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Imaging Studies and APOE Genotype in Persons at Risk for Alzheimer's Disease

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Abstract

Many studies have investigated APOE-related differences in cerebral structure, blood flow, metabolism, and activation in an attempt to detect early brain changes in subjects at risk for Alzheimer's disease (AD). Structural magnetic resonance imaging studies have produced conflicting results, with some failing to detect APOE-related differences and others suggesting that ε4 carriers have more pronounced atrophy, particularly at medial temporal structures. All functional imaging studies done during rest in middle-aged and elderly subjects have found decreased cerebral metabolism for ε4 carriers (mostly in areas that usually are affected by AD), and some have reported faster cerebral metabolic reductions over time. Areas with decreased resting cerebral perfusion and metabolism, in addition to other areas with increased perfusion, have been reported in young ε4 carriers. Imaging studies done during the performance of various cognitive tasks in middle-aged and elderly subjects, and a single study in young subjects, have produced mixed results with regionally nonspecific increased, decreased, or nondifferential APOE-related activations depending on the cognitive task used. APOE-related findings in imaging studies of nondemented subjects may be the result of incipient AD pathologic changes or of genetic heterogeneity in brain structure and function.

Introduction

Multiple epidemiologic studies have established that the APOE is the most important susceptibility gene for sporadic Alzheimer's disease (AD) [1–3]. The ε4 allele has a dose-related effect on risk for sporadic AD, whereas the ε2 allele seems to confer protection [4]. Although it is conceivable that the clinical heterogeneity observed in AD could derive from APOE-related underlying genetic variability [5], the relation of APOE to different AD clinical and phenotypic subtypes after the onset of disease is less clear. Many studies have attempted to investigate the effects of the APOE genotype on brain structure and function before [6–10,11•,12–[16],[17•],[18],19••,[20•],[21–24],[25•],26,27•,28,29••] or after [6,30–33] clinical AD onset. However, treatment for AD may be more effective if applied early in the disease process (if possible, before clinical disease is manifested). Therefore, it is very important that early AD changes in subjects at risk for AD, such as ε4 carriers, be identified early. In this article, we review and discuss imaging studies done in nondemented subjects, and investigate associations between the APOE genotype and structural and functional cerebral changes.

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Structural Imaging

Middle-aged and elderly subjects

In a magnetic resonance imaging (MRI) study of 125 cognitively normal elderly control subjects, MRI-assessed hippocampal volumes did not differ on the basis of APOE genotype [6]. Another MRI study included 137 subjects, comprising a mixture of participants with normal cognition, memory difficulties, and few subjects with mild dementia (n = 16) [7]. Entorhinal cortex and hippocampus volumes did not differ in relation to APOE genotype. According to an MRI study of 26 nondemented subjects, there were no APOE-related differences in hippocampal volumes [8]. The subjects had repeated MRIs approximately 2.5 years later. ε4 carriers showed significantly faster hippocampal volume loss (2.86% per year), as compared with non-ε4 carriers (0.85% per year). There were no significant differences between ε4 homozygotes and ε4 heterozygotes. Rates of change of total brain volume did not differ by APOE genotype.

In a study of 113 cognitively normal, late middle-aged adults, the presence of the ε4 allele had a dose-related reduction (*ie*, more prominent reduction for ε4 homozygotes, as compared with ε4 heterozygotes, and for ε4 heterozygotes as compared with non-ε4 carriers) of MRI gray matter in regions known to be affected early in AD, including the posterior cingulate, bilateral parahippocampal/lingual gyri, and left parietal and anterior cingulate/medial frontal areas [9].

In an MRI study of 32 healthy elderly subjects (16 with age-associated memory decline, and 16 with normal memory), ε4 homozygotes had significantly smaller right (as compared to left) hippocampus [10]. This pattern of hippocampal asymmetry was opposite to that observed in non-ε4 carriers (*ie*, larger right hippocampus). These results were interpreted as concordant with studies after the onset of AD, indicating a more severe volume loss in the right hippocampus for ε4 homozygotes [30].

