Family history of Alzheimer disease predicts hippocampal atrophy in healthy middle-aged adults

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ABSTRACT

Objective: To evaluate the longitudinal influence of family history (FH) of Alzheimer disease (AD) and apolipoprotein E ϵ4 allele (*APOE*4) on brain atrophy and cognitive decline over 4 years among asymptomatic middle-aged individuals.

Methods: Participants were cognitively healthy adults with (FH+) (n = 60) and without (FH−) (n = 48) a FH of AD (mean age at baseline 54 years) enrolled in the Wisconsin Registry for Alzheimer's Prevention. They underwent APOE genotyping, cognitive testing, and an MRI scan at baseline and 4 years later. A covariate-adjusted voxel-based analysis interrogated gray matter (GM) modulated probability maps at the 4-year follow-up visit as a function of FH and *APOE*4. We also examined the influence of parent of origin on GM atrophy. Parallel analyses investigated the effects of FH and *APOE*4 on cognitive decline.

Results: Neither FH nor *APOE*4 had an effect on regional GM or cognition at baseline. Longitudinally, a FH × *APOE*4 interaction was found in the right posterior hippocampus, which was driven by a significant difference between the FH+ and FH− subjects who were *APOE*4−. In addition, a significant FH main effect was observed in the left posterior hippocampus. No significant *APOE*4 main effects were detected. Persons with a maternal history of AD were just as likely as those with a paternal history of AD to experience posterior hippocampal atrophy. There was no longitudinal decline in cognition within the cohort.

Conclusion: Over a 4-year interval, asymptomatic middle-aged adults with FH of AD exhibit significant atrophy in the posterior hippocampi in the absence of measurable cognitive changes. This result provides further evidence that detectable disease-related neuroanatomic changes do occur early in the AD pathologic cascade. ***Neurology***® **2012;78:1769–1776**

GLOSSARY

AD = Alzheimer disease; **ANCOVA** = analysis of covariance; **FH** = family history; **GM** = gray matter; **mFH** = maternal family history; **MNI** = Montreal Neurological Institute; **pFH** = paternal family history; **WRAP** = Wisconsin Registry for Alzheimer's Prevention.

A greater understanding of brain changes that occur before symptomatic Alzheimer disease (AD) is imperative for the accurate prediction of subsequent clinical symptoms and would greatly inform the design of enriched treatment trials targeting the earliest phases of AD before extensive neurodegenerative changes.[1] Although apolipoprotein E ϵ4 allele (*APOE*4) has been the strongest genetic risk factor for sporadic or late-onset AD,[2] it has become increasingly clear that parental family history (FH) of AD[3] not only confers additional risk but also may account for as much or more variance in preclinical brain changes than *APOE*4.[4–9]

For several years, our group has been following a cohort of cognitively healthy middle-aged adults with a FH of AD known as the Wisconsin Registry for Alzheimer's Prevention

Supplemental data at www.neurology.org

Supplemental Data

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(WRAP).[10] Initial cross-sectional analyses found evidence for FH-related differences in brain activation,[11–13] white matter fiber integrity,[14] and list-learning efficiency[15] that were independent of *APOE*4. In the present article, we extend these prior findings by investigating the longitudinal effect of FH and *APOE*4 on brain morphometry within this cohort, with a particular focus on temporoparietal regions that are now known to be vulnerable to AD pathology.[16,17] In addition, because it has recently been shown that the sex of the AD-affected parent may be influential, with maternal FH being more deleterious,[5,7,8,18] we conducted supplementary analyses to determine whether any observed FH effects were possibly driven by maternal FH. In parallel analyses, we also investigated the effect of FH and *APOE*4 on cognitive decline.

METHODS

Subjects. A total of 108 subjects participated in this study. Eighty-nine subjects were consecutively recruited from the larger WRAP[10] cohort, a longitudinal registry of adults who were cognitively healthy and between the ages of 40 and 65 at study entry, and the remaining 19 subjects were consecutively recruited from the community. Of these 108 subjects, 60 persons (mean baseline age 53.40 years; SD 6.24) had at least one parent with a reported diagnosis of AD (FH+ group) and the other 48 individuals (mean baseline age 54.25 years; SD 6.54) reported no family history of AD (FH− group). All 60 FH+ subjects were from the larger WRAP cohort, whereas the 48 FH− subjects were either from the WRAP cohort (n = 29) or the community (n = 19). Among the 60 FH+ subjects, 44 persons had a maternal history of AD (mFH+), 13 had a paternal history (pFH+), and 3 had both parents afflicted with AD.

