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Neuroimaging and *APOE* Genotype: A Systematic Qualitative Review

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Key Words

Apolipoprotein E · Alzheimer's disease · Cognitive aging · Braak stages · Magnetic resonance imaging

Abstract

Apolipoprotein E *(APOE)* is the major genetic risk factor for late-onset Alzheimer's disease (AD) and has also been implicated in cardiovascular disease, cognitive decline and cognitive changes in healthy ageing. The aim of this paper is to systematically review and critically assess the association between the *APOE* genotype and structural/functional cerebral changes as evidenced by brain imaging studies. A second aim is to determine whether these observed associations between APOE and the brain reflect changes which are consistent with the progression of AD neurodegenerative changes described in Braak stages. A search of Pubmed, Psycinfo, and Web of Science databases identified 64 articles available for qualitative review. The review found that presence of the *APOE* ε4 allele is associated with (1) hippocampal, amygdalar and entorhinal cortex atrophy, (2) increased brain atrophy, (3) increased white matter hyperintensity volumes and (4) altered cerebral blood flow and glucose metabolism patterns. It is possible that there are critical age ranges when these effects are evident and that the *APOE* ε2 genotype might present a risk. We conclude that structural brain change is associated with the *APOE* genotype and that it is more salient in younger ageing individuals.

Apolipoprotein E *(APOE)* is the main known genetic risk factor for late-onset Alzheimer's disease (AD), and, since the discovery of this association, substantial research has been conducted to confirm and explain its involvement in the disease. Despite these efforts, the role of *APOE* in the development of AD remains unclear, and its contribution remains controversial.

APOE is a glycoprotein involved in the transport of cholesterol and other lipids through cell membranes. In the brain, *APOE* is mainly produced by glial cells and is thought to be involved in cell growth and neuronal regeneration. There are 3 common *APOE* gene alleles: ε2, ε3 and ε4. Their frequencies differ between populations, but the ε3 allele is the most common (78%), followed by the ε4 allele (15%), and the ε2 allele (7%). Individuals with at least 1 *APOE* ε4 allele have been found to be more likely to develop AD and to do so at an earlier age [1]. This effect is not well understood, but it appears that the *APOE* ε4 allele is less efficient at inducing cholesterol transport which may impact on the regeneration of neural cells and influence synaptic plasticity [2]. It appears that the effect of *APOE* ε4 might be dose dependent and affect more severely those individuals homozygous for this allele [3]. There is also some evidence of an association between *APOE* and multiple sclerosis [4], and the severity of cognitive deficits following traumatic brain injury [5].

The *APOE* genotype does not exclusively impact the central nervous system but has also been found to be a risk factor for cardiovascular disease. As such *APOE* might indirectly influence cerebral function through an effect on the cardiovascular system. The ε4 allele has been shown to be associated with higher levels of low-density cholesterol, increased levels of atherosclerosis and increased death rates due to cardiovascular disease, while the ε2 allele appears to be protective against cardiovascular effects, although findings have been inconsistent [6].

The cognitive effects associated with the *APOE* ε4 genotype are widespread in AD and dementia and include deficits in learning, memory, attention and global cognition, as well as an increased, dose-dependent rate of decline [3]. Non-demented *APOE* ε4 carriers have also been shown to perform worse on a large number of neuropsychological tests including episodic memory, visual and spatial attention, visuospatial ability, and verbal fluency and naming [7]. A recent study in younger healthy individuals [8] did not find such associations. However, since most studies have investigated older populations, it is not clear whether these findings indicate an *APOE* effect in healthy individuals or the preliminary stages of AD. In a critical review of the available findings, Savitz et al. [7] conclude that the latter is more likely. They argue that the *APOE* genotype does not have an independent effect in cognitively healthy individuals. Rather, *APOE* contributes to slow neurodegenerative processes that lead to dementia evidenced in the decline in cognitive performance and brain changes occurring up to two decades prior to the diagnosis of AD [9]. This view is supported by post-mortem studies investigating the histopathological progression of AD. Using Braak stages [10, 11] Ohm et al. [12] assessed the brain of 814 individuals post-mortem and found that neurofibrillary tangles, a hallmark of AD, were present from the third decade of life onwards in healthy individuals. This study also suggested that AD follows a slow progression starting in early adulthood rather than a sudden onset in old age. In another post-mortem study of 80 brains, Ohm et al. [13] showed that the average Braak stage was higher in *APOE* ε4 carriers than non-carriers. *APOE* ε4 carriers were more represented by a factor of 3 in the 2 highest Braak stages.

Based on Braak stages [11] it would be expected that brain changes detectable in neuroimaging studies (atrophy due to neuronal death associated with high level of neurofibrilary tangles and amyloid plaque) would be first apparent in the entorhinal cortex, hippocampus and insular cortex (stages I–IV) in younger ageing cohorts, progressing fan-like in frontal, superolateral and occipital directions (stage V), and with severe changes in most areas of the neocortex (stage VI) in older cohorts.

The aim of the present paper is to systematically review neuroimaging findings investigating an association between the *APOE* genotype and structural and metabolic brain changes. Although a substantial number of neuroimaging studies investigating the effect of the *APOE* genotype on brain structure and function have been conducted, there has been little formal synthesis of the findings. The following hypotheses were examined: First, relative to non-carriers, cerebral changes in those with the *APOE* ε4 genotype will be detectable in comparatively younger and non-symptomatic individuals. These changes might include regional and global atrophy, ventricular and sulcal atrophy, increased white matter lesion load, and decreased resting blood flow and metabolism. Second, *APOE*-associated cerebral changes in younger cohorts may be expected to be spatially localised to the parahippocampal region becoming more diffuse in older cohorts and particularly those suffering from dementia. Finally, we examined evidence for *APOE* ε4 dose effects expecting greater atrophy in individuals homozygous for *APOE* ε4.

Method

Literature Search

A search of the literature was conducted (April 2007) using the databases Pubmed, Psycinfo and Web of Science to identify studies reporting on the association between *APOE* and brain structures. Each search was limited to articles published in English and based on human research. A total of 286 unique articles were identified.

Key words used in the Pubmed search were: for APOE, 'APOE', 'apolipoprotein'; for brain, 'brain with {MeSH terms}', 'head {without MeSH terms}', 'intracranial', 'cerebral', 'hippocampus', 'amygdala', 'ventricle*', 'entorhinal cortex', 'medial temporal lobe', 'prefrontal cortex'; for brain indices, 'size', 'circumference', 'volume*', 'cavity', 'atrophy', 'asymmetry', 'white matter hyperintensities' (WMHs), 'cerebral blood flow', 'regional cerebral blood flow', 'cerebral perfusion', 'glucose metabolism'; for measurement type, 'magnetic resonance imaging' (MRI), 'positron emission tomography' (PET), 'single-photon emission tomography' (SPECT), 'voxel-based morphometry'. MeSH (medical subject headings) terms are a controlled vocabulary that Pubmed uses to index articles. These terms help to identify articles that may use different terminology, but are still relevant to the search. The asterisk symbol (*) indicates where a key word was truncated in order to capture variations of the word. The same set of key words was used for the searches conducted in Psycinfo and Web of Science, without the use of MeSH terms for the key word 'brain'.

Study Selection and Data Extraction

Selection of the relevant studies from the 286 abstracts identified was conducted in two stages. The first stage involved screening the titles and abstracts according to a set of criteria. Studies

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were included if they contained (a) a measure of both *APOE* and brain structure, (b) reported data on the association between these two factors and (c) were full-text original contributions. Studies were excluded if the aggregate sample size was smaller than 30, or if the sample had a concurrent mental illness, systemic illness or a major structural abnormality (e.g. head injury). Samples with AD or dementia were included in the review (including vascular, Lewy body and frontotemporal dementia). Functional studies using PET or MRI were excluded because there were too few and they could not easily be compared. The second stage of study selection involved obtaining and examining the full text of the remaining articles and applying the exclusion criteria with greater precision. The references of key articles were also examined for missed papers, resulting in a small number of additional studies. The full text of 145 articles was examined, and a final number of 64 studies were included in the review. Each study was read in detail, and the composition of the sample used (population, mean age, *APOE* distribution) and the main findings were extracted.

Methodological Considerations

Methodological features of the research papers were considered, and study quality was assessed. Relevant features included sample size and sample selection, sample age, classification of *APOE* genotype, and study design.

Sample selection is of great importance in *APOE* research since different associations are expected in AD compared to healthy samples, and in younger compared to older individuals. Consequently, findings in AD patients were primarily compared together, and findings in different age cohorts were also contrasted.

