD may influence brain function during subjective self-appraisal in regions commonly affected by AD. Although these participants were asymptomatic and middle-aged, the findings suggest there may be subtle alterations in brain function attributable to AD risk factors.

Neuropathology studies of people at risk for Alzheimer disease (AD) suggest that AD may be preceded by a silent preclinical phase in which the brain incurs neuropathological change.[1–4] Both the apolipoprotein E gene (APOE) ε4 allele (APOE4) and first-degree family history (FH)[5] are risk factors for developing late onset AD.[6] Identifying initial brain changes in at-

Send Correspondence to: Sterling C. Johnson, Wm. S. Middleton Memorial VA Hospital, Geriatric Research Education and Clinical Center, 2500 Overlook Terrace (11G), Madison, WI 53705, Phone 608-256-1901, Fax 608-280-7165, Email scj@medicine.wisc.edu.

risk individuals with non-invasive functional imaging may help elucidate pre-clinical presence and progression of early AD.

Most prior fMRI studies in populations at risk for AD have focused on the hippocampus with episodic memory tasks that draw on encoding or retrieval processes[7–15] because memory symptoms are among the earliest to occur in AD. We have recently shown that asymptomatic middle-aged adults (mean age 55) who have a parent with AD exhibit reduced BOLD responses in the mesial and ventral temporal lobe during an encoding task[12] and this effect was not explained by APOE. The findings suggested that memory-related brain changes attributable to FH may be occurring in regions vulnerable to AD approximately two decades prior to the typical age of 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 control processes that subserve executive function, including imperviousness to distraction, inhibition of prepotent responses, working memory, and mental flexibility and speed. These well-studied functions have generally been attributed to dorsolateral prefrontal cortex.[16] The metacognitive aspects of executive function are less well studied and include processes such as self-monitoring, self appraisal (the focus of the present report), planning prospective action, social tuning of one's behavior for adaptive functioning in the world of people (judgment), and in making inferential or subjective decisions.

Prior studies have implicated cortical midline structures including the anterior medial prefrontal cortex (AMPFC) and posterior cingulate for metacognitive processes,[17–19] particularly the processes of self-monitoring of actions and bodily states, self-regulation of affect, self-reflection on abilities and traits, and social cognition, such as making inferences about the mental states of others.[20] The hippocampus has also been implicated in cognitive self-appraisal.[21] Neuroimaging studies of the posterior cingulate have found decreased cerebral metabolic rate of glucose metabolism (rCMRglu),[22–24] cerebral atrophy, [22, 25] and amyloid binding [22, 26] in people with AD. In two studies, people at risk for AD also exhibited reductions in CMRglu in the posterior cingulate.[4, 24] Furthermore, in AD, "resting state" abnormalities have been found in the posterior cingulate and medial frontal lobe as well as hippocampus.[22, 27, 28]

No studies have yet examined metacognitive brain function in healthy people at risk for AD. This may be a useful avenue of study since AD patients often exhibit deficits in metacognitive abilities[29] such as appreciating the extent or severity of their deficits. The purpose 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 of healthy adults.[19, 30–32] We examined brain activation in 110 physically and cognitively asymptomatic middle-aged adults who differed on the presence of parental family history (FH) and APOE4 genotype. A 2 × 2 factorial design was used to examine the relative contribution of APOE and FH on the cerebral response. Based on our prior findings, we expected that parental family history of AD would have an effect on cerebral activation that was separable from APOE in cortical midline brain regions and hippocampus.

Methods

Participants

One hundred ten subjects underwent fMRI scanning and cognitive testing (Table 1). Fifty-one (mean age 53.6; SD 6.4) had at least one parent with AD (+FH) and were recruited from the Wisconsin Registry for Alzheimer's Prevention,[33] a longitudinal registry of cognitively

normal adults between the ages of 40–65 (at entry) who have at least one parent with sporadic AD. To verify the diagnosis of AD in the parent, parental medical records were obtained and reviewed by a multidisciplinary diagnostic consensus panel. Typically, the clinical work-up and diagnosis in the parent were conducted at the University of Wisconsin Memory Clinics and the adult children were then approached for participation. The average age of symptom onset in the affected parent was 73. All subjects in the +FH group underwent baseline neuropsychological evaluations and laboratory tests that included APOE genotyping using PCR and sequencing. Fifty-three percent were ε4 positive (ε3/ε3=24 ; ε3/ε4=20; ε4/ε4=7).