To verify the diagnosis of AD in the parent, parental medical records were obtained (including autopsy reports when available) and reviewed by a multidisciplinary diagnostic consensus panel. In the majority of cases, the parent's clinical workup and diagnosis of AD had occurred at the University of Wisconsin Memory Clinics. Parental reported onset of AD was, on average, at age 73. None of the families included had any of the known autosomal dominant mutations. Absence of FH of AD was verified through detailed medical history surveys and phone interview with the participants. Inclusion in the FH− group required that the father survive to at least age 70 and the mother to age 75 without incurring a formal diagnosis of dementia or exhibiting cognitive deterioration.

At baseline and approximately 4 years later, all subjects underwent a comprehensive neuropsychological evaluation and a high-resolution 3-dimensional T1-weighted anatomic MRI scan. The cognitive tests were administered per standard protocol[10,19] and included the following measures: the Mini-Mental State Examination, the Reading subtest of the Wide Range Achievement Test, third edition, the Rey Auditory Verbal Learning Test, the Trail Making Test, the Controlled Oral Word Association Test, the Boston Naming Test, and the Digit Span subtest of the Wechsler Adult Intelligence Scale, third edition. The MRI scans were acquired in the axial plane on a GE Signa 3.0-T scanner with a standard transmit-receive quadrature coil using the following parameters: inversion time/echo time/repetition time = 600 msec/5 msec/8.4 msec, flip angle = 10°, slice thickness = 1.2 mm, field of view = 240 mm, and matrix size = 256 × 256. All scans were reviewed by a neuroradiologist for potential abnormalities. At baseline, subjects also underwent *APOE* genotyping using PCR sequencing.

All neurocognitive and MRI procedures were executed using identical parameters at both baseline and 4-year study visits. Study exclusion criteria included MRI contraindications, major neurologic disorder (e.g., head trauma with loss of consciousness, neoplasms, and seizure disorders), current major psychiatric disease (e.g., schizophrenia), or abnormal MRI findings (e.g., ventriculomegaly).

Standard protocol approvals, registrations, and patient consents. The University of Wisconsin Institutional Review Board approved all study procedures and each subject provided signed informed consent before participation.

Image processing. The MRI images were processed using the newseg option in SPM8 (www.fil.ion.ucl.ac.uk/spm), which combines segmentation of the original anatomic image into 6 tissue classes/probability maps: gray matter (GM), white matter, CSF, skull, fat tissue, and image background; normalization of the segmented GM map to the Montreal Neurological Institute (MNI) template; and correction for image intensity nonuniformities within a unified, iterative framework. A modulation step was then used, which scaled each voxel in the final GM map by the amount of contraction/expansion required to warp the image to the MNI template. The resulting GM modulated probability map provides a measure of GM volume at the local (i.e., voxel) level. The normalized maps were then smoothed using an 8-mm isotropic Gaussian kernel, yielding images with a voxel size of 1.5 × 1.5 × 1.5 mm.

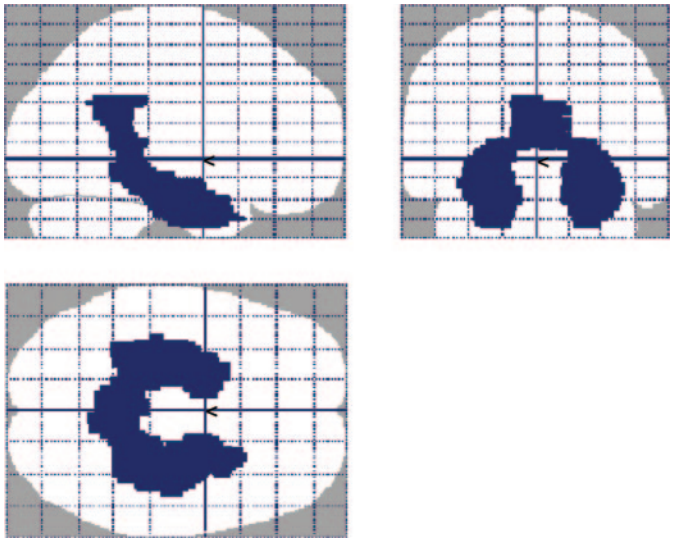
To focus our analyses on brain regions known to be implicated in AD pathogenesis and reduce the risk of false-positive errors, we 1) imposed an a priori anatomic mask that included the bilateral posterior cingulate, hippocampus, parahippocampal gyrus, and amygdala using the WFU_PickAtlas toolbox,[20] (figure 1) and 2) thresholded the GM maps at 0.1 to minimize inclusion of white matter and CSF in our analysis.