APOE genotype classification and reporting were assessed. *APOE* can be classified and analysed in a dichotomous way with pooled ε4 carriers (ε4+/+ or ε4+/–) being compared to non-carriers (all other genotypes) while in others carriers of 1 (ε4+/–) or 2 alleles (ε4+/+) are separately compared to non-carriers. More specific, usually larger studies, which considered each *APOE* ε4 genotype (ε4ε4, ε4ε3, ε4ε2) separately might be compared to each type of non-carrier (ε3ε3, ε3ε2, ε2ε2). The latter if adequately powered will be more informative of the *APOE* ε4 (and the other genotypes) effects.

All studies included fell into the Oxford Centre for Evidence-Based Medicine (www.cebm.net) '2b' category (differential diagnosis/symptom prevalence study) except for 3 longitudinal studies leading to an overall recommendation grade B.

Results

Hippocampus

As can be seen in table 1, in total 16 studies totalling 3,063 participants reported differences in hippocampal measures (decreased volume and asymmetrical effects), while 6 studies totalling 597 participants did not find significant differences in hippocampal volumes between carriers and non-carriers of the *APOE* ε4 allele (although one of these studies found trends suggesting a dose effect of the *APOE* genotype). Of particular interest when comparing the design of studies reporting significant results with those that do not is that whereas the former used samples in a fairly narrow age bracket with an average age of almost 70 years, the latter is represented in two clusters of younger (approx. 60 years) and older (approx. 79 years) samples. This suggests that the effect of the *APOE* genotype might be particularly influential in specific age ranges, with younger individuals possibly not being sufficiently affected to produce detectable results and with older individuals being more uniformly affected by age-related hippocampal shrinkage changes which might mask *APOE* effects. Consistent with this hypothesis, Bigler et al. [14] found in a sample of AD patients that ε4 carriers had smaller hippocampi than non-carriers but only in those patients with disease durations of less than 1 year. It is also possible that *APOE* ε4 carriers might drop out of studies more frequently in an older sample due to increased frailty, sickness and mortality.

Of the studies reporting significant associations between the *APOE* genotype and hippocampal volumes, most presented consistent effects. Hippocampal volumes were always reported as smaller and atrophy rates as greater in subjects homozygous for *APOE*. Heterozygous individuals, in contrast, had similar hippocampal volumes or atrophy rates to homozygous individuals in some studies, whereas in others they did not differ from ε4 non-carriers. This may be explained by variation in other sample characteristics such as sex, genotype ratios and clinical factors (AD, mild cognitive impairment, age-associated memory impairment, cognitively intact). However, findings of dose-dependent effects in 3 AD studies [15–17], 1 study in healthy volunteers [18] and a consistent trend in a fifth study [19] suggest that heterozygous carriers have reduced hippocampal volumes and greater atrophy rates but to a lesser extent than their homozygous counterparts.

A single study also suggests that these effects might be moderated by sex. Fleisher et al. [20] found in a sample of 193 subjects with mild cognitive impairment that women with 1 or 2 ε4 alleles but only men with 2 alleles had smaller hippocampal volumes and worse performance on a delayed recall task. These effects could not be explained by other demographic variables such as age or race since the two sex groups were well matched and might be related to the greater incidence of AD in women.

Hippocampal asymmetries also appear to be associated with the *APOE* genotype. Four out of 5 studies presenting asymmetric hippocampal measures report findings consistent with smaller right hippocampi being associated with the ε4 allele and more so in homozygous than heterozygous carriers [21–24]. The fifth study [25] reported smaller left hippocampi in patients with age-associated memory impairments and carrying the ε4 or ε2 allele compared to ε3ε3 carriers.

Together these findings suggest a strong association between the ε4 allele and hippocampal atrophy in non-symptomatic individuals (non-demented volunteers), non-demented but symptomatic individuals (mild cognitive impairment, age-associated memory impairment) and AD sufferers.

Table 1. Hippocampus: *APOE* effects in healthy and AD samples

Reference	Design	Age years	Outcome	Measurement method
Association found				
Healthy samples				
30	Cross-sectional, 92 healthy volunteers: 36 ε4+, 16 ε2+, 40 ε3/ε3	65.5	Hippocampal sulcal cavities: ε4+ and ε2+ > ε3/ε3	Semi-quantitative rating on T_2-weighted scans (κ = 0.73, slice thickness 2.5 mm)
60	Cross-sectional, 427 non-demented volunteers assessed for alcohol consumption: 115 ε4+, 312 ε4–	73	Hippocampal volume: ε4+ < ε4– only in abstainers or light drinkers (<1/week), and heavy drinkers (>4/day)	Manual tracing on T_1-weighted scans (slice thickness 1.5 mm)
29	Cross-sectional, 428 non-demented volunteers: 117 ε4+, 52 ε2+, 259 ε3ε3	72 (60–90)	Hippocampal volume: ε4+ and ε2+ < ε3ε3, no asymmetry	Manual tracing on T_1-weighted scans (intraclass corr. >0.77, slice thickness 1.5 mm)
61	Cross-sectional, 494 patients with mild cognitive impairment: 44 ε4+/+, 154 ε4+/–, 296 ε4–/–	70	Hippocampal volume: ε4+/+ and ε4+/– < ε4–/–, no asymmetry	MRI measure of volume, no details available
20	Cross-sectional, 193 subjects with mild cognitive impairment: 23 ε4+/+, 102 ε4+/–, 68 –/–	73	Hippocampal volume: ε4+/+ and ε4+/– women and ε4+/+ men < ε4–/–, no asymmetry	Manual tracing on T_1-weighted scans (interclass corr. >0.98, slice thickness 1.6 mm)
18	Cross-sectional, 750 healthy volunteers: 563 ε4–/–, 175 ε4+/–, 12 ε4+/+	69 (63–75)	Hippocampal volume: ε4+/+ < ε4+/– and ε4–/–, no asymmetry	Optimized voxel-based morphometry (SPM) using anatomical ROI from a parcellated template: p < 0.0001 uncorrected for multiple comparisons, cluster size >120, smoothing kernel 12 mm
21	Cross-sectional, 60 non-demented volunteers: 30 ε4+, 30 ε4–	66	Hippocampal asymmetry (right volume): ε4+ < ε4– (in younger group <65 years)	Manual tracing on T_1-weighted scans (slice thickness 1.8 mm)
25	Cross-sectional, 50 patients with age-associated memory impairments: 13 ε4+, 14 ε2ε3, 23 ε3/ε3	65.5	Hippocampal asymmetry (left volume): ε4+ and ε2+ < ε3ε3	Manual tracing on T_1-weighted scans (slice thickness 1 mm)
22	Cross-sectional, 16 subjects with age-associated memory impairment and 16 controls: 4 ε4+/+, 10 ε4+/–, 18 –/–	69	Hippocampal asymmetry: ε4+/+ more asymmetric (left > right) than ε4+/– and ε4–/–	Manual tracing on T_1-weighted scans
23	Cross-sectional, 54 non-demented volunteers: 14 ε4+, 40 ε4–	59	Hippocampal asymmetry (right area): ε4+ < ε4–	Manual tracing on T_1-weighted scans (slice thickness 1.3 mm)
AD samples				
15	Cross-sectional, 138 probable AD patients: 46 ε4+/+, 46 ε4ε3, 46 ε3ε3	69	Hippocampal volume: ε4+/+ < ε4ε3 < ε3ε3, no asymmetry	Manual tracing on T_1-weighted scans
17	Cross-sectional, 55 AD patients: 7 ε4+/+, 31 ε4+/–, 17 –/–	72 (60–80)	Hippocampal atrophy: ε4+/+ > ε4+/– > ε4 –/–, no asymmetry	Manual tracing on T_1-weighted scans (interclass corr. >0.98, slice thickness 1.5 mm)
16	Cross-sectional, 26 AD patients: 5 ε4+/+, 9 ε4+/–, 12 –/– and 16 controls	69.5	Hippocampal volume: ε4+/+ < ε4+/– < ε4–/– (54% atrophy in ε4+/+ compared to controls)	Manual tracing on T_1-weighted scans
44	Cross-sectional, 58 probable AD patients: 13 ε4+/+, 24 ε4+/–, 21 –/– and 34 controls	70.5	Hippocampal volume: ε4+/+ < ε4+/–, ε4–/– < controls	Manual tracing on T_1-weighted scans (slice thickness 1.5–1.8 mm)
24	Cross-sectional, 28 AD patients: 5 ε4+/+, 9 ε4+/–, 14 –/– and 30 controls	70.5	Hippocampal volume asymmetry: ε4+/+ more asymmetric (left > right) than ε4+/– (left = right) than ε4–/– (left < right) than controls (left << right)	Manual tracing on T_1-weighted scans (intraclass corr. = 0.95, slice thickness 2 mm)
62	Cross-sectional, 20 normal elders, 58 MCI, 20 mild AD patients: 29 ε4+, 69 ε4–	76	Hippocampal volume: ε4+ < ε4–; hippocampal volume correlated with memory scores (CASI, r = 0.411)	Manual tracing by one neuroradiologist on high-resolution T_2-weighted scans