A group of 59 participants (mean age 55.3; SD 6.2) with no family history of AD (−FH) were recruited from the community and matched to the demographic characteristics of the +FH sample. Absence of first-degree family history of AD was determined through self-report of the participant through phone interview as well as on a detailed medical history questionnaire. To be included in the −FH group, both parents had to survive to at least age 70 (most were well beyond this) and not carry a diagnosis of dementia or exhibit frank symptoms of dementia of any kind. Twelve (20%) of the controls were ε4 positive (ε3/ε4 = 11; ε4/ε4 = 1); 47 were ε4 negative (all ε3/ε3).

The demographics of the ε4 positive and negative subgroups are shown in Table 1 along with neuropsychological and fMRI task performance. We only included participants who had the ε4 or ε3 allele of APOE (21 participants with ε2 alleles were excluded). This was done in order to control for potential heterogeneity among genotypes. The proportion of women in the cells differed; therefore gender was used as a covariate in the fMRI data analysis. Exclusions for this imaging study included MRI scanner incompatibility, history of major psychiatric disease (e.g., schizophrenia; substance dependence; current or recent major depression) or major medical conditions (e.g., history of neurological disorders including prior head trauma with loss of consciousness, cancer requiring chemotherapy or radiation, insulin dependent diabetes) or abnormal structural MRI or neuropsychological testing as part of study participation. Most psychoactive drugs were excluded, though we did allow low dose selective serotonin reuptake inhibitors if stable for more than three months.

All subjects in this study received another 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 accordance with the Declaration of Helsinki.

fMRI task

The fMRI paradigm has been described in detail in prior studies with healthy young adults[30] and subjects with MCI.[34] Briefly, the task requires participants to make yes/no decisions based on individually presented trait adjectives across two conditions: referential self-appraisal (SA) and non-referential affective/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 own personal traits and abilities, whereas in the non-referential SEM condition, they decided whether or not adjectives in the set were of positive valence. 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 two conditions was presented in five pseudo-randomized cycles. Words were presented every 4 s (3 s on screen and 1 s interstimulus interval) in blocks of 6 per condition.

Imaging procedures

After higher order shimming, T2* weighted gradient-echo echoplanar images (EPI) were obtained: echo time 30 ms; repetition time (TR) = 2000 ms; flip angle = 90°; acquisition matrix = 64 × 64 voxels; field of view (FOV) = 240 mm. Thirty sagittal slices of the brain were acquired within the TR at each time point, with voxel resolution of 3.75 × 3.75 × 4 mm, 1 mm skip between slices. In both 4 min 8 s scanning trials, 124 time points were collected, of which 3 images acquired during the first 6 s were discarded (for a total of 242 reconstructed time points).

Residual magnetic field (Bo) inhomogeneity resulting in regional distortions are common with EPI. We corrected these by measuring 3D field maps across the brain (co-planar with the fMRI slices). This was accomplished by measuring the phase of non-EPI gradient echo images at 2 echo times (7 and 10 ms). The phase difference between the two echo images is proportional to the static field inhomogeneity.[35] The warp calculation and correction[36] was performed using the FMRIB Software Library (FSL3.2). Anatomic T1-weighted volumes and T2 weighted axial slices were also acquired using parameters previously described.[12]

Anatomic Imaging and VBM analysis—Axial T1 and T2 weighted images were acquired after the functional runs. A 3D IR-prepped fast gradient echo pulse sequence provided high-resolution T1-weighted structural images with the following parameters: inversion time = 600 ms, fast gradient echo read-out with TR/TE/flip = 9 ms/1.8 ms/20°; acquisition matrix = 256 × 192 × 124 (interpolated to 256 × 256 × 124); field of view = 240 mm; slice thickness = 1.2 mm (124 slices); ± 16 kHz receiver bandwidth.

