Apolipoprotein E ε4 is associated with disease-specific effects on brain atrophy in Alzheimer’s disease and frontotemporal dementia

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Apolipoprotein ε4 (apoE4) has been strongly linked with Alzheimer’s disease (AD) and contributes to several other neurological disorders. We investigated the influence of ε4 allele carrier status on the pattern of gray matter atrophy and disease severity in 51 patients with probable AD and 31 patients with behavioral variant frontotemporal dementia (bvFTD), compared with 56 healthy controls. Voxel-based morphometry was performed by using statistical parametric mapping. The ε4 allele frequency was higher in the AD group (P < 0.001) than the controls but not in the bvFTD group. No differences in demographic or cognitive profiles were observed between ε4 allele carriers and noncarriers within any of the diagnostic groups. However, ε4 carrier status was associated with more severe brain atrophy in disease-specific regions compared with noncarriers in both AD and bvFTD. AD ε4 carriers showed greater atrophy in the bilateral parietal cortex and right hippocampus, and bvFTD ε4 carriers demonstrated greater atrophy in the bilateral medial, dorsolateral, and orbitofrontal cortex, anterior insula, and cingulate cortex with right predominance. This regional ε4 effect is consistent with the hypothesis that apoE may affect the morphologic expression uniquely in different neurodegenerative diseases. The atrophy patterns in ε4 carriers may indicate that they are at greater risk for clinical progression.

The apolipoprotein E (apoE) gene is localized on chromosome 19 in a single locus with three alleles (ε2, ε3, and ε4) responsible for the three major apoE isoforms (apoE2, apoE3, and apoE4) (1). Through its function in lipid transport and cellular metabolism, apoE plays a fundamental role in cell maintenance and repair (2). However, in the CNS, apoE2 and E3 are more effective in this role than apoE4, and apoE4 may be detrimental in the process (1).

Possessing at least one ε4 allele is the major known genetic risk factor yet identified for sporadic Alzheimer’s disease (AD), with a dose-dependent effect on age of onset (3) and rate of cognitive decline (4). ApoE ε4 allele carrier status has been associated with subtle impairments in cognition in “normal” individuals including poorer verbal episodic memory (5). In addition, apoE4 may influence disease onset, risk, progression, or outcome in number of other neurological conditions including traumatic brain injury (6), aneurysmal subarachnoid hemorrhage (7), cerebral amyloid angiopathy (8), Parkinson’s disease (9), dementia with Lewy bodies (10), and ALS (11).

The mechanisms underlying the role of apoE4 in AD and other neurological disorders are still poorly understood. Emerging data suggest that apoE4 contributes to neurological disease through multiple pathways (1). In animal models of AD, apoE4 increases amyloid β (Aβ) deposition and impairs its clearance leading to plaque formation (12) and enhances lysosomal leakage (13). Also, in AD patients, apoE4 is associated with a higher density of amyloid plaques (14). ApoE4 may also act independently of the Aβ peptide through dysregulation of tau phosphorylation, disruption of cytoskeletal structure, and mitochondrial damage. In neurons that are uniquely vulnerable to injury in neurodegenerative diseases, apoE4 may exacerbate existing pathology (1).

Whether apoE4 may be a genetic disease modifier in frontotemporal lobar degeneration (FTLD) remains poorly understood. Studies on the effect of apoE4 on FTLD have yielded contradictory results (15–18), which likely reflects the complex clinical, pathological, and genetic underpinnings of this disease. The only prospective study that has investigated the effect of apoE genotype on clinical expression in frontotemporal dementia (FTD) revealed an ε4 dose-dependent influence on behavioral symptoms in behavioral variant frontotemporal dementia (bvFTD) (18).

Neuroimaging studies mapping brain structural changes associated with apoE in AD have shown an ε4 allele dose-effect on hippocampal, amygdalar, and entorhinal cortical atrophy (19–21). To our knowledge, only one small case series investigated the apoE4 morphologic effect in bvFTD, showing a trend of greater right frontal lobar atrophy in patients carrying the ε4 allele (21).