Table 1 (continued)

Reference	Design	Age years	Outcome	Measurement method
Association not found				
Healthy samples				
63	Cross-sectional, 33 non-demented volunteers: 11 ε4+, 22 ε4–	(50–65)	Hippocampal volume: no *APOE* effect (8% smaller in ε4+/+)	Manual tracing on T_1-weighted scans (interclass corr. = 0.99, slice thickness 1.5 mm)
64	Cross-sectional, 130 non-demented volunteers: 22 ε4+/+, 108 ε4–/–	60.5 (50–75)	Hippocampal volume: no *APOE* effect	Manual tracing on T_1-weighted scans (slice thickness 3 mm)
AD samples				
34	Cross-sectional, 76 demented patients (AD, VAD, dementia with Lewy bodies) and 26 controls: *APOE* genotype distribution not described	76.5	Total brain, frontal and temporal lobe volumes: no *APOE* effect	Manual tracing on T_1-weighted scans (intraclass corr. = 0.96–0.99, slice thickness = 1 mm)
65	Cross-sectional, 55 AD patients: 32 ε4+, 23 ε4– and 42 controls	72	Hippocampal volume: no APOE effect	Manual tracing on T_1-weighted scans (κ = 0.8–0.9)
66	Longitudinal over 12 months: 24 AD patients, 24 controls: 17 ε4+/+, 31 ε4–/–	81 (70–89)	Hippocampal atrophy (12 months): no *APOE* effect	Manual tracing on T_1-weighted scans (slice thickness 1.6 mm)
67	Cross-sectional, 62 AD patients 125 controls: 66 ε4+, 121 ε4–	78	Hippocampal volume: no *APOE* effect	Manual tracing on T_1-weighted scans (intraclass corr. = 0.98, slice thickness 1.6 mm)

SPM = Statistical parametric mapping; ROI = regions of interest; MCI = mild cognitive impairment; CASI = Cognitive Abilities Screening Instrument; VAD = vascular dementia.

The *APOE* ε2 allele has been found to be a protective factor for dementia [26], but other studies suggest that it may also be a risk factor [27, 28]. Three studies separately assessed the effect of the *APOE* ε2 allele, and they all found no significant difference in comparison to the effect of the ε4 allele which was associated with greater hippocampal atrophy [25, 29], and larger sulcal cavities [30].

Amygdala

Nine studies (pooled n = 1,476) reporting on the relationship between *APOE* genotype and amygdalar measures were found (table 2). All studies but 1 (n = 102) reported an association between *APOE* ε4 genotype and greater atrophy. This consistency relative to hippocampal volume may be due to the less frequent measure and analysis of amygdalar measures in the literature or the more comparable samples (particularly in relation to age) used in these studies. The studies were very consistent, and all found that the ε4 allele was associated with smaller amygdalar volumes. Three studies found a dose effect, with homozygous carriers being more affected than heterozygous carriers. Two studies also found an asymmetrical effect with the right amygdala being more atrophied in ε4 carriers. The amygdalar atrophy varied between 10 and 37% across studies.

Entorhinal Cortex

Three studies specifically investigated the relationship between *APOE* genotype and entorhinal cortex (table 3). One longitudinal study in non-demented elderly [31] found no association between these variables. Two other studies [32, 33] found a consistent, dose-dependent negative association between the number of ε4 alleles and entorhinal cortex volume in AD patients. This effect was substantial with volume differences between ε4 carriers and non-carriers in the order of 30%. Juottonen et al. [33] also found an interaction between AD, *APOE* genotype and sex. Female and male AD patients without the ε4 allele had similar entorhinal cortex volumes. However, females with the ε4 allele had a smaller right entorhinal cortex than males. In the same sample, ε4 carriers also had lower verbal and visual memory functions than non-carriers.

Cerebral Atrophy

Ten studies (pooled n = 1,156) reported a significant association between *APOE* genotype and cerebral atrophy while 3 studies (pooled n = 731) reported negative findings (table 4). All studies varied in a large number of parameters (participant's age, heterogeneity of diagnosis, *APOE* genotype distribution, measures of cerebral volume/atrophy and statistical analyses) making it difficult to summarise their findings in a meaningful way.

Table 2. Amygdala: *APOE* effects in healthy and AD samples

Reference	Design	Age years	Outcome	Measurement method
Association found				
Healthy samples				
29, 60	Cross-sectional, 427 non-demented volunteers assessed for alcohol consumption: 115 ε4+, 312 ε4–	73	Amygdalar volume: ε4+ < ε4– only in abstainers or light drinkers (<1/week) and heavy drinkers (>4/day)	Manual tracing on T_1-weighted scans (slice thickness 1.5 mm)
	Cross-sectional, 428 non-demented volunteers: 117 ε4+, 52 ε2+, 259 ε3ε3	72 (60–90)	Amygdalar volume: ε4+ and ε2+ < ε3ε3, no asymmetry	Manual tracing on T_1-weighted scans (intraclass corr. >0.77, slice thickness 1.5 mm)
AD samples				
65	Cross-sectional, 55 AD patients: 32 ε4+, 23 ε4– and 42 controls	72	Amygdalar volume: ε4+ < ε4– in AD patients	Manual tracing on T_1-weighted scans (κ = 0.8–0.9)
39	Cross-sectional, 18 AD, 8 FTD: 13 ε4+, 13 ε4– and 26 controls	70	Voxel-based morphometry: greater amygdalar atrophy (AD only) in ε4+ vs. ε4–	Non optimized voxel based morphometry (SPM): $p < 0.05$ corrected for multiple comparisons
15	Cross-sectional, 138 AD patients: 46 ε4 +/+, 46 ε4ε3, 46 ε3ε3	69	Amygdalar volume: ε4+/+ < ε4ε3 < ε3ε3, no asymmetry	Manual tracing on T_1-weighted scans
16	Cross-sectional, 26 AD patients: 5 ε4+/+, 9 ε4+/–, 12 –/– and 16 controls	69.5	Right amygdalar volume: ε4+/+ < ε4+/– < ε4–/– (37% atrophy in ε4+/+ compared to controls)	Manual tracing on T_1-weighted scans
44	Cross-sectional, 58 AD patients: 13 ε4+/+, 24 ε4+/–, 21 –/– and 34 controls	70.5	Right amygdalar volume: ε4+/+ < ε4+/–, ε4–/– and controls	Manual tracing on T_1-weighted scans (slice thickness 1.5–1.8 mm)
62	Cross-sectional, 20 normal elders, 8 MCI, 20 mild AD patients: 29 ε4+, 69 ε4–	76	Amygdalar volume: ε4+ < ε4–	Manual tracing by one neuroradiologist on high-resolution T_1-weighted scans
Association not found				
AD sample				
34	Cross-sectional, 76 demented patients (AD, VAD, dementia with Lewy bodies) and 26 controls: *APOE* genotype distribution not described	76.5	Total brain, frontal and temporal lobes volumes: no *APOE* effect	Manual tracing on T_1-weighted scans (intraclass corr. = 0.96–0.99, slice thickness = 1 mm)

FTD = Frontotemporal dementia; SPM = statistical parametric mapping; MCI = mild cognitive impairment; VAD = vascular dementia.

One study [34] reporting negative results did not describe the composition of the *APOE* groups compared nor the statistics of the tests used to compare them. The second negative study [35] in non-demented subjects (mean age 60 years) with a large sample size found a trend ($p = 0.07$) suggesting a possible association between the *APOE* ε4 allele and the annual rate of brain atrophy.

Seven studies with positive findings showed an association between the *APOE* genotype and cerebral atrophy and particularly in the temporal lobes. In one study [32] the ε4 allele was found to be associated with between 30 and 50% smaller volumes in the temporal lobes of AD patients compared to controls. Paradoxically, the same study found an opposite *APOE* dose effect in the frontal lobe, with subjects with 2 ε4 alleles presenting with less atrophy than those with only 1 allele or none. These findings might help reconcile the results of 3 other studies which found an *APOE* dose effect with a larger number of ε4 allele being associated with larger whole-brain volumes [15, 36] and larger white matter volumes in ε4+ and ε3ε3 carriers compared to ε2ε3 carriers [25]. Thus, the ε4 allele appears to be associated with opposite effects in different brain regions and, at least in these studies, the ε2 allele does not appear to be associated with protective effects.

APOE effects also seem to be moderated by intracranial volume and cardiovascular disease. It was found that the ε4 allele was associated with smaller brain volume in subjects suffering from cardiovascular disease [37] and with greater cognitive decline over 10 years in individuals with smaller intracranial volumes [38]. Two studies [15, 39] also found that an association between *APOE* genotype and cerebral atrophy was stronger in the right than in the left hemisphere.