Statistical analysis. Neuropsychological and demographic data were analyzed in SPSS 20.0 (IBM Corp., Armonk, NY). For the analyses of demographic measures, a FH of AD was cross-tabulated with *APOE*4 status to yield 4 groups: negative FH and *APOE*4-negative (FH−*APOE*4−); negative FH and *APOE*4-positive (FH−*APOE*4+); positive FH and *APOE*4-negative (FH+*APOE*4−); and positive FH and *APOE*4-positive (FH+*APOE*4+). Categorical variables were analyzed using χ^2 tests, whereas continuous variables were analyzed using 1-way analyses of variance.

The analysis of neuropsychological measures was done using a series of 2 × 2 factorial analyses of covariance (ANCOVAs) with FH and *APOE*4 status as fixed factors. For baseline models, cognitive test scores were the dependent variables and age was entered as a covariate. For the longitudinal models, test scores at the 4-year follow-up visit served as dependent measures with baseline age and the respective baseline test scores serving as covariates.

We evaluated the effects of family history of AD and *APOE*4 status on GM cross-sectionally and longitudinally using a voxel-based morphometry framework implemented in SPM8. For the cross-sectional analysis, we entered participants' baseline GM

Figure 1 Anatomic search region examined in the study



A glass brain rendering of the a priori anatomic mask used in this study. The mask, which was constructed using the WFU_PickAtlas toolbox,[20] included the bilateral posterior cingulate, hippocampus, parahippocampal gyrus, and amygdala. The left side of image is the left side of the brain.

modulated probability voxel-wise maps into a 2 × 2 factorial ANCOVA with FH and *APOE*4 status as fixed factors and age and sex as covariates. To assess for longitudinal change in GM as a function of FH and *APOE*4 status, we performed a 2 × 2 factorial ANCOVA on participants' 4-year follow-up scans using the Biological Parametric Mapping toolbox of SPM8,[21] with FH and *APOE*4 status as fixed factors and age, sex, and the baseline GM modulated probability voxel-wise map as covariates.

To determine whether maternal history of AD had a differential effect on GM atrophy than paternal history of AD,[5,8] we repeated the longitudinal analysis described above but this time using a one-way ANCOVA design to assess whether there was a parent of origin effect on participants' 4-year follow-up scans, while adjusting for age, sex, baseline voxel-wise GM, and *APOE*4 status (see Results section for specific a priori contrasts tested). For all the imaging analyses described above, only clusters with a minimum of 188 continuous voxels and $p_{voxel} < 0.005$ were deemed significant. This a priori threshold was derived via Monte Carlo simulations (AlphaSim, AFNI, http://afni.nimh.nih.gov).

RESULTS

Demographic findings. Table 1 shows the results of group comparisons on demographic variables. The groups were statistically equated on all measures, except age: the FH−*APOE*4+ group was, on average, younger than the other groups.

Neuropsychological findings. Results of the analyses of neuropsychological measures are displayed in table 2. There were no significant FH or *APOE*4 main effects and no significant FH × *APOE*4 interactions at baseline or at the 4-year follow-up assessment.

Neuroimaging findings. Our cross-sectional analyses did not reveal any significant FH or *APOE*4 main effects or FH × *APOE*4 interactions on baseline GM.