In this study, we performed a clinical and voxel-based morphometry (VBM) analysis to investigate the influence of apoE ε4 allele carrier status on disease severity and gray matter (GM) atrophy in a large cohort of patients with probable AD and bvFTD at presentation. VBM is an unbiased neuroimaging technique for the detection of regional brain atrophy by voxel-wise comparison of GM volume between groups of subjects, and it has been shown to be sensitive in detecting specific regions of GM atrophy in neurodegenerative diseases (22). Based on current hypotheses regarding the role of apoE4 on the pathogenesis of neurodegenerative disease, we hypothesized that apoE4 would show different, disease-specific effects in both AD and bvFTD.

Results

Genetic, Demographic, Clinical and Cognitive Data. ApoE genotype and allele frequencies for all subjects are given in Table 1. ApoE ε4 carriers (possessing at least one ε4 allele) were 30 (58.8%) within the AD group, eight (25.8%) within the bvFTD group,


The authors declare no conflict of interest.

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We first searched for any regions where presence or absence of e4 influences GM atrophy in similar regions across all diagnostic groups. No significant regions of atrophy shared by AD and bvFTD carriers or noncarriers were found. We then moved to investigate the effect of genotype on areas typical of each disease.

Table 1. ApoE genotype and allele frequencies for patients with AD, bvFTD, and healthy controls

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>Apo genotype</th>
<th>Allele frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>e2/e2</td>
<td>e2/e3</td>
</tr>
<tr>
<td>AD (51 subjects)</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td>bvFTD (31 subjects)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Controls (56 subjects)</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

Differences among the groups in apoE genotypes and allele frequencies were tested by using the Pearson χ² test.

*Significantly lower than controls (P < 0.05).
**Significantly higher than controls (P < 0.05).

Table 2. Main demographic and clinical characteristics of apoE e4 carriers and noncarriers, stratified by diagnostic group

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>e4− (21)</th>
<th>e4+ (30)</th>
<th>e4− (23)</th>
<th>e4+ (8)</th>
<th>e4− (46)</th>
<th>e4+ (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), years</td>
<td>67.9 (11.2)</td>
<td>66.5 (10.7)</td>
<td>58.4 (10.9)</td>
<td>58.9 (4.3)</td>
<td>66.5 (9.4)</td>
<td>66.9 (7.6)</td>
</tr>
<tr>
<td>Women/Men</td>
<td>14/7</td>
<td>13/17</td>
<td>7/16</td>
<td>3/5</td>
<td>27/19</td>
<td>5/5</td>
</tr>
<tr>
<td>Mean education (SD), years</td>
<td>15.1 (3.4)</td>
<td>15.4 (3.3)</td>
<td>16.0 (2.4)</td>
<td>15.8 (2.5)</td>
<td>17.5 (1.8)</td>
<td>18.6 (2.7)</td>
</tr>
<tr>
<td>Mean MMSE (SD)</td>
<td>21.6 (4.4)</td>
<td>21.5 (6.2)</td>
<td>22.7 (7.0)</td>
<td>22.0 (7.8)</td>
<td>29.6 (0.6)</td>
<td>29.7 (0.7)</td>
</tr>
<tr>
<td>Median CDR total (range)</td>
<td>1.0 (0.5–2)</td>
<td>1.0 (0.5–2)</td>
<td>1.0 (0.5–3)</td>
<td>1.0 (0.5–2)</td>
<td>0.0 (NA)</td>
<td>0.0 (NA)</td>
</tr>
<tr>
<td>Median CDR box score (range)</td>
<td>5.0 (1.5–10)</td>
<td>4.8 (2–12)</td>
<td>8.0 (2.5–15)</td>
<td>7.3 (4.8–5)</td>
<td>0.0 (0–5)</td>
<td>0.0 (0–5)</td>
</tr>
</tbody>
</table>