A Fast Recovery Fast Spin Echo 2D T2-weighted axial sequence was also acquired with the same start and stop locations as the T1 weighted images. The parameters were: field of view = 240 mm, matrix 256 × 256, TR = 9000 ms, TE = 93 ms, flip angle = 90. Seventy slices were acquired; slice thickness = 1.7 mm with 0.3 mm skip. An experienced neuroradiologist examined all images prior to 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 accomplished with Statistical Parametric Mapping SPM2 software (www.fil.ion.ucl.ac.uk/spm). The image time-series was motion-corrected, field map corrected as described above, normalized into the Montreal Neurological Institute (MNI) standard space using the T2* weighted template provided through SPM2 (written out with 2×2×2 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 (HRF) as implemented in SPM2.[37] The statistical model included high frequency signal filtering (high pass filter = 128 seconds) and the AR1 method of estimating temporal autocorrelation. The SA versus SEM contrast was computed for each participant and entered into second level analyses.

The average effect of task (SA vs SEM), collapsed across groups, was first computed and thresholded at $p_{unc} < .005$ which corresponded to $p_{FDR\text{-}corrected} < .04$. This map was written out (see Fig 1) and used to constrain the subsequent analyses of group differences to only those brain voxels that were relevant to the task. With ANCOVA, a 2×2 factorial analysis was conducted that examined between group effects of FH, APOE, and FH*APOE interactions. Gender was used as a covariate. This same design was also 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.

Anatomic analyses—In order to determine whether group activation differences were due to anatomical differences in gray matter volume, we conducted voxel-based morphometry (VBM) 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 we used have been described in detail elsewhere.[12, 38, 39]

Results

Demographic characteristics and task performance are shown in Table 1. The Chi-Square statistic indicated the proportion of men and women differed in one of the groups and therefore gender was used as a covariate in subsequent behavioral and fMRI ANCOVAs. Factorial ANCOVA of demographic and neuropsychological indicated no APOE*FH interactions. Tests for main effects of APOE and FH in these healthy asymptomatic subjects were also non-significant with the exception of Trail Making Test part A on which the −ε4 subjects performed 3.7 s faster than the +ε4 subjects. There were no differences in the fMRI behavioral data with regard to reaction time and response bias.

Functional imaging findings

The Effect of Task—The average response to the task (SA > SEM) is shown in Figure 1 with statistics and MNI locations reported in Table 2. Active regions included two prominent midline clusters; the posterior cluster spans the ventral PCC and retrosplenial cortex (RSC).[40] The large AMPFC cluster spans the medial surface of the superior frontal gyrus and rostral anterior cingulate. Also two 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.

The effect of risk factors—Using factorial ANCOVA, an F-test for the interaction between FH and APOE yielded prefrontal clusters at voxel location −26, 36, 36 (F=9.73, p_{unc}=.002; 102 voxels) in the left superior frontal gyrus, and at voxel location −10, 48, 2 (F=9.71, p_{unc} =.002; 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_{unc} =.005, 33 voxels). These clusters and associated plots of signal change are shown in Figure 2. Post-hoc analyses were conducted and significant mean differences are indicated on the plots. Group differences were only significant relative to the −FH,+e4 group. The other three groups did not differ from each other.

The main effects of FH and APOE were tested next. Because main effects are not readily interpretable in the presence of interactions, voxels that were identified as 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 > +FH was significant in the left hippocampus (x,y,z; −16 −22 −14; T=4.05; p_{unc}<.00001; 233 voxels) and the left ventral posterior cingulate (−14 −66 20; T=3.33; p_{unc}=.001; 50 voxels). These results are shown in Figure 3. No significant results were found in the reverse comparison (+FH > −FH). The effect of APOE was tested with the contrast +ε4 > −ε4 (and its reverse). Significant voxels in the interaction were again excluded. The results revealed no significant voxels in either contrast.