In a large MRI study of 1077 nondemented subjects in their early 70s, ε4 carriers had significantly more hippocampal and amygdala atrophy than ε3/ε3 subjects on the left and right sides [11•]. Hippocampal and amygdalar volumes decreased with increasing ε4 doses. There was no difference between ε2 carriers and ε3/ε3 subjects. Measures of global (cortical and subcortical) brain atrophy did not differ by APOE genotype. The results were similar when subjects with low memory performance were excluded.

Another MRI study included 193 subjects with mild cognitive impairment (MCI) as compared with non-ε4 carriers. Women with one or two ε4 alleles were found to have significantly reduced hippocampal volume, whereas men only showed a significant reduction in hippocampal volume when carrying two ε4 alleles [12]. When controlling for memory performance on delayed word recall, the APOE effect on hippocampal volumes was attenuated in men, but remained significant in women. The authors concluded that the APOE genotype status seems to have a greater deleterious effect on gross hippocampal pathology in women than in men.

In an MRI study of 21 cognitively normal elderly twin subjects, six ε4 carriers and 14 noncarriers were indistinguishable based on neuropsychologic measures [13]. Nevertheless, mean right and left hippocampal volumes were significantly smaller for ε4 carriers.

Young subjects

In a study of 70 healthy pediatric subjects who received brain MRI at age 10 years, there was no relation between APOE status and hippocampal volume [34]. For 50 of these

subjects who received a second MRI 2 years later, there was no association between APOE status and longitudinal changes in hippocampal volume [34].

Functional Imaging During Rest

Middle-aged and elderly subjects

In a study of nondemented middle-aged subjects with memory complaints who had at least two relatives with AD, 12 participants with ε4 and 19 participants without the ε4 allele were scanned with fluorodeoxyglucose positron-emission tomography (FDG-PET) [14]. Subjects with the ε4 allele did not differ from those without the ε4 allele in mean age or in neuropsychologic performance. Parietal metabolism was significantly lower, and left-right parietal asymmetry was significantly higher in subjects with the ε4 allele, as compared with those without the ε4 allele.

The same investigators reported similar results from a FDG-PET study that included 27 ε4 carriers and 27 ε4 noncarriers who were elderly, dementia-free, and who had memory complaints and/or family history of dementia [15]. In region of interest (ROI) analyses, compared with ε4 noncarriers, ε4 carriers had significantly lower metabolism in bilateral inferior parietal (18% lower on the right, and 12% lower on the left) regions. Statistical parametric mapping (SPM) analyses showed similar results: ε4 carriers had lower metabolism in inferior parietal and posterior cingulate and left lateral temporal areas. The results were similar even when the two ε4 homozygotes were removed from the analyses. Baseline glucose metabolic rates in several ROIs predicted 2-year memory decline in ε4 carriers. In repeat PET scans that were obtained for 10 ε4 carriers and 10 non-ε4 carriers after 2 years, a significant metabolic decline was noted for ε4 carriers (but not for non-ε4 carriers) in posterior cingulate (4%; ROI analyses) and in inferior parietal and lateral temporal cortices (5%; SPM analyses). Non-ε4 carriers showed metabolic decline, primarily in the frontal cortex, consistent with normal aging.

As part of a study of cognitively normal late middle-aged subjects with family history of probable AD, FDG-PET was done in 11 ε4 homozygotes and 22 control subjects without the ε4 allele who were matched for gender, age, education, and level of cognitive performance [16]. The ε4 homozygotes had significantly reduced rates of glucose metabolism in the same posterior cingulate, parietal, temporal, and prefrontal regions as in previously studied patients with probable AD. They also had reduced rates of glucose metabolism in additional prefrontal regions, which may be preferentially affected during normal aging.