In the longitudinal analyses, we found a significant FH × *APOE*4 interaction at the right posterior hippocampus (figure 2, cyan color and bar graph) with a cluster of 201 voxels and maximum T of 3.63 ($p_{voxel} < 0.0001$) at x,y,z [36,−39,−5]. Follow-up simple effects analyses found that, among persons who were *APOE*4+, there was no significant FH effect, whereas among persons who were *APOE*4−, there was a significant FH effect (i.e., FH+ subjects showed more atrophy than FH− subjects) at the right posterior hippocampus with a cluster of 193 voxels and maximum T of 4.80 ($p_{voxel} < 0.0001$) at x,y,z [34,−36,−5].

In addition to the above interaction effect, we found a main effect of FH (wherein FH+ subjects exhibited more GM atrophy than FH− subjects) at the left posterior hippocampus (figure 2, red color) with a cluster of 286 voxels and maximum T of 3.65 ($P_{voxel} < 0.0001$) and at x,y,z coordinate [−26,−37,−6]. No *APOE*4 effects were observed. Of note, for the main effects analyses, in addition to limiting our search region to the AD-related areas defined by our anatomic mask, we also imposed a statistical mask that excluded from consideration those voxels that were identified in the FH × *APOE*4 status analysis. This guarded against the statistical misstep of testing for main effects in the same regions where interactions were observed.

For our examination of potential parent of origin effects, we performed the following a priori contrasts: 1) no family history of AD vs maternal history of AD

Table 1 Demographics of study participants at baseline

Variable	FH−*APOE*4− (n = 40)	FH−*APOE*4+ (n = 8)	FH+*APOE*4− (n = 27)	FH+*APOE*4+ (n = 33)	*p* Value
Female sex, %	70.0	62.5	63.0	63.6	0.915
Caucasian, %	92.5	100.0	96.3	100.0	0.512
Age, y, mean (SD)	55.48 (5.99)	48.13 (5.94)	52.78 (6.77)	53.91 (5.83)	0.018
Education, y, mean (SD)	16.40 (3.03)	16.75 (1.83)	15.56 (2.14)	16.27 (2.18)	0.488
CES-D score	4.45 (4.80)	7.38 (8.86)	5.15 (5.31)	4.73 (4.54)	0.728
Follow-up interval, mo, mean (SD)	46.91 (5.60)	44.92 (6.60)	48.57 (4.75)	48.29 (6.47)	0.321

Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale; FH = family history.

Table 2 Participants' performance scores on neuropsychological tests at baseline and 4-year follow-up[a]

	FH−		FH+				
	APOE4− (n = 40)	*APOE4*+ (n = 8)	*APOE4*− (n = 27)	*APOE4*− (n = 33)	p_{FH}	p_{APOE}	$p_{FH\times APOE}$
Baseline scores, mean (SD)							
MMSE	NA	NA	NA	NA	NA	NA	NA
WRAT-III Reading	108.00 (10.28)	109.25 (6.82)	106.63 (10.22)	107.24 (7.25)	0.434	0.666	0.883
COWAT	45.52 (10.96)	48.87 (11.15)	45.13 (10.86)	46.91 (10.79)	0.646	0.325	0.766
Boston Naming Test	57.61 (2.93)	56.51 (2.99)	56.95 (0.55)	56.31 (0.50)	0.544	0.225	0.760
WAIS-III Digit Span	18.08 (4.23)	19.17 (4.33)	18.58 (4.21)	17.43 (4.19)	0.531	0.976	0.274
RAVLT total	52.91 (7.36)	51.45 (7.47)	52.50 (7.28)	51.68 (7.23)	0.957	0.512	0.856
RAVLT immediate recall	10.81 (2.50)	10.68 (2.52)	11.20 (2.44)	10.95 (2.41)	0.567	0.740	0.915
RAVLT delayed recall	10.64 (1.19)	10.58 (2.87)	10.74 (2.81)	10.74 (2.81)	0.841	0.959	0.963
Trails A	25.46 (7.49)	25.59 (7.70)	27.93 (7.48)	28.04 (7.46)	0.162	0.947	0.994
Trails B	60.15 (20.28)	54.54 (20.57)	56.24 (20.02)	63.26 (19.92)	0.609	0.883	0.195
Follow-up scores, mean (SD)							
MMSE	29.67 (0.73)	29.64 (0.74)	29.54 (0.73)	29.46 (0.75)	0.377	0.736	0.893
COWAT	47.69 (7.16)	45.53 (7.29)	48.61 (7.09)	48.73 (7.00)	0.232	0.556	0.536
Boston Naming Test	57.90 (1.92)	58.35 (1.96)	57.43 (1.87)	57.99 (1.89)	0.395	0.316	0.905
WAIS-III Digit Span	18.79 (2.46)	17.89 (2.49)	17.87 (2.44)	18.50 (2.41)	0.789	0.819	0.200
RAVLT total	52.27 (5.58)	53.83 (5.64)	53.82 (5.51)	53.50 (5.51)	0.650	0.649	0.503
RAVLT immediate recall	11.20 (2.01)	11.35 (2.04)	10.64 (1.98)	10.49 (1.95)	0.147	0.994	0.765
RAVLT delayed recall	10.91 (1.92)	11.85 (1.96)	10.98 (1.92)	10.76 (1.89)	0.277	0.447	0.233
Trails A	24.07 (6.42)	22.75 (6.44)	23.81 (6.29)	26.62 (6.26)	0.248	0.630	0.195
Trails B	54.42 (16.74)	56.08 (16.99)	53.98 (16.54)	58.73 (16.53)	0.785	0.439	0.714