Anatomical Analysis—Using VBM no group differences in gray matter volume were found, suggesting that the fMRI findings above were not attributable to atrophy.

Discussion

This study examined the cerebral response during a metacognitive task, appraisal of the self on trait adjectives. We used this task in people at risk for AD because converging research has indicated that the regions normally responsive on this task [30–32] appear to overlap with brain regions affected by AD. Our analyses indicated differences in task-related activation associated with FH as well as regions where APOE and FH risk factors interacted. Parental FH 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, this risk factor interacted with FH in left dorsolateral prefrontal cortex, AMPFC, and retrosplenial posterior cingulate; plots indicated that e4 carriers who were −FH exhibited greater signal change to the task. The observed effects were not due to gray matter atrophy, nor global cognitive function.

The medial parietal cortex has been implicated in memory retrieval and recognition[22, 41, 42] as well as metacognitive appraisals.[19, 31, 32, 43–46] Several recent studies report medial parietal hypometabolism[47] or hypoperfusion[48] in individuals with Mild Cognitive Impairment (MCI), a diagnosis that confers considerable risk for developing AD. Longitudinal studies also indicate that posterior cingulate metabolism and regional blood flow discriminate between individuals with MCI who soon develop AD and those MCI patients who remain stable.[49–51] Reiman and colleagues [4, 24] found that the medial parietal lobe including the posterior cingulate (PCC) and precuneus were hypometabolic for glucose in cognitively normal APOE4 carriers relative to noncarriers (the effect of FH was not tested in these earlier studies). The medial parietal findings observed in the present study during a cognitive challenge appear 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 al studied amnestic MCI patients with the same paradigm reported here and with ratings of anosognosia. A significant positive correlation was found between insight and activation; MCI subjects who exhibit diminished insight for their cognitive impairment also exhibit diminished responses in the posterior cingulate and mesial frontal lobe.[34] The data from Ries et al. and the present study suggest that risk factors for AD are influencing systems supporting metacognition, which may eventually become part of the symptom picture of AD.

Areas of the left MTL were also differentially active in −FH subjects on this task. In a young adult sample we have 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 [52, 53] in rhesus monkeys. Phillips et al[21] 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] Interestingly, 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 deserving of much more study.

In this sample, APOE4 and FH interacted (Figure 2), but there were no APOE4 main effects. The interaction was largely due to the finding that e4 positive, but FH negative subjects exhibited the greatest activation. An intriguing study by Mondadori et al[55] points out several salutary affects of APOE4 on the brain in early life, and they present fMRI results with a memory encoding task indicating that young adult ε3/ε4 carriers exhibit hippocampal learning-

related signal adaptation but young non-carriers do not. There is still much to learn about the effect of APOE4 across the lifespan, but in the context of the recent literature and the findings in the present report, it is likely that interactions are occurring between APOE4 and age and/or other AD risk factors which manifests as a putative salutary effect early in life, but a deleterious effect later in life.

The results in this report are consistent with a prior report of an episodic encoding task with most of these same subjects[12] in which we found a robust effect of FH in the hippocampus and ventral temporal lobes during object encoding. In that prior report we also found that the −FH,+ ε4 group again exhibited the greatest cerebral response in the hippocampus, while +FH, +ε4 subjects had the least. A similar finding was observed when subjects possessing the ε2 allele were removed.[15]

It is noteworthy that at least two other recent studies have reported first-degree family history effects. In a behavioral experiment of odor identification it was found that siblings of AD patients exhibited reduced accuracy relative to controls. This effect was more pronounced in siblings who were APOE4 positive.[56] With fMRI, Bassett et al[7] examined first-degree family history and APOE in a large sample (n=195) and found FH affected brain activation during a paired-associate encoding task, whereas APOE did not.