Table 3. Entorhinal cortex: *APOE* effects in healthy and AD samples

Reference	Design	Age years	Outcome	Measurement method
Association found				
AD samples				
32	Cross-sectional, 28 AD patients: 5 ε4+/+, 9 ε4+/−, 14 −/− and 30 controls	70.5	Entorhinal cortex volume: ε4+/+ < ε4+/− < ε3+/+ < controls	Manual tracing on T_1-weighted scans (intraclass corr. = 0.93, slice thickness 2 mm)
33	Cross-sectional, 27 AD patients: 16 ε4+, 11 ε4− and 31 controls	71	Entorhinal volume: ε4+/+ < ε4+/− < ε4−/− (particularly on the left in AD)	Manual tracing on T_1-weighted scans (slice thickness 1.5–1.8 mm)
Association not found				
Healthy sample				
31	Longitudinal over 3.5 years, 42 non-demented subjects: 12 ε4+, 30 ε4−	73.5	Entorhinal volume: no *APOE* effect	Manual tracing on T_1-weighted scans (intraclass corr. = 0.99, slice thickness 1.4 mm)

Ventricles

Only 5 studies reported analyses on the relationship between *APOE* genotype and ventricular measures (table 5). One study (n = 77) found that a greater ventricular volume increase over 16 months was associated with the presence of at least 1 *APOE* ε4 allele. Four studies (pooled n = 368) found no association between *APOE* genotype and ventricular measures. An association between *APOE* genotype and ventricular size is therefore not well supported. Given the strong findings above showing an association between *APOE* and cerebral atrophy, these results might suggest that grey matter atrophy is most likely associated with sulcal widening rather than ventricular dilation.

White Matter Hyperintensities

WMHs are areas of hyperintense signal identified on T_2-weighted or proton density MRI scans. There is some controversy as to their precise clinical significance, but they have been shown to be more prevalent in older people and particularly in AD sufferers. WMHs have also been shown to be negatively associated with cognitive performance including processing speed, immediate and delayed memory, executive functions and global cognitive functioning [40], but negative findings have also been reported [41]. WMHs are thought to be due to small vessel disease and hypoxia, and are strongly associated with cardiovascular disease; therefore, the *APOE* genotype could have a direct effect on the cerebral parenchyma or could be mediated by cardiovascular disease which is exacerbated in ε4 carriers [6].

Table 6 shows that of 12 studies assessing the relationship between WMHs and *APOE* genotype, 5 report significant associations whereas 8 report no significant finding. These outcomes might suggest that WMHs are only weakly related to *APOE*, especially since most of the studies reporting negative findings are reasonably sized and have used adequate methodologies. However, 2 important variables seem to differ between studies that report significant findings and those that do not. Firstly, 4 out of 5 studies reporting significant findings were conducted with non-demented subjects, whereas 6 of 7 studies reporting negative findings were conducted in primarily demented subjects. Secondly, the average age of subjects assessed in the positive finding studies was somewhat lower (70.2 years) than that of the subjects in the studies with negative findings (73.5 years). The positive studies also assessed more subjects (pooled n = 2,331) than the negative studies (pooled n = 1,074) with 2 studies surveying more than 800 people.

Cerebral Blood Flow

Seven studies (pooled n = 399) investigated the relationship between regional cortical blood flow (rCBF) measured by SPECT or transcranial Doppler ultrasonography and *APOE* genotype and all reported significant results (table 7). Contrary to some of the brain structures discussed above, these studies were mostly consistent in respect to subjects' age, clinical distribution and relative proportion of *APOE* genotype.

The main findings were that rCBF was decreased in AD patients with the *APOE* ε4 allele compared to both non-carriers and to controls. Decreases in rCBF were reported for the frontal, temporal, parietal and occipital lobes. Little or no *APOE* dose effect was found, but asymmetrical effects were present in 4 studies [42–45]. The most consistent asymmetric effect was a lower rCBF in the left occipital cortex of *APOE* carriers. In contrast, van

Table 4. Brain atrophy: *APOE* effects in healthy and AD samples

Reference	Design	Age years	Outcome	Measurement method
Association found				
Healthy samples				
37, 38	Cross-sectional and longitudinal over 10 years, 390 male twins: 82 ε4+, 308 ε4−	72	Total brain volume: ε4+ < ε4− (in conjunction with cardiovascular disease) Relationship between ICV and cognition: ε4+ carriers showed greater cognitive decline over 10 years than ε4− carriers in a group with smaller ICV, no difference found in larger ICV group	Semi-automated segmentation by an experienced neurologist on T_1-weighted scans (slice thickness 5 mm)
68	Cross-sectional, 97 healthy volunteers: 37 ε4+, 60 ε4−; also assessed for nicotinic receptor gene *(CHRNA4)*	64.5 (46–75)	White matter volume: ε4+ and *CHRNA4* TT homozygous < all other groups	Cortical surface reconstruction
69	Cross-sectional, 51 patients with mild cognitive impairment: 8 ε4+/+, 15 ε4+/−, 28 ε4−/− and 32 controls	72	Right parahippocampal gyrus (all), right and left amygdala (ε4+/+ only), left medial dorsal thalamic nucleus (ε4+/+ only): ε4+/+ < ε4+/− < ε4−/−	Optimized voxel-based morphometry (SPM): $p < 0.001$ uncorrected for multiple comparisons, cluster size >1,000, smoothing kernel 12 mm
25	Cross-sectional, 50 patients with age-associated memory impairments: 13 ε4+, 14 ε2ε3, 23 ε3/ε3	65.5	White matter volume: ε4+ and ε3ε3 > ε2ε3	Manual tracing on T_1-weighted scans (slice thickness 1 mm)
70	Cross-sectional, 76 healthy volunteers: 27 ε4ε3, 49 ε3ε3	54	Distributed frontal and temporal regions, right medial temporal lobe, cerebellum: ε4ε3 < ε3ε3; grey matter atrophy in the medial temporal lobe correlated with delayed recall (CVLT, r = 0.39)	Non-optimized voxel-based morphometry (SPM): $p < 0.005$, cluster size >100, smoothing kernel 12 mm
AD samples				
39	Cross-sectional, 18 AD, 8 FTD: 13 ε4+, 13 ε4− and 26 controls	70	Voxel-based morphometry: greater right lobar atrophy (FTD only) in ε4+ vs. ε4−	Non-optimized voxel-based morphometry (SPM): $p < 0.05$ corrected for multiple comparisons
32	Cross-sectional, 28 AD patients: 5 ε4+/+, 9 ε4+/−, 14 −/− and 30 controls	70.5	Temporal lobe volume: ε4+/+ < ε4+/− < ε3+/+ < controls Frontal lobe volume: ε3+/+ < ε4+/− < ε4+/+ < controls	Semi-automated segmentation on T_1-weighted scans (intraclass corr. = 0.97–0.98, slice thickness = 2 mm)
15	Cross-sectional, 138 probable AD patients: 46 ε4+/+, 46 ε4ε3, 46 ε3ε3	69	Total brain volume: positive correlation with number of ε4 alleles	Automated segmentation on T_1-weighted scans with custom software (slice thickness = 1.5 mm)
71	Cross-sectional, 34 AD patients: 4 ε4+/+, 8 ε4+/−, 22 ε3+/+	83	Inferior temporal lobe indexes: ε4+/+ = ε4+/− < ε3+/+	Manual tracing on one slice of T_1-weighted scan (slice thickness = 10 mm)
36	Cross-sectional, 178 AD patients: 23 ε4ε4, 93 ε4ε3, 62 ε3/ε3	74.5	Total brain volume: ε4ε4 > ε4ε3 > ε3/ε3	Automated segmentation on T_1-weighted scans with custom software (intra-class corr. = 0.99, slice thickness = 1.5 mm)
Association not found				
Healthy samples				
35	Longitudinal over 6 years, 201 non-demented subjects: 34 ε4+, 167 ε4−	60	Annual brain atrophy (over 6 years): no significant effect of *APOE* (trend for greater atrophy in ε4+, p = 0.07)	Co-registration and automated segmentation of T_1-weighted scans using SIENA (slice thickness = 5 mm)
29	428 non-demented volunteers: 117 ε4+, 52 ε2+, 259 ε3ε3	72 (60–90)	Brain atrophy (graded): no *APOE* effect	Visual grading in 5 locations on T_1-weighted scans and ventricle-to-brain ratio (slice thickness = 1.5 mm)
AD sample				
34	Cross-sectional, 76 demented patients (AD, VAD, dementia with Lewy bodies) and 26 controls; *APOE* genotype distribution not described	76.5	Total brain, frontal and temporal lobe volumes: no *APOE* effect	Semi-automated segmentation (intraclass corr. = 0.96–0.99, slice thickness = 1 mm)

ICV = Intracranial volume; SPM = statistical parametric mapping; CVLT = California Verbal Learning Test; FTD = frontotemporal dementia; SIENA = structural image evaluation using normalisation of atrophy; VAD = vascular dementia.