Abbreviations: COWAT = Controlled Oral Word Association Test, C-F-L version; FH = family history; MMSE = Mini-Mental State Examination; NA = not administered (i.e., the MMSE was not administered at the baseline visit because of the subjects' youth at that visit); p_{APOE} = *p* value for the *APOE*4 status main effect; p_{FH} = *p* value for the FH main effect; $p_{FH\times APOE}$ = *p value for the FH* × *APOE*4 interaction; RAVLT = Rey Auditory Verbal Learning Test; WAIS-III = Wechsler Adult Intelligence Scale, third edition; WRAT-III = Wide Range Achievement Test, third edition.

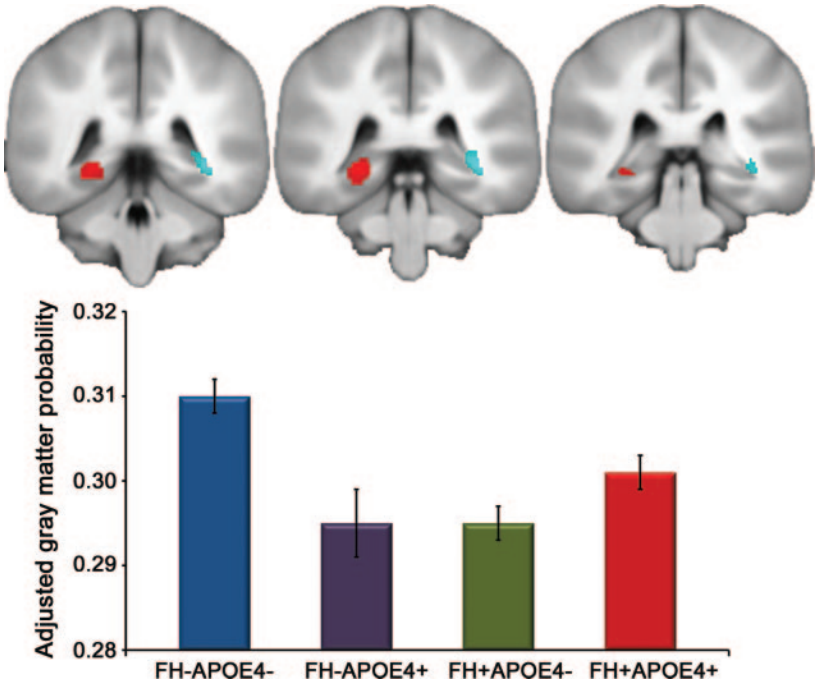
[a] Baseline values are raw scores statistically adjusted for age except for WRAT-III Reading which represents standard scores that were normed on age-stratified groups. Follow-up values are raw scores statistically adjusted for age and baseline test scores, except for the MMSE, which was only adjusted for age because it was not administered at baseline.