There remains a fundamental issue regarding fMRI group differences in cognitively normal versus 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 with fMRI, some possible reasons for these study differences may be: A) task difficulty. Increased difficulty has the effect of increasing fMRI activation;[64, 65] B) 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 cross hair fixation versus an active cognitively challenging baseline produce very different results; [66, 67]; and/or C) choice of analysis methods and statistical model—for example spatially normalizing to a standard space versus native space,[68] or counting of suprathreshold voxels within a region versus statistical parametric mapping.[10] Given the variability across studies, researchers that 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 to normative data,[55] and characterizing tasks across larger samples and across a range of demographic (e.g. age) and clinical parameters (e.g. genes, cognitive status[61]).

In conclusion, these data suggest that first-degree family history of AD may influence brain function many years prior to typical disease onset. The genetic and environmental factors that embody family history are still largely unknown and further study is required. The results highlight the idea that factors beyond APOE 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 with a self-referential decision task suggest that brain areas underlying metacognitive functions may also show compromise in people at risk, and may correspond, in part, to the metacognitive deficits that are observed in symptomatic AD.

Acknowledgement

This study was supported by R01 AG21155 (SCJ) and a Merit Review grant from the Department of Veterans Affairs. The first author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The assistance of Britta Jabbar, Shelly Fitzgerald, Gemma Gliori, Lisa Newman, Allison Wichmann, Taylor Schmitz, Mehul Trivedi, PhD, Michael Anderle, and Ron Fisher is greatly appreciated.

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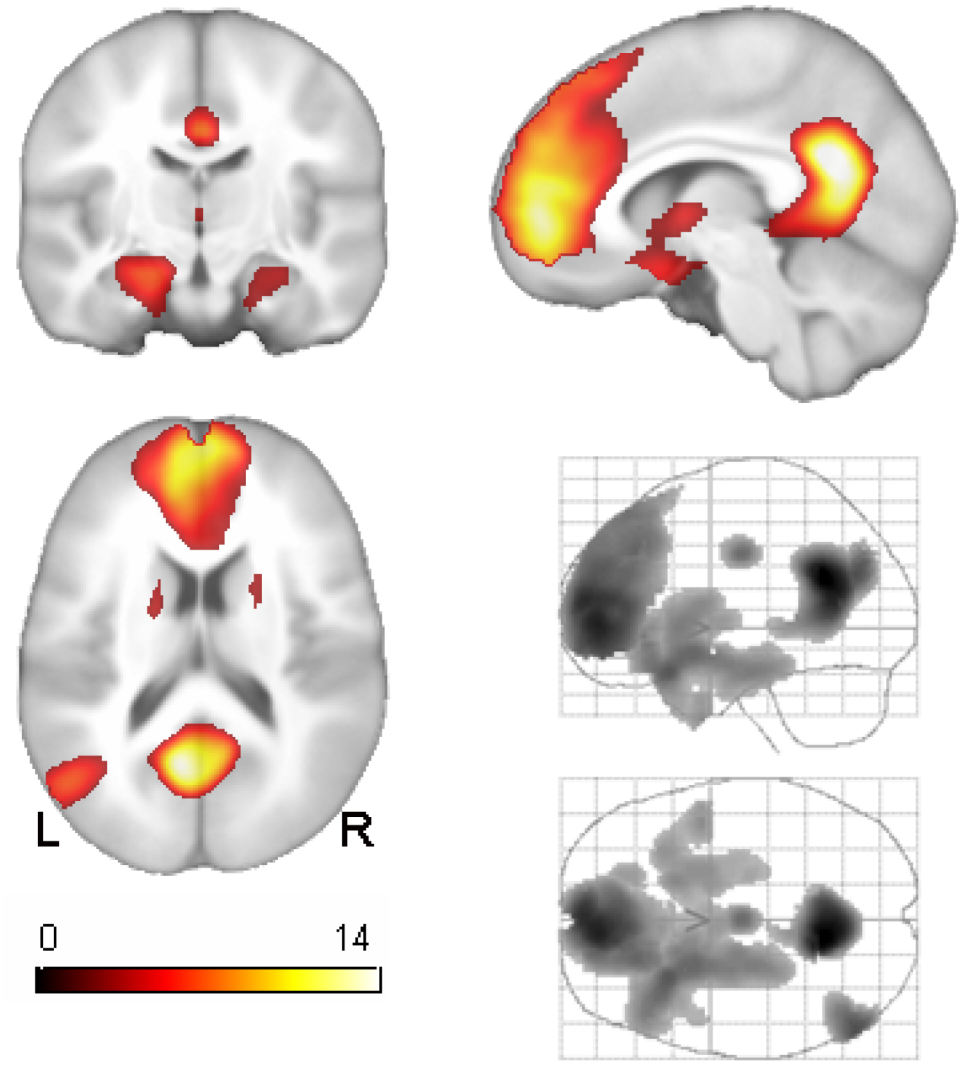