Comparisons between e4 carriers and noncarriers within each diagnostic group were performed by using the Pearson χ² test for gender and CDR, and Kruskal-Wallis one-way ANOVA by ranks test for age, education, and CDR box score. No significant differences were found between e4 carriers and noncarriers within any of the groups. NA, not applicable.
was associated with a more severe disease-specific pattern of brain atrophy in patients with probable AD and bvFTD at presentation. However, no significant differences were observed in cognitive profiles between e4 carriers and noncarriers in either of the disease groups. This disease-specific regional e4 effect is consistent with the hypothesis that apoE4 may affect the morphologic expression uniquely in different neurodegenerative diseases.

In AD, we found the strongest e4 effect in neocortical regions, particularly in bilateral inferior parietal cortex but also in the precuneus and right dorsolateral prefrontal cortex. One possible explanation for this finding in our study is the inclusion of early age-of-onset AD (age of onset below 65) because these same neocortical regions coincide with areas most severely affected in younger AD patients (24). AD e4 carriers also had more hippocampal atrophy than noncarriers, which is consistent with the majority of existing in vivo neuroimaging studies (19–21). Although this was not a longitudinal study, apoE e4 dose has also been correlated with the rate of hippocampal atrophy (25). When considering the effect of apoE4 on AD pathology, e4 carriers have more senile plaques than noncarriers (14).

In bvFTD, the e4 allele influenced GM atrophy in a specific subset of frontal and insular regions, predominately in the right hemisphere. These regions fall within the atrophy pattern typically seen in bvFTD (26). Interestingly, within these same right-sided areas of e4 effect are the regions recently identified as the sites of earliest injury in bvFTD (27) and associated with more severe behavioral impairments in dementia (26). A regional-specific e4 effect in bvFTD was also proposed by a small exploratory study that showed a trend of greater atrophy in the ventral striatum and right frontotemporal regions in two bvFTD e4 carriers relative to six noncarriers (21). The only available study that looked at the clinical effect of apoE4 in FTD showed more severe behavioral disturbances in e4 carriers vs. noncarriers (18). Similarly, we recently observed two first-degree relatives with familial FTD-motor neuron disease who had dramatically different clinical presentations; the patient who was homozygous e4/e4 presented with more profound cognitive and behavioral changes than his sibling who was homozygous e3/e3 (28). One may speculate that these observed behavioral changes associated with e4 were due to the involvement of similar brain regions to those we found more atrophied in e4 carriers. The findings of the present study, when considered together with these previous observations, suggest that apoE4 may influence the pathology of bvFTD.

The pathologic role of apoE4 in the CNS is mostly based on AD models, where both Aβ-dependent and independent mechanisms have been proposed (1). Through Aβ-independent pathways (1), apoE4 may contribute to neurodegenerative diseases other than AD. One such mechanism is the "two-hit" hypothesis (13, 29). In response to stressors or injury ("first hit"), neurons begin to synthesize apoE (1, 29). Although apoE may promote neuronal repair (2, 29), it can also undergo proteolytic cleavage. Carboxyl-terminal-truncated apoE fragments may disrupt the cytoskeleton, stimulate tau phosphorylation, impair mitochondrial function, and ultimately cause cell death ("second hit") (29). The apoE4 isoform may have the most detrimental effect because it is more susceptible to proteolytic cleavage than E3 or E2 (1). This "two hit" phenomenon may be particularly relevant to our neuroimaging findings because of the unique, disease-specific, neural networks that were most severely atrophied in association with e4 carrier status. Under this paradigm, these same diseased regions are the initial sites of injury ("first hit") and are particularly vulnerable in the presence of apoE4 fragments ("second hit"). apoE4 influences both disease risk and brain atrophy in AD but only brain atrophy in bvFTD; this finding further highlights the different molecular mechanisms that may involve apoE4 in neurodegenerative disease. Clearly, apoE4 effects may occur either upstream or downstream of the initial "hit".