or paternal history of AD, 2) no family history of AD vs maternal history of AD, 3) no family history of AD vs paternal history of AD, and 4) maternal history of AD vs paternal history of AD. Consistent with the FH findings from the 2 × 2 analysis (cf. preceding paragraph), contrast 1 revealed that subjects who were either mFH+ or pFH+ harbored greater posterior hippocampal atrophy bilaterally than FH− subjects. For the right posterior hippocampus, cluster size = 911 voxels, maximum T = 4.20 ($p_{voxel} < 0.0001$), and x,y,z coordinate = [34,−27,−11] (see bar graph in figure 3). For the left posterior hippocampus, cluster size = 466 voxels, maximum T = 4.12 ($p_{voxel} < 0.0001$), and x,y,z coordinate = [−32,−34,−6].

Contrast 2 revealed that mFH+ subjects had greater bilateral posterior hippocampal atrophy than FH− subjects (figure 3, green color). For the left posterior hippocampus, cluster size = 268 voxels, maximum T = 3.55 ($p_{voxel} < 0.0001$), and x,y,z coordinate = [−30,−36,−6]. For the right posterior hippocampus, cluster size = 907 voxels, maximum T = 3.50 ($p_{voxel} < 0.0001$), and x,y,z coordinate = [32,−25,−11]. Similarly, contrast 3 revealed that pFH+ subjects experienced greater bilateral posterior hippocampal atrophy than FH− subjects (figure 3, red color). For the right posterior hippocampus, cluster size = 425 voxels, maximum T = 3.79 ($p_{voxel} < 0.0001$), and x,y,z coordinate = [34,−25,−12]. For the left posterior hippocampus, cluster size = 301 voxels, maximum T = 3.50 ($p_{voxel} < 0.0001$), and x,y,z coordinate = [−34,−28,−9]. Contrast 4 did not reveal any regions where mFH+ subjects had greater GM atrophy than pFH+ subjects or vice versa.

Exploratory whole-brain analyses. In addition to the targeted longitudinal neuroimaging analyses re-

Figure 2 Effects of family history (FH) and apolipoprotein E4 ε4 allele (*APOE4*) status on gray matter (GM) atrophy



A 2 × 2 analysis of covariance that examined the effects of FH and *APOE4* status on GM atrophy found a significant FH × *APOE4* interaction in the right posterior hippocampus (cyan color, $p_{voxel} < 0.0001$, cluster size = 201 voxels) and a significant FH effect in the left posterior hippocampus (red color, $p_{voxel} < 0.0001$, cluster size = 286 voxels). Results are displayed on the coronal view of the ICBM452 atlas, conforming to Montreal Neurological Institute space at y-plane locations −22, −18, and −14. The left side of image is the left side of the brain. The bar graph displays the adjusted mean (SE) GM modulated probability from the FH × *APOE4* interaction effect, extracted from the cluster in the right posterior hippocampus.

ported above, we also conducted exploratory longitudinal whole-brain analyses to determine whether there were any FH, *APOE*, or parent of origin-related effects outside of our anatomic search region. The findings from our focused analyses were essentially replicated, one notable exception being an *APOE* main effect in the right middle temporal gyrus (for details, see appendix e-1 and table e-1 on the *Neurology*® web site at www.neurology.org).