The same investigators observed similar results with a larger dataset of 160 cognitively normal late middle-aged subjects who had a first-degree relative with AD (36 ε4 homozygotes, 46 heterozygotes, and 78 ε4 non-carriers who were individually matched for their gender, age, educational level, and cognitive performance) ε4 gene dose was correlated with lower FDG-PET-assessed cerebral glucose metabolism in regions of the precuneus and the posterior cingulate, parietotemporal, and frontal cortices [17•].

In another report from the same group, longitudinal PET cerebral glucose metabolic data after 2 years were available for 10 cognitively normal ε4 heterozygotes and 15 non-carriers 50 to 63 years of age, with a reported family history of AD [35]. The ε4 heterozygotes had significant cerebral metabolism declines in the vicinity of temporal, posterior cingulate, and prefrontal cortex, basal forebrain, parahippocampal gyrus, and thalamus, and these declines were significantly greater than those noted for the ε4 noncarriers.

A 3-year FDG-PET longitudinal study of 48 healthy normal elderly (12 of whom showed cognitive decline, 11 to MCI, and one to AD) included eight ε4 carriers and 17 noncarriers

[18]. ε4 carriers showed lower lateral temporal lobe and superior temporal gyrus metabolism. Among subjects who showed cognitive decline, ε4 carriers (but not ε4 noncarriers) showed lower baseline lateral temporal lobe metabolism and more prominent lateral temporal lobe reductions over time (13% for ε4 carriers vs 3% for noncarriers).

Young subjects

Association between APOE genotype and functional brain imaging changes has been addressed by only two studies. In one, FDG-PET scans were obtained for normal volunteers 20 to 39 years of age (12 ε4/ε3 and 15 ε4 noncarriers) individually matched for gender, age, educational level, and cognitive performance [19••]. Similar to previously studied patients with probable AD and late middle-aged ε4 carriers, the young ε4 carriers had abnormally low rates of glucose metabolism bilaterally in the posterior cingulate, parietal, temporal, and prefrontal cortex.

Our group used H215O PET to measure cerebral blood flow for younger college-age subjects (three ε4 carriers and 15 noncarriers) [20•]. The groups were of similar age (26 vs 23 years), gender, education, and neuropsychologic performance. ε4 carriers showed significantly lower cerebral blood flow in the left and right inferior temporal gyri. However, ε4 carriers also had higher flow in the left insula, right supramarginal gyrus, and the inferior occipital gyrus.

Functional Imaging During Cerebral Activation

Middle-aged and elderly subjects

One study used functional MRI (fMRI) during visual naming and letter fluency tasks in 26 middle-aged, cognitively normal women who were classified as high risk (ε4 carriers with at least one first-degree relative with AD) and low risk (neither of the above). High-risk women showed decreased fMRI activation in bilateral mid and posterior inferotemporal regions during naming and fluency tasks despite identical performance [22].

In a follow-up study from the same group of investigators, with 38 middle-aged women participants, the high-risk group showed significantly decreased activation at left posterior fusiform and bilateral anterolateral occipital areas [23]. However, increased activation in the left parietal regions (mostly extent and less so magnitude) also was noted for the ε4 carriers.

In a small pilot study of nondemented elderly subjects, three ε4 carriers and three noncarriers had fMRI during learning and recall of a face-naming task [26]. ε4 carriers seemed to have increased activation in dorsolateral prefrontal cortex during the easy version of the task, but were unable to further increase the activation during the more demanding version of the task.

In another study of cognitively intact elderly subjects, 13 ε4 carriers (12 ε4 heterozygotes) and 12 non-ε4-carriers had fMRI during performance of a verbal working memory task [21]. No APOE-related differences were detected for various levels of task difficulty. The authors concluded that the effect of APOE was specific to memory and not related to general task difficulty.

The same group of investigators used fMRI during performance of a verbal memory task for 16 elderly ε4 carriers (14 heterozygotes) and 14 elderly ε3 homozygotes who were cognitively normal [27•]. The magnitude and the extent of fMRI activation were greater among ε4 carriers in the left prefrontal and bilateral orbitofrontal, superior temporal, and inferior and superior parietal regions. During recall, the average increase in signal intensity was nearly twice as great among ε4 carriers as compared with ε4 noncarriers. The results

were interpreted as evidence of compensatory processing in subjects at risk for AD; that is, the APOE ε4 subjects use additional cognitive resources to bring their performance to a normal level.