In the present study, the more severe pattern of brain atrophy in e4 carriers did not correlate with the severity of cognitive impairment at presentation in any of the diagnostic groups. In AD patients, this finding agrees with the available literature, showing an inconsistent effect of apoE genotype on clinical severity at presentation (30, 31). The majority of longitudinal studies, although, have shown that e4 is associated with more rapid cognitive decline in AD (4). One may postulate that the higher risk for cognitive decline in AD e4 carriers may, in fact, be associated with the more severe brain atrophy found early in
Materials and Methods

Patient Selection. We searched the University of California, San Francisco Memory and Aging Center (UCSF MAC) database for all patients with known apoeE4 genotypes who were seen between 1999 and 2007. From this group, we selected patients with clinical diagnoses of AD, bvFTD, and healthy controls. These diagnoses were derived by a multidisciplinary team consisting of neurologists, neuropsychologists, and psychiatrists who performed extensive behavioral, neuropsychological, and neuroimaging assessments. Patients who did not meet standard research criteria for probable AD National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) (34) or bvFTD (35) were excluded. During the selection process, neuroimaging findings were used only to exclude other causes of focal or diffuse brain damage, including idiopathic white matter disease.

From this cohort, we excluded two AD patients who had presenilin1 (PSEN1) mutations of four AD patients screened for PSEN1, three bvFTD patients with PGRN mutations of 31 bvFTD screened for PGRN, and one control subject who was a blood relative of a patient with a PGRN mutation because of reports that these genetic mutations may influence brain morphology (36, 37). In addition, no microtubule associated protein tau (MAPT) mutations were found in the 14 bvFTD patients screened for MAPT. Then, we excluded one AD and three bvFTD cases because poor image quality precluded proper brain segmentation in Statistical Parametric Mapping (SPM).

We included 51 patients with AD (age 51 to 86), 31 patients with bvFTD (age 29 to 80), and 56 healthy controls (age 38 to 82). Autopsies were performed on available cases at the University of Pennsylvania or at UCSF by using a published protocol (38); no cases were excluded based on autopsy results. Three patients in the AD group came to autopsy, and all met pathologic criteria for moderate-to-high likelihood AD (NIA-Reagan) (39); one of these cases had additional body pathology. Of the five bvFTD cases that came to autopsy, the pathologic diagnoses were as follows: Pick’s disease (two cases) (40), “taupathy” with features of FTLD and PSP, PSP comorbid with AD, and CBD. Seven AD and three bvFTD patients underwent 11C-PIB PET imaging to assess for evidence of amyloid deposition by using a described protocol (41). Distribution volume ratio images (cerebellar reference) were visually assessed by two investigators blinded to clinical diagnosis, and scans were read as positive or negative for cortical 11C-PIB uptake. In agreement with their clinical diagnoses, all seven AD cases were PIB-positive and all three bvFTD cases were PIB-negative. This study was approved by the UCSF and University of Pennsylvania committees on human research. All subjects provided written informed consent before participating.

Genetic Analysis. ApoE DNA was purified from peripheral blood samples (Genta PureGene Blood Kit, Qiagen) by using the recommended protocol. Primers GCATCTGCTCTCGTCTCAGTCTTCG (forward) and ACCTGGCTCTCCATCGTGC (reverse) were chosen to straddle a 687-bp region spanning the e4 and e2 polymorphisms. Genomic DNA was amplified by standard PCR methods, labeled, and sequenced by using a 3730 XL ABI Prism. Polymorphism calls were performed by Sequencher (GeneCodes) and manually confirmed for accuracy. PSEN1. Primer pairs complementary to the intronic regions of PSEN1 were used to amplify exon 3–12. Both strands of the PCR products were sequenced by using the CEQ dye terminator cycle sequencing kit on a CEQ 8000 using both the forward and reverse PCR primers. If a mutation was identified, confirmatory sequencing was performed. Sequence analysis was performed with Sequencer software.