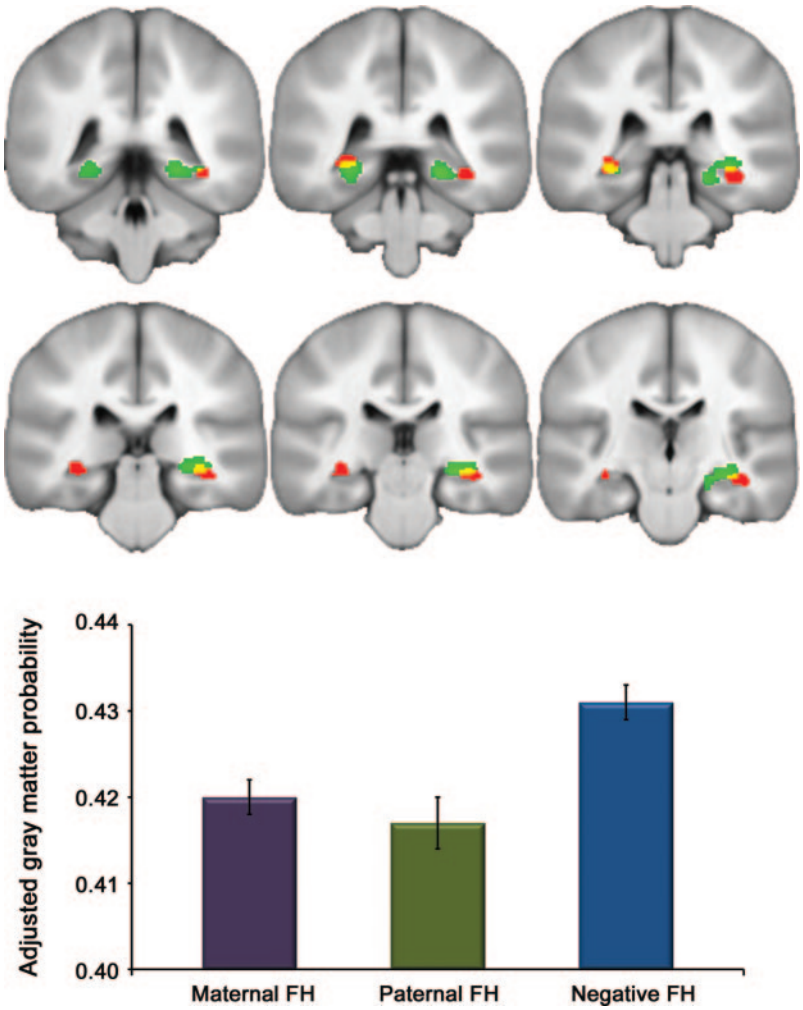
DISCUSSION In this study, we found that whereas neither FH nor *APOE4* appeared to affect cerebral GM at baseline, FH exerted both independent and interactive (with *APOE4*) effects on longitudinal atrophy of brain regions susceptible to AD pathology. Specifically, there was a significant longitudinal FH × *APOE4* interaction at the right posterior hippocampus. Further interrogation of this interaction revealed that FH was associated with increased atrophy of the right posterior hippocampus among persons who were *APOE4*−, but that this effect was absent (at the prespecified threshold) among persons who were *APOE4*+. In addition to this interactive effect, FH was independently associated with greater atrophy of the left posterior hippocampus. In contrast, we did not find any associations between *APOE4* status and GM atrophy within our search region. It is noteworthy that the observed FH-associated GM atrophy was found in the absence of any detectable decline on standard measures of cognitive functioning in this cohort during the same 4-year interval.

Prior studies from our group and other centers have shown that FH is associated with AD-related abnormalities in cerebral structure and function even after adjustment for the potentially confounding effect of *APOE4*. For example, recent cross-sectional[18] and longitudinal[5] studies have found evidence for GM volume reductions in AD-susceptible brain regions, such as the precuneus, among cognitively intact FH+ individuals relative to FH− peers. Our study extends these findings[5,18] by using a considerably larger sample, implementing a longer follow-up, and, more importantly, showing that FH-related hippocampal atrophy is present at a relatively young age (our cohort's mean baseline age was 54 years). The relative consistency of these FH findings across diverse neuroimaging modalities[4,7–9,11] suggests that FH is a prominent, even if nonspecific, risk factor for AD perhaps embodying an array of genetic and environmental indices that remain to be fully elucidated.[10,22]

Contrary to prior reports suggesting that maternal history of AD might confer a greater risk of AD-related cerebral abnormalities than paternal history of AD,[5,7,8,18,23] we found that pFH+ subjects were just as likely as mFH+ subjects to experience atrophy of the posterior hippocampus. This observation suggests that, in our cohort, the FH effect was not driven by a particular parent of origin. The reasons for this discrepancy in study findings are not entirely clear. One possibility has to do with the age of the cohorts being studied. The participants in our study were, on average, considerably younger (in some cases by as much as 20 years) than the participants in these other studies. It might be that the effect of parent of origin only becomes detectable in older age, given that advanced age itself is a well-established risk factor for AD.[22]