Table 5. Ventricular atrophy: *APOE* effects in healthy and AD samples

Reference	Design	Age years	Outcome	Measurement method
Association found				
AD sample				
72	Longitudinal over 16 months, 22 AD, 13 other dementia and 42 cognitive impairment patients: 34 ε4+, 43 ε4–	61.5	Ventricular volume increase over 16 months: ε4+ > ε4– but only for the other dementia group	Manual quantification using a 0.5-cm grid on T_1-weighted scans (slice thickness = 2.8 mm)
Association not found				
Healthy samples				
25	Cross-sectional, 50 patients with age-associated memory impairments: 13 ε4+, 14 ε2ε3, 23 ε3/ε3	65.5	Ventricular system volume: no *APOE* effect	Semi-automated measurement on T_2-weighted scans
64	Cross-sectional, 214 non-demented volunteers: 39 ε4+/+, 175 ε4–/–	60.5 (50–75)	Ventricular temporal horn width, third ventricular ratio, ventricular-to-intracranial volume ratio: no *APOE* effect	Subjective (3-point scale) and objective (temporal horn width, third ventricular ratio, ventricular-to-intracranial volume ratio) on T_1-weighted scans (slice thickness 3 mm)
AD samples				
71	Cross-sectional, 34 AD patients: 4 ε4+/+, 8 ε4+/–, 22 ε3+/+	83	Surface of the temporal horn of lateral ventricle: no *APOE* effect	Manual tracing on one slice of T_1-weighted scan (slice thickness = 10 mm)
73	Cross-sectional, 32 AD patients and 38 controls: 28 ε4+, 42 ε4–	70	Inferior horn of left ventricle: no *APOE* effect	Manual tracing by trained psychiatrists on T_1-weighted scans

Dyck et al. [45] found no overall decrease in rCBF in *APOE* ε4 carriers but reported a greater asymmetry in blood flow (left < right) in non-carrier patients.

Glucose Metabolism

Twelve studies investigated the relationship between cerebral glucose metabolism measured by PET and *APOE* genotype (table 8) at rest (except for 1 functional study). Two studies (pooled n = 126) did not find any association between *APOE* genotype and cerebral glucose metabolism.

Nine studies (pooled n = 693) found a significant association between glucose metabolism and *APOE* genotype with ε4 allele carriers having decreased glucose metabolism mostly in the frontal, temporal and parietal lobes and in the cingulate cortex. Of particular interest was that 3 studies [46–48] which investigated this relationship in first-degree non-demented relatives of AD patients found similar associations. Reiman et al. [48] also found a strong ε4 allele dose effect with homozygous carriers being more affected than heterozygous ones. These findings suggest an early effect of the *APOE* genotype apparently involved in the precursor pathological events leading to AD which are not initially associated with detectable neuropsychological deficits. However, 2 studies hint at the possibility that the *APOE* genotype might precipitate the disease but might not necessarily be involved in its later stages. Lee et al. [49] found a decreased temporal glucose metabolism in mild AD sufferers but not in more severely affected groups, while Hirono et al. [50] found an *APOE* effect in early-onset but not late-onset sufferers.

An asymmetrical effect of the *APOE* genotype also appears to be present, although different studies report somewhat conflicting results with the ε4 allele being associated with a significant decrease in glucose metabolism in the left inferior temporal lobe [49], or a combination of decrease in the right temporal, frontal and occipital cortices and an increase in metabolism in the left temporal and parietal cortices [50].

Discussion

The studies reviewed above differ substantially on a large number of variables, particularly in regard to sample mean age, sample composition (demented vs. non-demented), sample size and the type of measures used. These differences might in part explain some of the incongruent results presented. However, despite these dissimilarities, a number of conclusions can be drawn from these findings.

It is clear that structural brain anomalies detectable by brain imaging are present in *APOE* ε4 carriers compared to non-carriers. Across studies, consistent effects were identified and more salient associations with *APOE* ε4 genotype were: (1) increased hippocampal, amygdalar and cerebral atrophy (particularly in the temporal lobe); (2) decreased cerebral blood flow and glucose metabolism (frontal, temporal, parietal and occipital lobes); (3) an *APOE* dose effect on cerebral atrophy and glucose metabolism; (4) an *APOE* age-dependent effect, and (5) asymmetric effects (right hippocampus and right temporal lobe atrophy, decreased blood flow and glucose metabolism mostly in the left hemisphere).

Table 6. WMHs and grey matter hyperintensities: *APOE* effects in healthy and AD samples

Reference	Design	Age years	Outcome	Measurement method
Association found				
Healthy samples				
74	Cross-sectional, 829 non-demented subjects: 261 ε4+, 568 ε3ε3	72	WMH volume: ε4+ > ε3ε3 (subcortical but not periventricular)	Semi-quantitative rating on T_1- and T_2-weighted scans (3-point scale)
75	Cross-sectional, 145 depressed (non-demented), 42 ε4+ and 103 ε4– and 100 non-depressed subjects, 25 ε4+, 75 ε4–	70	GMH volume: ε4+ > ε4–	Semi-automated measurement on T_2-weighted scans (intraclass corr. = 0.99)
54	Cross-sectional, 929 non-demented subjects: 269 ε4+, 660 ε4–	72	WMH volume (subcortical): in ε4 carriers, plasma amyloid β was positively associated with WMHs but not in non-carriers; same relationship for visually graded periventricular WMHs	Semi-quantitative visual rating on T_2-weighted and PD scans
76	Cross-sectional, 272 community volunteers: 51 ε4/ε3, 184 ε3/ε3, 37 ε2/ε3	60.5	WMH and lacunar lesions rating: ε2/ε3 > ε4/ε3 and ε3/ε3	Visual rating (absent, punctate, early confluent, confluent; κ = 0.9)
AD sample				
77	Cross-sectional, 56 AD patients: 13 ε4+/+, 19 ε4+/–, 24 ε3/ε3	64	WMH volume: subcortical ε4+/+ > ε4+/– and ε3ε3, periventricular ε4+/+ and ε3ε3 > ε4+/–, basal ganglia ε4 +/+ > ε4+/– and ε3ε3	Semi-quantitative visual rating on T_2-weighted scans
Association not found				
Healthy sample				
64	Cross-sectional, 214 non-demented volunteers: 39 ε4+/+, 175 ε4–/–	60.5 (50–75)	No *APOE* effect	Qualitative visual rating (4-point scale)
AD samples				
78	Cross-sectional, 137 demented, 36 memory-impaired and 9 -unimpaired patients: 26 ε4+/+, 82 ε4+/–, 74 ε4–/–	71.5	No *APOE* effect	Visual assessment by one neuroradiologist (present-absent)
79	Cross-sectional, 25 AD, 24 VaD, 22 Lewy body dementia patients: 38 ε4+, 33 ε4–	77.5	No *APOE* effect	Semi-quantitative rating on T_2-weighted scans (6-point scale)
80	Cross-sectional, 141 demented, 30 cognitively impaired, 20 controls: *APOE* allelic distribution not reported	82 (67–96)	No *APOE* effect	Qualitative visual rating (4-point scale)
81	Cross-sectional, 82 AD patients: 8 ε4+/+, 30 ε4+/–, 44 ε3/ε3	72	No *APOE* effect	Semi-quantitative rating on T_2-weighted, PD and FLAIR scans by two neuroradiologists (4-point scale)
82	Cross-sectional, 104 AD patients: 30 ε4+/+, 53 ε4+/–, 21 ε4–/–	74	No *APOE* effect	Visual rating by one neuroradiologist
83	Cross-sectional, 36 AD, 18 MCI, 42 amyloid angiopathy subjects: 37 ε4+, 59 ε4–	75.5	No *APOE* effect	Semi-automated segmentation on FLAIR scans (intraclass corr. = 0.97, interrater reliability = 0.98)
84	Cross-sectional, 131 AD patients: 10 ε4ε4, 59 ε4ε3, 62 ε3/ε3	73.5	No *APOE* effect	Visual rating (intraclass corr. = 0.82)

GMH = Grey matter hyperintensity; PD = proton density; VaD = vascular dementia; FLAIR = fluid-attenuated inversion recovery; MCI = mild cognitive impairment.