Figure 1.
Main effect of task across all 110 cognitively normal participants. Orthographic coronal, sagittal and axial views are shown as well as lateral and transverse maximum intensity projections of the result. Left is on left. The map is thresholded at p_{FDR} <.05 corresponding to t>2.57. The main 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.

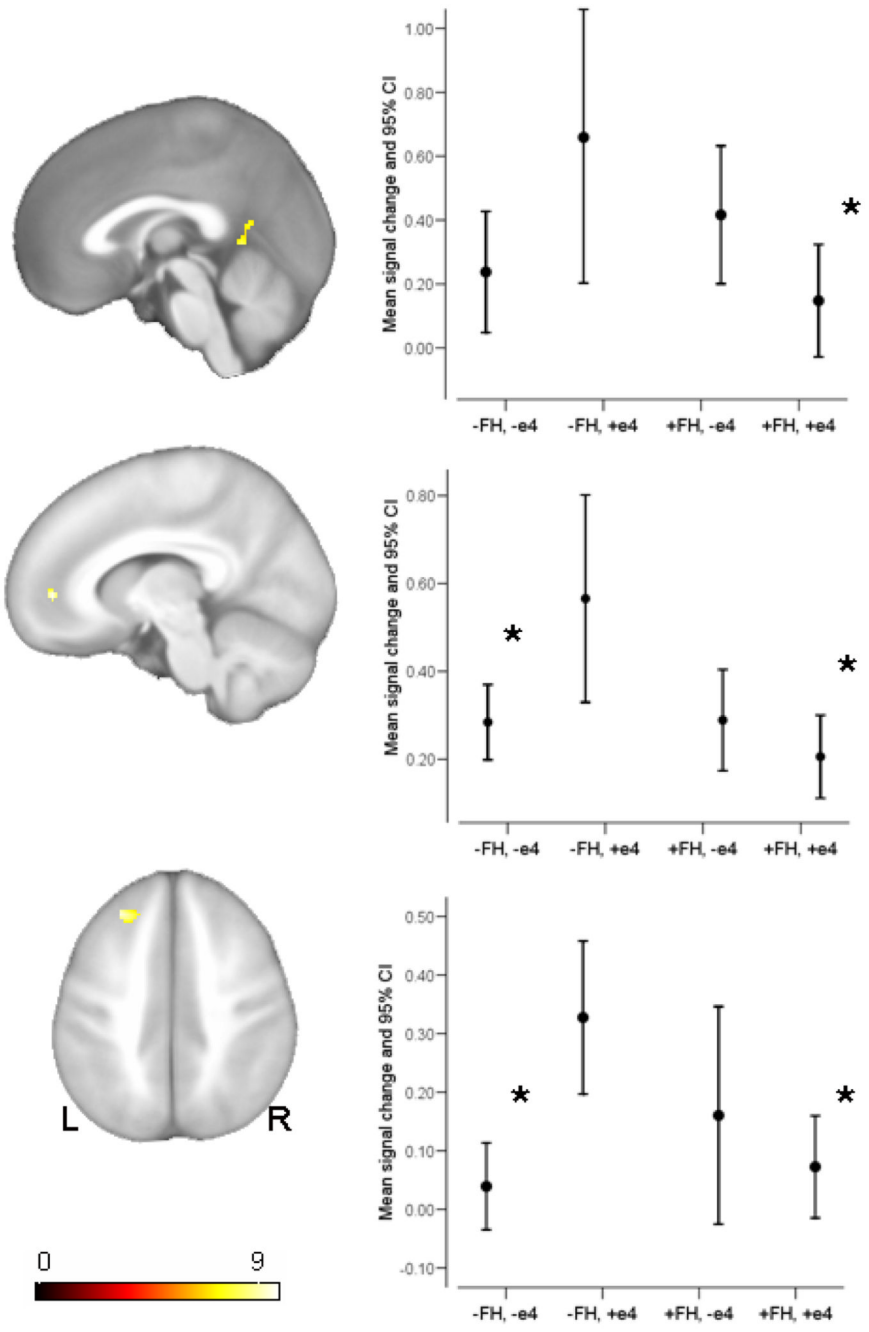

Figure 2.

The interaction between FH and APOE4 status. The three clusters that reached statistical significance are shown in sagittal and axial views. The corresponding plots depict the mean for the four groups (error bars 95% confidence interval), derived from the first eigenvariate of each subject across the entire cluster. A * indicates the mean differed significantly from the −FH,+e4 group ($p<.005$).