PGRN. DNA was isolated from peripheral blood. Primer pairs complementary to the intronic regions of tau were used to amplify exons 1–5, 7, and 9–13. Both strands of the PCR products were sequenced. Sequence analysis was performed with Sequencer software.

Cognitive Assessment. The neuropsychological measures included in our bedside screening protocol have been described in ref. 26. Briefly, general intellectual functioning was assessed with the MMSE whereas global functional assessment was evaluated by using CDR. Verbal episodic memory was evaluated by using the California Verbal Learning Test - Short Form (CVLT-SF) and visual-nonverbal episodic memory was measured with the 10-min free recall (CVLT-10M) and Rey-Osterrieth complex figure test. Rey-O assessed visuospatial functioning. Language assessment included the abbreviated (15 item) Boston Naming Test and semantic fluency (animals generated in 1 min). Tests of executive functioning included a modified version of the Trails B test (correct lines in 120 s), maximum backward digit span, and phonemic fluency (D-words generated in 1 min).

Statistical Analysis. Differences among the groups in apoeE4 genotypes and allele frequencies were tested by using the Pearson χ² test; all probability (P) values < 0.05 are reported. Differences between apoeE4 carriers and noncarriers within each diagnostic group were performed by using the Pearson χ² test for gender and CDR, and Kruskal-Wallis one-way ANOVA by ranks test for sex, education, CDR box score, MMSE, and neuropsychological measures. Post hoc analysis included Bonferroni correction for multiple pairwise comparisons, and a P value < 0.01 was considered significant. Statistical analyses were performed with SPSS software version 16.0 for Windows.

MRI Study. MRI scans were obtained on a 1.5 Tesla Magnetom VISION system (Siemens). Structural MRI sequences included the following: (i) double spin echo sequence (repetition time (TR) = 5000 ms, echo time (TE) = 20/80 ms, 51 contiguous axial slices, thickness = 3 mm, 1.0 × 1.0 mm² in-plane resolution) and (ii) volumetric magnetization prepared rapid gradient echo sequence (TR = 2700 ms, TE = 4 ms, three-dimensional, orientation perpendicular to the double echo sequence, matrix size = 256 × 192, voxel resolution = 1.0 × 1.0 × 1.0 mm, slab thickness = 1.5 mm). VBM analysis includes two steps: spatial preprocessing (normalization, segmentation, Jacobian modulation, and smoothing) and statistical analysis (22). Both stages were performed by using the SPMS software package (Welcome Department of Imaging Neuroscience) running on Matlab 7.0.1 (MathWorks). MRI images were segmented, normalized, and modulated by using the unified segmentation model (42). This model also includes parameters that account for image intensity nonuniforminess. To help remove nonbrain tissue, the “clean-up” procedure was applied to the segmented GM images. The final voxel resolution after normalization was 2.0 × 2.0 × 2.0 mm. Spatially normalized, modulated GM images were then smoothed with a 12-mm FWHM isotropic Gaussian kernel.

Age, gender, disease severity (CDR box score), and total intracranial volume were entered into the design matrix as nuisance variables. Regionally specific differences in GM volumes were assessed by using the general linear model for the disease. In bvFTD, no studies have assessed the effects of apoeE4 on cognitive measures such as we studied. However, one study that characterized a cohort of FTD patients with progranulin (PGRN) mutations found that e4 carriers complained of earlier memory impairment than noncarriers (32). Clearly, longitudinal studies are needed to assess whether apoE status may influence disease progression, as has been shown in AD. Certainly, the atrophy patterns in our VBM study suggest that the FTD e4 carriers may be at higher risk for rapid clinical decline.

This study is not without limitations. First, the sample sizes may have been insufficient to detect small differences in cognitive measures within each diagnostic group. Second, a vast majority of our cases are not pathology-confirmed; however, these patients were well characterized by a multidisciplinary team, and the accuracy of the clinical diagnoses was supported in all cases that underwent 11C-labeled Pittsburgh Compound-B (11C-PIB) PET imaging or that came to autopsy. The autopsy results on the available five bvFTD cases highlight the pathological heterogeneity of FTLD with Pick’s disease, progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), all falling within the FTLD spectrum of disease (33), and additional AD features present in one case. Finally, although we performed extensive neuropsychological testing, no quantitative social-behavioral measures are available to fully characterize FTD patients.