In a more recent study of nondemented elderly, 10 ε4 carriers and 10 ε4 noncarriers had fMRI during a picture learning task [24]. In SPM analyses, ε4 carriers showed significantly greater activations during novel picture encoding in bilateral fusiform gyrus, right superior parietal lobule, left cerebellum, left middle frontal gyrus, and medial frontal gyrus. In ROI analyses, ε4 carriers had greater fMRI responses in left inferior frontal, bilateral fusiform, and right hippocampal and parahippocampal cortices. However, there also were areas within the left hippocampal and parahippocampal cortex where ε4 carriers showed smaller activations.

In another study, fMRI was used to record cerebral activation during performance of a face-name associative encoding task in a mixture of 10 cognitively intact elderly subjects, nine subjects with MCI, and 10 subjects with probable AD [28]. As compared to the 16 non-ε4 carriers, the 13 ε4 carriers showed a greater extent of entorhinal cortex activation.

Our group used H215O PET for imaging of 26 non-ε4 carriers and six elderly ε4 carriers while they did a serial recognition nonverbal memory task with titrated task difficulty so that recognition accuracy was similar for all subjects [25•]. As compared with non-ε4 carriers, ε4 carriers showed significantly decreased activation in left precuneus, left superior temporal, right superior frontal, left postcentral, and posterior cingulate gyri. Because recognition accuracy was titrated, the differences in activation were considered not to reflect task difficulty, but to indicate memory-related altered cognitive processing for different APOE genotypes.

Young subjects

To our knowledge, there is only one study that has investigated APOE-related differences during functional activation in this age group. Using H215O PET, we did scans of 20 healthy young adults (age, 19 to 28 years; four ε4 carriers and 16 non-ε4 carriers) while they did a nonverbal memory task [29••]. In comparison to subjects without the ε4 allele, ε4 carriers showed significantly lower activation in right superior temporal and left fusiform gyri and significantly higher activation in left middle temporal and right transverse temporal gyri. These results suggest that APOE-dependent modulation of cerebral flow during cognitive activation may be present even at a very young age.

Discussion

Many studies have investigated APOE-related differences in cerebral structure, blood flow, metabolism, and activation in an attempt to detect early changes in subjects at risk for AD.

Structural MRI studies have produced conflicting results. Three structural imaging studies have failed to detect APOE-related differences [6–8], whereas five studies seem to suggest that ε4 carriers have more pronounced atrophy [9,10,11•,12,13]. This seems to be the case in particular for medial temporal structures (which are the areas that usually are investigated). The effect seems to be more prominent on the right hippocampus according to one study [10]. According to another, the association between ε4 allele and increased hippocampal atrophy is stronger in women [12]. Faster hippocampal volume loss has been shown for nondemented ε4 carriers by one study [8].

The associations are more consistent when it comes to functional imaging during rest. All five studies in middle-aged and elderly subjects have found decreased cerebral metabolism

for ε4 carriers [14–16,17•,18]. Decreases in metabolism have been noted mostly in areas that usually are affected by AD. Additionally, two studies have found that ε4 carriers also show faster cerebral metabolic reductions over time [18,35]. For young subjects, one study found decreased cerebral metabolism [19••], and another found decreased perfusion [20•] in areas affected by AD at older ages. Nevertheless, the latter study also reported brain regions of increased perfusion for young ε4 carriers [20•]. Therefore, carriers of the ε4 allele seem to have resting metabolism and flow changes in young adulthood, several decades before the possible onset of dementia.