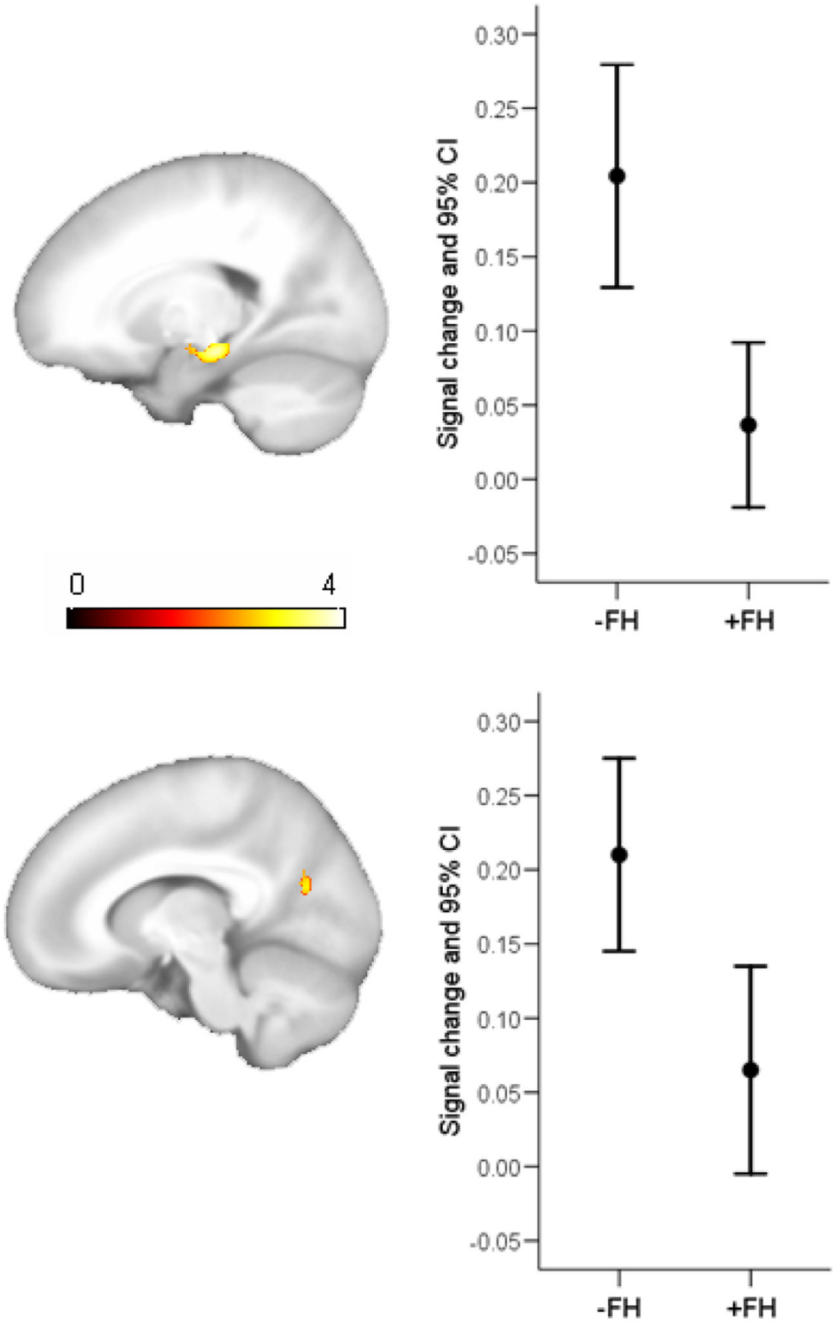

Figure 3.
Statistical parametric map of the main effect of first-degree family history. The figure shows regions where the −FH groups activate more on average than the +FH groups. Select brain slices are shown (left is on left) depicting the result in the posterior cingulate and subiculum with corresponding plots of the mean signal change, derived from the first eigenvariate across the cluster (error bars 95% confidence interval).

Table 1

Demographic Neuropsychological and Performance Data for Each Group

	Negative Family history				Positive Family history				
	ε4 neg		ε4 pos		ε4 neg		ε4 pos		
	mean	SD	mean	SD	mean	SD	mean	SD	
N	47	--	12	--	24	--	27	--	--
Age	55.2	6.3	55.7	5.8	52.2	6.6	54.9	6.0	NS
Education	16.2	2.6	17.1	2.2	16.3	2.5	16.8	2.3	NS
Gender M / F	9 / 38	--	7 / 5	--	11 / 13	--	13 / 14	--	*a*
Neuropsychological Function									
WRAT-Reading	109.0	8.3	108.5	7.6	108.3	8.9	108.15	7.6	NS
RAVL1-5	50.2	7.3	49.1	7.3	51.7	7.2	47.3	8.7	NS
RAVL7	10.0	2.6	9.8	2.3	10.7	3.0	8.9	2.9	NS
Trail Making A	27.0	8.2	31.5	8.6	24.9	6.5	29.5	7.5	*b*
Trail Making 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