This study shows that apoeE4 not only influences brain morphology in AD but also has an effect in another neurodegenerative disease. Remarkably, the e4 effect is restricted to disease-specific regions in both disorders. Understanding the role of apoE4 as a potential causative factor in neurodegeneration is especially appealing because therapies that target the structure and function of apoE are under investigation. To confirm whether our findings of e4 effects in vulnerable neural networks are clinically meaningful, larger studies are needed to investigate the association of e4 on clinical progression in FTLD-spectrum disorders.
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## Supporting Information

**Agosta et al. 10.1073/pnas.0812697106**

### Table S1. Neuropsychological testing results for apoE ε4 carriers and noncarriers, stratified by diagnostic group

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>AD ε4− (21)</th>
<th>ε4+ (30)</th>
<th>bvFTD ε4− (23)</th>
<th>ε4+ (8)</th>
<th>Controls ε4− (46)</th>
<th>ε4+ (10)</th>
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<tr>
<td></td>
<td>ε4− (21)</td>
<td>ε4+ (30)</td>
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<td><strong>Memory</strong></td>
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<tr>
<td>CVLT-SF, Trial 4 (Correct)</td>
<td>4.5 (1.5)</td>
<td>4.6 (1.9)</td>
<td>4.8 (2.8)</td>
<td>4.8 (2.8)</td>
<td>8.1 (1.0)</td>
<td>8.0 (1.2)</td>
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<tr>
<td>CVLT-SF Long Delay (Free Recall)</td>
<td>1.2 (1.3)</td>
<td>1.0 (1.8)</td>
<td>3.0 (3.1)</td>
<td>2.4 (2.1)</td>
<td>7.1 (1.8)</td>
<td>6.0 (4.2)</td>
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<tr>
<td>CVLT Delayed (Recognition Hits)</td>
<td>7.1 (2.2)</td>
<td>7.0 (1.8)</td>
<td>8.1 (2.1)</td>
<td>7.6 (1.8)</td>
<td>8.2 (1.6)</td>
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<tr>
<td>CVLT Recognition (False Positives)</td>
<td>6.9 (4.7)</td>
<td>5.5 (3.0)</td>
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<tr>
<td>Modified Rey-O 10-min recall (0–17)</td>
<td>3.0 (3.3)</td>
<td>2.1 (3.5)</td>
<td>7.2 (5.0)</td>
<td>6.7 (5.2)</td>
<td>12.9 (3.4)</td>
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<tr>
<td><strong>Visuospatial function</strong></td>
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<td>Modified Rey-O Copy (0–17)</td>
<td>11.5 (5.0)</td>
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<td>14.8 (2.9)</td>
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<tr>
<td>Boston Naming Test (0–15)</td>
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<td>Animal Fluency (1 min)</td>
<td>9.1 (3.7)</td>
<td>9.4 (4.8)</td>
<td>9.7 (7.6)</td>
<td>9.0 (5.5)</td>
<td>22.1 (5.3)</td>
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<td><strong>Executive function</strong></td>
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<td>Modified Trails (correct lines per min)</td>
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<td>8.9 (10.1)</td>
<td>14.3 (19.5)</td>
<td>31.7 (12.2)</td>
<td>35.6 (18.9)</td>
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<tr>
<td>Backward Digit Span</td>
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<td>3.6 (1.5)</td>
<td>3.3 (2.3)</td>
<td>4.0 (2.0)</td>
<td>5.4 (1.2)</td>
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<tr>
<td>D-word Fluency (1 min)</td>
<td>8.9 (4.7)</td>
<td>9.6 (5.6)</td>
<td>7.0 (5.3)</td>
<td>4.6 (3.6)</td>
<td>16.2 (4.6)</td>
<td>16.8 (3.9)</td>
</tr>
</tbody>
</table>