It has been hypothesized that imaging during performance of cognitive tasks may be more sensitive in revealing earlier and subtler changes in cognitive function in subjects at risk for AD, such as ε4 carriers. However, activation imaging studies in middle-aged and elderly subjects have produced variable results. One study found no APOE-related activation differences during performance of a verbal working memory task [21]. Four studies have reported that there are brain regions in which ε4 carriers show decreased activation during cognitive task performance [22–24,25•]. Five studies have found increased activation in various brain regions for ε4 carriers [23,24,26,27•,28]. Increased activations often have been interpreted as evidence of compensatory processing in subjects at risk for AD; that is, APOE ε4 subjects use additional cognitive resources to bring their performance to a normal level. The single existing study in young subjects has reported areas with increased activation and other areas with decreased activation for ε4 carriers during performance of a nonverbal memory task [29••], suggesting that APOE-dependent modulation of cerebral flow during performance of cognitive tasks may be present even at a very young age.

Overall, many of the imaging studies conclude that in carriers of the ε4 allele, a common AD susceptibility polymorphism that identifies genetically at-risk individuals, subtle changes in cerebral structure of function occur long before the onset of clinical manifestations of disease. Therefore, many authors raise the possibility of using imaging as a quantitative presymptomatic endophenotype to help evaluate the individual and aggregate effects of putative genetic and nongenetic modifiers of AD risk. Assuming that structural and metabolic declines are related to predisposition for AD, some authors advocate possible use of imaging as a therapeutic response monitor (*ie*, a surrogate endpoint for testing the potential of experimental treatments to prevent the disorder) without having to study thousands of research subjects or wait many years to determine whether or when treated individuals develop symptoms.

Possible reasons for study discrepancies

Decreased power cannot fully explain why some structural MRI studies have failed to detect more prominent atrophy for middle-aged and elderly ε4 carriers because some of them have included a large number of participants [6,7,34], whereas APOE-related associations with atrophy have been detected by considerably smaller studies [10,13]. Various methodological differences may account for the differences among studies. Examples include differences in subject selection, differences in levels of cognitive performance, different age groups, etc. All of these may affect relative percentages of subjects harboring subclinical AD-type pathologic changes in each study, and therefore different degrees of underlying MRI brain atrophy. Differences in cerebral activation studies can be accounted for by various other additional factors: different imaging modalities (FDG assessing brain metabolism versus H215O assessing blood flow), different methods of analysis (ROI versus SPM voxel-wise), different applied statistical thresholds, differences in power (more spatially restricted activations in some studies may be the result of a limited number of participants), etc. The relative proportions of homozygotes and heterozygotes in different studies also may have an important impact on power. Presence of parametric changes in activation with increasing

number of ε4 alleles would provide a much more convincing association between the APOE genotype and cerebral activation.

More importantly, it is not surprising that activation task differences may result in activations and deactivations of variable brain regions. First, there are differences in underlying cognitive functions being tested (*ie*, naming, fluency [22,23], face naming [26,28], verbal working memory [21], verbal episodic memory [27•], nonverbal memory [25•], picture learning [24]). Second, there are differences regarding acquisition of scanning data during different phases of cognitive tasks (*ie*, encoding and retrieval [21,25•], or learning and recall separately [27•]). Third, variable experimental designs have been used. Although most studies have used varying degrees of task difficulty, some studies have used equated task difficulty so that recognition accuracy was similar for each participant [20•, 25•], or have compared subjects at various levels of task difficulty [21]. Several functional imaging studies suggest that a common response to increasing task difficulty in normal individuals is increased activation of areas involved in an easier version of the task and/or the recruitment of additional brain areas [36,37]. Therefore, areas reportedly associated with APOE-related compensatory activation that have been identified in experiments with uncontrolled task difficulty may reflect modulation of the same networks in response to differential difficulty (*ie*, increased task-related effort rather than APOE-related compensatory recruitment).

Biopathological and functional considerations

Effects of the APOE genotype on lipid metabolism [38], blood pressure [39], atherosclerosis [40], ischemic heart disease [41], myocardial infarction [42], and cognitive performance in type I diabetes [43] have been documented in very young subjects and in children [44,45]. Animal studies have indicated that the APOE genotype seems to affect stress response and spatial memory [46] and regulates synaptic plasticity and long-term potentiation in the hippocampus [47] of young mice. Therefore, it is conceivable that APOE-related alterations in cerebral physiology may exist from a very young age.