Table 7. Cerebral blood flow: *APOE* effects in healthy and AD samples – association found

Reference	Design	Age years	Outcome	Measurement method
Healthy sample				
85	Cross-sectional, 52 frontotemporal degeneration patients: 17 ε4+, 35 ε4–	67.5	Medial frontal cortex, uncus and parahipocampal gyrus: ε4+ < ε4–	SPECT (Tc-ECD)
AD samples				
42	Cross-sectional, 41 AD patients: 27 ε4+, 14 ε4– and 15 controls	71	rCBF right frontal and left occipital lobes: ε4+ < ε4– and controls	SPECT (Tc-HMPAO); dark quiet room
44	Cross-sectional, 58 AD patients: 13 ε4+/+, 24 ε4+/–, 21 –/– and 34 controls	70.5	Left occipital rCBF: ε4+/+ < ε4+/–, ε4–/–, and controls	SPECT (Tc-HMPAO)
43	Longitudinal over 3 years, 31 AD patients: 8 ε4+/+, 13 ε4+/–, 10 ε3+/+ and 8 controls	71.5	rCBF temporal and parietal cortex (bilateral): ε4+/+ and ε4+/– and ε4–/– < controls; left occipital cortex: ε4+/+ and ε4+/– < ε4–/– and controls Decrease in rCBF over 3 years, left parietal: ε4+/– < controls; right occipital: ε4+/+ < controls	SPECT (Tc-HMPAO); dark quiet room
86	Cross-sectional, 30 MCI patients and 30 controls: 17 ε4+, 43 ε4–	70	Cerebral blood flow velocity: MCI ε4+ < MCI ε4– < controls (ε4+ and ε4–)	Transcranial Doppler ultrasonography in anterior and middle cerebral arteries
71	Cross-sectional, 34 AD patients: 4 ε4+/+, 8 ε4+/–, 22 ε3+/+	83	rCBF frontal, temporal and parietal lobes: ε4+ < ε4– and controls	SPECT (^{133}Xe)
45	Cross-sectional, 52 AD patients: 30 ε4+, 22 ε4– and 14 controls	70	rCBF asymmetry (left < right): ε4+ less asymmetric than ε4–; superior parietal lobe rCBF: ε4+ > ε4– and controls	SPECT (Tc-HMPAO); eyes and ears unoccluded, dimly lit room

ECD = Ethyl cysteinate dimer; HMPAO = hexamethylpropylene amine oxime; MCI = mild cognitive impairment.

In support of our first and second hypotheses, these findings show that *APOE* effects were already present in younger non-symptomatic cohorts and are congruent with the progression of the neurodegenerative processes involved in AD described in Braak stages [11]. *APOE* effects described tended to start earlier and have more marked influences in the parahippocampal region before spreading to neighbouring areas, and finally generalising to the whole cortex in older individuals and those suffering from AD. These effects were also stronger in individuals homozygous for *APOE* ε4 [13]. This progression also mirrored that of the cognitive effects associated with the *APOE* genotype. For instance, healthy middle-aged ε4 carriers were shown to have more visual attention deficits [51] and a greater rate of decline in visual attention [52] than non-carriers. In non-demented older adults, the ε4 allele was associated with increased memory complaints and a faster rate of cognitive decline [53], while in AD greater global cognitive deficits have been associated with ε4 carriers.

The cerebral atrophy associated with the *APOE* genotype is consistent with the neuropathology reported in AD, supports a strong association between the *APOE* genotype and AD and is also largely congruent with associated decreases in blood flow and metabolism. It is particularly interesting, and consistent with our third hypothesis, that most of these effects appear to be at least partly dose-dependent with homozygous ε4 carriers being more affected than heterozygous carriers who in turn are more affected than non-carriers.

Findings also supported an association between the *APOE* ε4 allele and WMHs but possibly more so in younger and non-demented cohorts. Positive studies were consistent in showing a relationship between the presence of the ε4 allele and greater WMH volumes, but the location of WMHs seems to also have an effect with more studies reporting an association between subcortical than periventricular WMHs and the *APOE* genotype. One study [54] showed that WMHs were associated with the amyloid β plasma level but only in *APOE* ε4+ carriers, while Skoog et al. [55] showed that decreased levels of cerebrospinal *APOE* (no differentiation between alleles) were lower in individuals with WMHs and in individuals with dementia. This is particularly interesting because new evidence suggests that a lower individual amyloid β plasma level might be an indicator of transition to AD

Table 8. Cerebral glucose metabolism: *APOE* effects in healthy and AD samples

Reference	Design	Age years	Outcome	Measurement method
Association found				
Healthy samples				
46	Cross-sectional, 160 cognitively normal first-degree AD relatives: 36 ε4+/+, 46 ε4+/–, 78 ε4–/–	56	Cingulate, precuneus, parietotemporal and frontal regions: ε4+/+ < ε4+/– < ε4–/–	FDG-PET; at rest, quiet environment, eyes closed
48	Cross-sectional, 33 volunteers: 11 ε4+/+, 6 ε2/ε3, 16 ε3/ε3 with family history of AD	56	Posterior cingulate, parietal, temporal and prefrontal regions: ε4+/+ < ε4–/–	FDG-PET
47	Cross-sectional, 31 cognitively normal first-degree AD relatives: 12 ε4+, 19 ε4–	56	Parietal lobe: ε4+ < ε4– and greater asymmetry in carriers (left > right)	FDG-PET; at rest, eyes and ears unoccluded, low-noise environment
AD samples				
87	Cross-sectional, 83 AD patients: 42 ε4+, 41 ε4– and 16 healthy age-matched controls	66	Temporal and parietal lobes, and posterior cingulate: ε4+ < ε4– < controls	FDG-PET; at rest, eyes closed
50	Cross-sectional, 57 AD patients (early- and late-onset groups): 19 ε4+/+, 38 ε3+/+	69	ε4+ < ε4- in right medial temporal, right basal frontal cortex, and right medial occipital cortex, ε4+ > ε4– in left posterior temporal cortex and left inferior parietal cortex in early-onset AD; no effect in late-onset AD	FDG-PET; at rest, eyes closed, ears unoccluded
49	Cross-sectional, 63 AD patients (3 groups of different severity): 28 ε4+, 35 ε4–	68	Left inferior temporal cortex: ε4+ < ε4– in the very mild AD group, no effect in severer AD groups	FDG-PET; at rest
88	Cross-sectional, 92 AD patients (early- and late-onset groups): 43 ε4+, 49 ε4–	62 (early onset) 77 (late onset)	Basal frontal cortex and hippocampus: ε4+ < ε4– in early-onset but not late-onset group	FDG-PET; at rest, eyes closed, ears unoccluded
89	Cross-sectional, 37 amnestic MCI: 16 ε4+, 21 ε4–	68	Inferior frontal and anterior cingulate cortex: ε4+ < ε4–	FDG-PET; at rest, eyes closed, ears unoccluded
	Longitudinal, 8 converters and 29 non-converters to AD after 1 year		Together glucose metabolism and *APOE* genotype are excellent predictors of conversion to AD: 100% sensitivity, 90% specificity, 94% accuracy	
90, 91	Cross-sectional, 86 AD patients: 13 ε4ε4, 27 ε4ε3, 46 ε3/ε3 and 35 healthy age-matched controls	74	Frontal lobe, right occipital lobe and anterior cingulate cortex: ε4ε4 < ε4ε3 < ε3ε3 < controls	FDG-PET; at rest, eyes closed, ears unoccluded
Association not found				
AD samples				
92	Cross-sectional, 31 AD patients and 12 patients with memory complaints: 21 ε4+, 25 ε4–	60 (41–80)	No *APOE* effect (comparing measurements with normalised values)	FDG-PET; standardised to the sensory-motor area
93	Cross-sectional, 83 AD patients: ε4+/+, 39 ε4+/–, 35 ε4–	69.5	No *APOE* effect (correlation with number of allele)	FDG-PET; at rest, eyes closed, ears unoccluded

FDG = Fluorodeoxyglucose; MCI = mild cognitive impairment.

[56]. These findings might indicate that decreased cerebral levels and/or less effective variants (ε4) of the *APOE* genotype might be less efficient at transporting amyloid β leading to decreased plasma levels and increased amyloid plaque [57].

One of the more important findings is that the *APOE* genotype appears to be more influential in the early stages of the degenerative processes and might disappear or be masked in the later development of AD. A number of studies have found significant effects of *APOE* in younger individuals with no or less cognitive impairment while other studies failed to demonstrate any effect in older or more impaired samples. Particularly significant is also the fact that *APOE* ε4 carriers seem to be at great-

er risk of developing early-onset AD. Some effects, such as the increase in blood flow and metabolism, appear to be compensatory and might be a response to less efficient degenerative brain structures in some cerebral regions in ε4 carriers and might disappear in the more advanced stages of AD.