Data are presented as mean (standard deviation). Comparisons between ε4 carriers and noncarriers within each diagnostic group were performed by using Kruskal–Wallis one-way ANOVA. No significant differences were found between ε4 carriers and noncarriers in any of the groups.
Table S2. VBM results of statistical significance of apoE ε4 carriers versus controls in each disease group in regions of gray matter that were identified in the contrast carriers vs. both noncarriers and controls

<table>
<thead>
<tr>
<th>Anatomic region (Brodman area)</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>AD ε4+ vs. controls T value</th>
<th>AD ε4− vs. controls T value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior parietal/angular gyrus (39)</td>
<td>R 38</td>
<td>−64</td>
<td>44</td>
<td>6.1</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>L −34</td>
<td>−68</td>
<td>44</td>
<td>5.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Inferior parietal/supramarginal gyrus (40)</td>
<td>R 50</td>
<td>−40</td>
<td>54</td>
<td>5.6</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>L −66</td>
<td>−30</td>
<td>28</td>
<td>4.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Hippocampus (NA)</td>
<td>R 28</td>
<td>−12</td>
<td>−14</td>
<td>6.0</td>
<td>3.4</td>
</tr>
<tr>
<td>Precuneus (7)</td>
<td>R 2</td>
<td>−56</td>
<td>48</td>
<td>6.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Middle frontal gyrus (46)</td>
<td>R 50</td>
<td>30</td>
<td>34</td>
<td>5.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Dorsolateral frontal cortex/ inferior frontal gyrus (pars triangularis) (45/46)</td>
<td>R 48</td>
<td>32</td>
<td>28</td>
<td>7.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Inferior front gyrus (operculum) (44)</td>
<td>L −48</td>
<td>44</td>
<td>−6</td>
<td>5.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Supplementary motor area (6)</td>
<td>R 8</td>
<td>14</td>
<td>50</td>
<td>6.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Anterior insula (48)</td>
<td>R 38</td>
<td>20</td>
<td>4</td>
<td>7.1</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>L −36</td>
<td>16</td>
<td>6</td>
<td>5.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Superior frontal gyrus (8/9)</td>
<td>R 18</td>
<td>22</td>
<td>56</td>
<td>6.2</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>L −20</td>
<td>52</td>
<td>30</td>
<td>4.9</td>
<td>4.5</td>
</tr>
<tr>
<td>Middle frontal gyrus (46)</td>
<td>R 40</td>
<td>40</td>
<td>32</td>
<td>7.5</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>L −44</td>
<td>48</td>
<td>12</td>
<td>5.0</td>
<td>3.3</td>
</tr>
<tr>
<td>Superior orbitofrontal gyrus (11)</td>
<td>R 30</td>
<td>60</td>
<td>−4</td>
<td>6.7</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>L −28</td>
<td>62</td>
<td>−4</td>
<td>5.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Inferior orbitofrontal gyrus (46)</td>
<td>L −48</td>
<td>44</td>
<td>−6</td>
<td>5.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Anterior cingulate cortex (32)</td>
<td>R 6</td>
<td>44</td>
<td>24</td>
<td>6.3</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>L −2</td>
<td>36</td>
<td>36</td>
<td>5.8</td>
<td>4.3</td>
</tr>
<tr>
<td>Middle cingulate cortex (32)</td>
<td>R 8</td>
<td>24</td>
<td>42</td>
<td>6.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Superior temporal gyrus (22)</td>
<td>R 68</td>
<td>−38</td>
<td>−28</td>
<td>4.8</td>
<td>3.3</td>
</tr>
</tbody>
</table>

The table illustrates how the regions involved in carriers vs. noncarriers are the same but with greater significance and slightly greater extent in the carriers. L, left; R, right; NA, not applicable.