Although we believe that our finding of FH-associated hippocampal atrophy is bona fide and probably a signal for preclinical AD, we also acknowledge that the question of hippocampal atrophy in the context of normal cognitive aging continues to be actively investigated with some reports suggesting that, even in the absence of neurodegenerative diseases, there is veritable shrinkage of the hippocampus as people age.[24–26] It is unlikely that the differential

Figure 3 Effects of parent of origin on gray matter (GM) atrophy



Contrast tests of parent of origin effects on GM atrophy found significantly greater posterior hippocampal atrophy, bilaterally, in the maternal family history−positive (mFH+) group compared with the family history-negative (FH−) group (green color, $p_{voxel} < 0.0001$, cluster size >268 voxels). The contrasts also revealed significantly greater posterior hippocampal atrophy, bilaterally, in the paternal family history−positive (pFH+) group compared with the FH− group (red color, $p_{voxel} < 0.0001$, cluster size >301 voxels). Overlapping regions are shown in yellow. There were no regions where mFH+ subjects had greater GM atrophy than pFH+ subjects or vice versa. Results and displayed on the coronal view of the ICBM452 atlas, conforming to Montreal Neurological Institute space at y-plane locations −22, −18, −14, −10, −6, and −2. The left side of the image is the left side of the brain. The bar graph displays the adjusted mean (SE) GM modulated probability from the FH− vs (mFH+ or pFH+) effect, extracted from the cluster in the right posterior hippocampus.

hippocampal atrophy we observed between FH− and FH+ subjects is merely a proxy for naturally occurring age-associated hippocampal shrinkage because our FH+ and FH− groups were essentially matched on age (mean age difference = 0.85 year, $p = 0.493$), and, furthermore, we adjusted for age in our statistical model, thereby accounting for whatever contribution it may have made to the observed atrophy. In addition, data from other groups have indicated that normal aging is not necessarily accompanied by hippocampal atrophy[27–30] and that the observation of age-associated hippocampal atrophy in some studies might reflect either the contamination of such studies with participants harboring diseases that are potentially inimical to the hippocampus[31] or the differential inclusion of persons with preexisting, developmentally determined, smaller hippocampi.[32]

Our study had some limitations. First, parental history of AD was mostly established via clinical diagnosis in consensus diagnostic conferences using established criteria. Therefore, we cannot entirely rule out the possibility that the FH+ group may have contained people whose parents did not have AD. Similarly, negative parental history of AD was determined by self-report which may not be entirely reliable. However, the net effect of either form of misclassification would have been a diminution of our findings, as opposed to an augmentation. Another potential limitation is the racial homogeneity of our cohort. Although this reflects the demographic of the locale in which the study was conducted, it limits our ability to generalize our findings to non-Caucasian samples. We also acknowledge the modest size of the FH−*APOE*4+ group. However, this reflects the true state of affairs given that the joint probability of being *APOE*4+ and having no parental history of AD is small. Last, whereas the regression approach to longitudinal analyses has been shown to confer specific advantages over change score approaches,[33–36] it is possible that a somewhat different pattern of findings might have emerged had we used analytical approaches that estimate atrophy by computing change between follow up and baseline scans, such as tensor-based morphometry[37] or boundary shift integral.[38]

The present study demonstrates that relatively young cognitively healthy persons with a parental FH of AD experience detectable shrinkage of brain regions that are implicated in the pathology of AD and that this atrophy occurs before measurable decline in cognitive function. This is a notable finding because current models of the AD pathologic cascade suggest that brain atrophy is a later event, occurring closer to the manifestation of clinical AD,[39] whereas we show that, at least in at-risk individuals, atrophy of vulnerable brain regions exist much earlier (our cohort's mean age at baseline was 54 years). This and other studies reviewed above suggest that the AD pathophysiologic cascade may be expressed differently in enriched risk groups. Continued follow-up of our FH+ subjects would be helpful in determining whether those who subsequently experience clinical decline are identifiable by the observed atrophy of the posterior hippocampus. This would greatly boost the potential utility of such early posterior hippocampal atrophy as an endophenotype of preclinical AD.[1] Furthermore, it would be useful to

characterize the correspondence between such morphometric changes and other brain measures such as amyloid load and metabolic function within this relatively young cohort.

AUTHOR CONTRIBUTIONS

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DISCLOSURE

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