It is not completely clear whether the reported asymmetrical findings in the left and right hemispheres are epiphenomena or whether they are directly related to the *APOE* genotype. How these asymmetries might affect neuropsychological functioning is not clear either. Consistent asymmetrical effects have been reported in AD with the left hemisphere being affected earlier and/or more strongly than the right hemisphere [58]. In the present review the ε4 allele seems to be associated with greater atrophy in the right hemisphere while cerebral blood flow and metabolism seem to be more decreased in the left hemisphere. These somewhat incongruent findings might suggest that the *APOE* atrophy effect might be dissociated from other lateralised effects present in AD and which may be compounded by possible *APOE* effects affecting blood flow and metabolism. In addition, laterality effects in glucose metabolism studies were not completely consistent with one study reporting increased metabolism in the left hemisphere which, as suggested by Small et al. [47], might be due to compensatory mechanisms attempting to drive harder cerebral areas more affected by the early stages of neurodegenerative processes involved in dementia. However, a functional study [59] found a decreased glucose metabolism during a non-verbal memory task in non-symptomatic APOE ε4 carriers compared to non-carriers at risk of AD (mean age 68 years) particularly in the left frontal and temporal lobes. Consequently, differences between groups (Lee et al. [49] demonstrated their findings in very mild AD patients, while Hirono et al. [50] studied early- and late-onset AD patients) might explain these divergent results.

A particular mention should be made of the occipital lobe which is usually regarded as mostly preserved even in the more advanced stages of AD. It can be seen here that consistent reports of occipital atrophy, and decreased cerebral blood flow and metabolism in association with the *APOE* ε4 genotype suggest that this cortical area might also be significantly affected by the neurodegenerative processes associated with AD and more research should be targeted at the neurological deficits associated with these changes.

It has been suggested that the *APOE* ε2 genotype might be a protective factor in neurodegeneration [26]. The findings reviewed above do not support this theory and for some even contradict it [25, 29]. It is possible that the ε2 allele contributes to the heterogeneity of results found in studies investigating *APOE* effects. To minimise such confounds, it is important, when possible, to analyse separately the effect of ε4ε2 and ε4ε3 genotypes. It is likely that inconsistencies in the literature are partly due to collapsing of genotypes with differing effects, due to small sample sizes.

In summary, strong and mostly consistent evidence is available from imaging studies linking *APOE* genotypes and the neurodegenerative processes associated with ageing and dementia. However, a greater number of large and well-controlled studies are required to further assess the time course and mechanisms underlying this association.

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References

1 Blacker D, et al: ApoE-4 and age at onset of Alzheimer's disease: The NIMH genetics initiative. Neurology 1997;48:139–147.
2 Gong J-S, et al: Apolipoprotein E (ApoE) isoform-dependent lipid release from astrocytes prepared from human ApoE3 and ApoE4 knock-in mice. J Biol Chem 2002;277:29919–29926.
3 Martins CA, et al: APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model. Neurology 2005;65:1888–1893.
4 Fazekas F, et al: The impact of our genes: consequences of the apolipoprotein E polymorphism in Alzheimer disease and multiple sclerosis. J Neurol Sci 2006;245:35–39.
5 Horsburgh K, et al: The role of apolipoprotein E in Alzheimer's disease, acute brain injury and cerebrovascular disease: evidence of common mechanisms and utility of animal models. Neurobiol Aging 2000;21:245–255.
6 Smith JD: Apolipoproteins and aging: emerging mechanisms. Ageing Res Rev 2002;1:345–365.
7 Savitz J, et al: Apolipoprotein E variants and cognition in healthy individuals: a critical opinion. Brain Res Rev 2006;51:125–135.
8 Jorm AF, et al: APOE genotype and cognitive functioning in a large age-stratified population sample. Neuropsychology 2007;21:1–8.
9 Teter B: Life-span influences of apoE4 on CNS function. Neurobiol Aging 2006;28:693–703.
10 Braak H, et al: Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol (Berl) 2006;112:389–404.
11 Braak H, et al: Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl) 1991;82:239–259.
12 Ohm TG, et al: Close-meshed prevalence rates of different stages as a tool to uncover the rate of Alzheimer's disease-related neurofibrillary changes. Neuroscience 1995;64:209–217.
13 Ohm TG, et al: Apolipoprotein E isoforms and the development of low and high Braak stages of Alzheimer's disease-related lesions. Acta Neuropathol 1999;98:273–280.
14 Bigler ED, et al: Dementia, quantitative neuroimaging, and apolipoprotein E genotype. Am J Neuroradiol 2000;21:1857–1867.
15 Hashimoto M, et al: Apolipoprotein E epsilon 4 and the pattern of regional brain atrophy in Alzheimer's disease. Neurology 2001;57:1461–1466.
16 Lehtovirta M, et al: Volumes of hippocampus, amygdala and frontal lobe in Alzheimer patients with different apolipoprotein E genotypes. Neuroscience 1995;67:65–72.
17 Mori E, et al: Accelerated hippocampal atrophy in Alzheimer's disease with apolipoprotein E epsilon 4 allele. Ann Neurol 2002;51:209–214.
18 Lemaitre H, et al: No epsilon 4 gene dose effect on hippocampal atrophy in a large MRI database of healthy elderly subjects. Neuroimage 2005;24:1205–1213.
19 Yamaguchi S, et al: Temporal progression of hippocampal atrophy and apolipoprotein E gene in Alzheimer's disease. J Am Geriatr Soc 1996;44:216–217.
20 Fleisher A, et al: Sex, apolipoprotein E epsilon 4 status, and hippocampal volume in mild cognitive impairment. Arch Neurol 2005;62:953–957.
21 Lind J, et al: Reduced hippocampal volume in non-demented carriers of the apolipoprotein E epsilon 4: relation to chronological age and recognition memory. Neurosci Lett 2006;396:23–27.
22 Soininen H, et al: Decreased hippocampal volume asymmetry on MRIs in nondemented elderly subjects carrying the apolipoprotein E epsilon 4 allele. Neurology 1995;45:391–392.
23 Tohgi H, et al: Reduced size of right hippocampus in 39- to 80-year-old normal subjects carrying the apolipoprotein E epsilon 4 allele. Neurosci Lett 1997;236:21–24.
24 Geroldi C, et al: Apolipoprotein E genotype and hippocampal asymmetry in Alzheimer's disease: a volumetric MRI study. J Neurol Neurosurg Psychiatry 2000;68:93–96.
25 Serra-Grabulosa JM, et al: Apolipoproteins E and C1 and brain morphology in memory impaired elders. Neurogenetics 2003;4:141–146.
26 Talbot C, et al: Protection against Alzheimer's disease with apoE ε2. Lancet 1994;343:1432–1433.
27 Kaur M, et al: APOE2 and consanguinity: a risky combination for Alzheimer's disease. J Alzheimers Dis 2005;8:293–297.
28 van Duijn CM, et al: The apolipoprotein E epsilon 2 allele is associated with an increased risk of early onset Alzheimer's disease and a reduced survival. Ann Neurol 1995;37:605–610.
29 den Heijer T, et al: Hippocampal, amygdalar, and global brain atrophy in different apolipoprotein E genotypes. Neurology 2002;59:746–748.
30 Barboriak DP, et al: Hippocampal sulcal cavities on MRI: relationship to age and apolipoprotein E genotype. Neurology 2000;54:2150–2153.
31 Du AT, et al: Age effects on atrophy rates of entorhinal cortex and hippocampus. Neurobiol Aging 2006;27:733–740.
32 Geroldi C, et al: APOE-epsilon 4 is associated with less frontal and more medial temporal lobe atrophy in AD. Neurology 1999;53:1825–1832.
33 Juottonen K, et al: Major decrease in the volume of the entorhinal cortex in patients with Alzheimer's disease carrying the apolipoprotein E epsilon 4 allele. J Neurol Neurosurg Psychiatry 1998;65:322–327.
34 Barber R, et al: MRI volumetric study of dementia with Lewy bodies – A comparison with AD and vascular dementia. Neurology 2000;54:1304–1309.
35 Enzinger C, et al: Risk factors for progression of brain atrophy in aging – Six-year follow-up of normal subjects. Neurology 2005;64:1704–1711.
36 Yasuda M, et al: Apolipoprotein E epsilon 4 allele and whole brain atrophy in late-onset Alzheimer's disease. Am J Psychiatry 1998;155:779–784.
37 DeCarli C, et al: Impact of apolipoprotein E epsilon 4 and vascular disease on brain morphology in men from the NHLBI twin study. Stroke 1999;30:1548–1553.
38 Carmelli D, et al: The joint effect of apolipoprotein E epsilon 4 and MRI findings on lower-extremity function and decline in cognitive function. J Gerontol Ser A Biol Sci Med Sci 2000;55:M103–M109.
39 Boccardi M, et al: APOE and modulation of Alzheimer's and frontotemporal dementia. Neurosci Lett 2004;356:167–170.
40 Gunning-Dixon FM, et al: The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. Neuropsychology 2000;14:224–232.
41 Wahlund LO, et al: White matter hyperintensities in dementia: does it matter? Magn Reson Imaging 1994;12:387–394.
42 Hogh P, et al: Single photon emission computed tomography and apolipoprotein E in Alzheimer's disease: impact of the epsilon 4 allele on regional cerebral blood flow. J Geriatr Psychiatry Neurol 2001;14:42–51.
43 Lehtovirta M, et al: Longitudinal SPECT study in Alzheimer's disease: relation to apolipoprotein E polymorphism. J Neurol Neurosurg Psychiatry 1998;64:742–746.
44 Lehtovirta M, et al: SPECT and MRI analysis in Alzheimer's disease: relation to apolipoprotein E epsilon 4 allele. J Neurol Neurosurg Psychiatry 1996;60:644–649.
45 van Dyck CH, et al: Absence of an apolipoprotein E epsilon 4 allele is associated with increased parietal regional cerebral blood flow asymmetry in Alzheimer disease. Arch Neurol 1998;55:1460–1466.
46 Reiman EM, et al: From The cover: correlations between apolipoprotein E ε4 gene dose and brain-imaging measurements of regional hypometabolism. PNAS 2005;102:8299–8302.
47 Small GW, et al: Apolipoprotein E type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer disease. JAMA 1995;273:942–947.
48 Reiman EM, et al: Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. N Engl J Med 1996;334:752–758.
49 Lee KU, et al: Influence of the apolipoprotein E type 4 allele on cerebral glucose metabolism in Alzheimer's disease patients. J Neuropsychiatry Clin Neurosci 2003;15:78–83.
50 Hirono N, et al: The effect of APOE epsilon 4 allele on cerebral glucose metabolism in AD is a function of age at onset. Neurology 2002;58:743–750.
51 Greenwood PM, et al: Genetics and visual attention: selective deficits in healthy adult carriers of the epsilon 4 allele of the apolipoprotein E gene. Proc Natl Acad Sci USA 2000;97:11661–11666.
52 Greenwood PM, et al: Scaling of visuospatial attention undergoes differential longitudinal change as a function of APOE genotype prior to old age: results from the NIMH BIOCARD study. Neuropsychology 2005;19:830–840.
53 Dik MG, et al: Memory complaints and APOE-epsilon 4 accelerate cognitive decline in cognitively normal elderly. Neurology 2001;57:2217–2222.
54 van Dijk EJ, et al: Plasma amyloid beta, apolipoprotein E, lacunar infarcts, and white matter lesions. Ann Neurol 2004;55:570–575.
55 Skoog I, et al: Apolipoprotein E in cerebrospinal fluid in 85-year-old subjects. Relation to dementia, apolipoprotein E polymorphism, cerebral atrophy, and white matter lesions. Arch Neurol 1997;54:267–272.