There are known early biochemical changes in neuronal processes and synapses (which may be manifested in cerebral blood flow activation studies) long before structural pathology is detected [48]. It is also known that symptoms of AD are preceded by a period of unknown duration during which neuropathologic alterations accumulate in the brain without associated memory loss or other detectable cognitive change. The increased risk for AD in subjects carrying the ε4 allele has been thought to be mediated by the APOE genotype being implicated in β amyloid and/or neurofibrillary tangle [49,50] biochemical pathways. In a neuropathological study of 105 autopsy cases who showed no signs of dementia, abnormally high brain β amyloid levels (the deposition of which is the hallmark of AD) were reported for ε4 carriers as young as 40 years [51]. That study concluded that the ε4 allele predisposes the carriers to begin accumulating β amyloid earlier in life than noncarriers. In another study, the ε4 allele was associated with presence of neurofibrillary tangle changes in 44 autopsy cases of young subjects (mean age, 38 years old; range, 22 to 46 years) [52]. After AD onset, patients with AD with the ε4 allele have been reported to carry increased β amyloid burden [1,50]. The ε4 allele also has been associated with more profound deficits in cholinergic neurons [53,54]. Therefore, brain regions in which APOE-related significant differences have been detected in structural or functional imaging studies may have already been affected by AD pathology in subjects at risk for AD (the absence of clinical dementia may be the result of unaffected brain regions providing enough redundancy for normal cognitive performance).

Increased and decreased activations for the ε4 carriers have been observed in imaging studies during cognitive tasks. Overall, the interpretation of increased or decreased

activation has been very controversial. There have been activation imaging studies in healthy subjects [37,55–57] but also in AD patients [58] in whom decreased activation reflected more efficient processing, whereas increased activation was associated with less effective cognitive strategies. Therefore, it is not clear how AD pathology relates to the APOE-dependent activation differences. Areas with differential activation in the ε4 carriers may reflect malfunctioning (taking the form of either overactivation or deactivation) because of more severe AD pathological involvement for ε4 carriers in these regions. Alternatively, some of these regions may still be spared by AD pathology and are recruited for task performance by ε4 carriers because of more severe pathologic involvement in other regions.

However, several other considerations make the possibility of indolent AD pathology causing APOE-related differences less plausible. That the APOE-related differences in resting flow and activation are detected at such a young age (four to five decades before the possible onset of dementia) weakens the hypothesized link with AD. The presence of the ε4 allele is not equivalent to early AD: a significant proportion of ε4 heterozygotes will never develop AD. It has been proposed that ε4 facilitates rather than causes AD [59], and ε4 has been implicated in impaired brain repair mechanisms that may place subjects at risk for AD or other brain diseases. Important direct effects of the ε4 allele on the nervous system include impaired neuroregeneration within the dentate gyrus [60] and increased vulnerability to exogenous neurotoxins [61]. Therefore, the observed imaging patterns of ε4 carriers may be the early signature of an APOE-dependent alteration in brain physiology, which may result in greater vulnerability to environmental effects (such as traumatic brain injury or other insult) later in life. Subsequently, the detected activation differences may reflect an APOE-dependant physiologic heterogeneity (*ie*, different structure or different resting flow-metabolism or different utilization of brain regions during task performance), which may not necessarily lead to disease.

Conclusions

Overall, subjects with a genetic risk for AD (ε4 allele carriers) have alterations in brain structure and function, even at a point in time when behavioral, cognitive, or clinical evidence of disease is absent. These alterations may be markers of early AD or they may just reflect an APOE-related cerebral physiologic heterogeneity. There exists significant variability of scientific findings, which may be related to underlying methodological differences among imaging studies. Nevertheless, imaging may be a more sensitive tool than behavioral-cognitive tests for measuring early cerebral structure-function or reorganization in response to possible incipient pathological processes.

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