CES-Depression Scale	5.0	5.8	6.3	5.1	3.9	4.0	5.5	5.6	NS
Hemoglobin	13.87	.81	14.00	1.34	14.00	1.08	14.12	.87	NS
Systolic blood pressure	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	.21	1.61	.19	1.60	.29	1.62	.22	NS
Reaction time Semantic	1.69	.26	1.77	.21	1.70	.31	1.74	.27	NS

a * Chi Square statistic p<.05.

b significant main effect of APOE p<.05.

WRAT=Wide Range Achievement Test-III; RAVL=Rey Auditory Verbal Learning Test; CES=Center for Epidemiologic Studies

Table 2

Average Effect of the Appraisal Task

Number of 2×2×2mm voxels	Voxel -T	x,y,z (MNI)	Location
3649	15.92	−10 −54 26	posterior cingulate
10149	13.17	−6 54 2	AMPFC
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 acumbens
	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 acumbens
	5.25	32 22 −24	right lateral orbital
	3.83	24 −10 −20	right hippocampus
304	8.12	0 −10 36	mid-cingulate
87	6.49	28 −80 −40	right cerebellum

Note: All voxel-level t values are significant at p_{unc} <.005 (critical t 2.62) corresponding to p_{FDR}<.04.

AMPFC—anterior medial prefrontal cortex

MNI—Montreal Neurological Institute standard space