56 Pesaresi M, et al: Plasma levels of beta-amyloid (1–42) in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging 2006;27:904–905.
57 Russo C, et al: Opposite roles of apolipoprotein E in normal brains and in Alzheimer's disease. PNAS 1998;95:15598–15602.
58 Thompson PM, et al: Dynamics of gray matter loss in Alzheimer's disease. J Neurosci 2003;23:994–1005.
59 Scarmeas N, et al: Altered PET functional brain responses in cognitively intact elderly persons at risk for Alzheimer disease (carriers of the epsilon 4 allele). Am J Geriatr Psychiatry 2004;12:596–605.
60 den Heijer T, et al: Alcohol intake in relation to brain magnetic resonance imaging findings in older persons without dementia. Am J Clin Nutr 2004;80:992–997.
61 Farlow MR, et al: Impact of APOE in mild cognitive impairment. Neurology 2004;63:1898–1901.
62 Wang PN, et al: The MCI study in Taiwan. Acta Neurol Taiwan 2006;15:66–68.
63 Reiman EM, et al: Hippocampal volumes in cognitively normal persons at genetic risk for Alzheimer's disease. Ann Neurol 1998;44:288–291.
64 Schmidt H, et al: Apolipoprotein E ε4 allele in the normal elderly: neuropsychologic and brain MRI correlates. Clin Genet 1996;50:293–299.
65 Basso M, et al: Apolipoprotein E epsilon 4 is associated with atrophy of the amygdala in Alzheimer's disease. Neurobiol Aging 2006;27:1416–1424.
66 Jack CR, et al: Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. Neurology 1998;51:993–999.
67 Jack CR, et al: Hippocampal atrophy and apolipoprotein E genotype are independently associated with Alzheimer's disease. Ann Neurol 1998;43:303–310.
68 Espeseth T, et al: Interactive effects of APOE and CHRNA4 on attention and white matter volume in healthy middle-aged and older adults. Cogn Affect Behav Neurosci 2006;6:31–43.
69 Pennanen C, et al: The effect of apolipoprotein polymorphism on brain in mild cognitive impairment: a voxel-based morphometric study. Dementia Geriatr Cogn Disord 2006;22:60–66.
70 Wishart HA, et al: Regional brain atrophy in cognitively intact adults with a single APOE epsilon 4 allele. Neurology 2006;67:1221–1224.
71 Tanaka S, et al: Inferior temporal lobe atrophy and APOE genotypes in Alzheimer's disease – X-ray computed tomography, magnetic resonance imaging and Xe-133 SPECT studies. Dementia Geriatr Cogn Disord 1998;9:90–98.
72 Wahlund LO, et al: Inheritance of the ApoE epsilon 4 allele increases the rate of brain atrophy in dementia patients. Dementia Geriatr Cogn Disord 1999;10:262–268.
73 Yoshida S, et al: Clinical features and alterations in the inferior horn sizes in lateral ventricle in Alzheimer's patients with different ApoE genotype in Japanese population. Progr Neuropsychopharmacol Biol Psychiatry 2001;25:1377–1384.
74 de Leeuw FE, et al: Interaction between hypertension, apoE, and cerebral white matter lesions. Stroke 2004;35:1057–1060.
75 Steffens DC, et al: Apolipoprotein E genotype and subcortical vascular lesions in older depressed patients and control subjects. Biol Psychiatry 2003;54:674–681.
76 Schmidt R, et al: Apolipoprotein E polymorphism and silent microangiopathy-related cerebral damage: results of the Austrian Stroke Prevention Study. Stroke 1997;28:951–956.
77 Bronge L, et al: White matter lesions in Alzheimer patients are influenced by apolipoprotein E genotype. Dementia Geriatr Cogn Disord 1999;10:89–96.
78 Amar K, et al: Are genetic factors important in the aetiology of leukoaraiosis? Results from a memory clinic population. Int J Geriatr Psychiatry 1998;13:585–590.
79 Barber R, et al: Apolipoprotein E epsilon 4 allele, temporal lobe atrophy, and white matter lesions in late-life dementias. Arch Neurol 1999;56:961–965.
80 Bigler ED, et al: Dementia, asymmetry of temporal lobe structures, and apolipoprotein E genotype: relationships to cerebral atrophy and neuropsychological impairment. J Int Neuropsychol Soc 2002;8:925–933.
81 Bracco L, et al: Alzheimer's disease: role of size and location of white matter changes in determining cognitive deficits. Dementia Geriatr Cogn Disord 2005;20:358–366.
82 Doody RS, et al: Does APO epsilon 4 correlate with MRI changes in Alzheimer's disease? J Neurol Neurosurg Psychiatry 2000;69:668–671.
83 Gurol ME, et al: Plasma β-amyloid and white matter lesions in AD, MCI, and cerebral amyloid angiopathy. Neurology 2006;66:23–29.
84 Hirono N, et al: Effect of the apolipoprotein E epsilon 4 allele on white matter hyperintensities in dementia. Stroke 2000;31:1263–1268.
85 Borroni B, et al: Functional correlates of apolipoprotein E genotype in frontotemporal lobar degeneration. BMC Neurol 2006;6:31.
86 Sun ZW, et al: Decreased cerebral blood flow velocity in apolipoprotein E epsilon 4 allele carriers with mild cognitive impairment. Eur J Neurol 2007;14:150–155.
87 Drzezga A, et al: Cerebral glucose metabolism in patients with AD and different APOE genotypes. Neurology 2005;64:102–107.
88 Mosconi L, et al: Metabolic interaction between ApoE genotype and onset age in Alzheimer's disease: implications for brain reserve. J Neurol Neurosurg Psychiatry 2005;76:15–23.
89 Mosconi L, et al: MCI conversion to dementia and the APOE genotype: a prediction study with FDG-PET. Neurology 2004;63:2332–2340.
90 Mosconi L, et al: Brain metabolic decreases related to the dose of the ApoE ε4 allele in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2004;75:370–376.
91 Mosconi L, et al: Age and ApoE genotype interaction in Alzheimer's disease: an FDG-PET study. Psychiatry Res Neuroimag 2004;130:141–151.
92 Corder EH, et al: No difference in cerebral glucose metabolism in patients with Alzheimer disease and differing apolipoprotein E genotypes. Arch Neurol 1997;54:273–277.
93 Hirono N, et al: Lack of association of apolipoprotein E epsilon 4 allele dose with cerebral glucose metabolism in Alzheimer disease. Alzheimer Dis Assoc Disord 1998;12:362–367.