APOE related alterations in cerebral activation even at college age

N Scarmeas, C G Habeck, J Hilton, K E Anderson, J Flynn, A Park, Y Stern


Methods: Using H215O positron emission tomography (PET), imaging was carried out in 20 healthy young adults (age 19 to 28 years; four ε4 carriers and 16 non-ε4 carriers) during a non-verbal memory task. Voxel-wise multiple regression analyses were undertaken, with the activation difference PET counts as the dependent variable and the APOE genotype as the independent variable.

Results: Brain regions were identified where ε4 carriers showed significantly lower or higher activation than non-carriers.

Conclusions: The results suggest that APOE dependent modulation of cerebral flow may be present even at a young age. This may reflect an APOE related physiological heterogeneity which may or may not predispose to brain disease in the ensuing decades or, less likely, the effect of very early Alzheimer’s disease related pathological changes.

Effects of the APOE genotype on lipid metabolism, blood pressure, atherosclerosis, ischaemic heart disease, myocardial infarction, and cognitive performance in type I diabetes have been documented in very young subjects or even in children. Animal studies have indicated that the APOE genotype seems to affect the stress response and spatial memory and to regulate synaptic plasticity and long term potentiation in the hippocampus of young mice. It is therefore conceivable that APOE related alterations in cerebral physiology may exist even from a very young age. The association between the APOE genotype and various medical conditions have been documented at a very young age. The association between the APOE genotype and cognitive performance varies at different ages. APOE related changes in brain activation have been recently reported for middle aged and elderly subjects.

Objective: To explore APOE related alterations during cognitive activation in a population of young adults.

Methods: Using H215O positron emission tomography (PET), imaging was carried out in 20 healthy young adults (age 19 to 28 years; four ε4 carriers and 16 non-ε4 carriers) during a non-verbal memory task. Voxel-wise multiple regression analyses were undertaken, with the activation difference PET counts as the dependent variable and the APOE genotype as the independent variable.

Results: Brain regions were identified where ε4 carriers showed significantly lower or higher activation than non-carriers.

Conclusions: The results suggest that APOE dependent modulation of cerebral flow may be present even at a young age. This may reflect an APOE related physiological heterogeneity which may or may not predispose to brain disease in the ensuing decades or, less likely, the effect of very early Alzheimer’s disease related pathological changes.
MNI coordinates were converted to standard Talairach brain atlas coordinates. A search for the closest grey matter Brodmann areas was carried out using the “Talairach Daemon” database server http://biad02.uthscsa.edu/RIC_WWW.data/Components/talairach/talairachdaemon.html.

RESULTS

Age, education, and neuropsychological performance did not differ among the groups (table 1). There was no association between APOE genotype and ethnicity: e4 carriers, three white and one African American; non-e4 carriers, 11 white, one African American, one Hispanic, and three other ethnicities ($\chi^2 = 2.1$, $p = 0.54$). All e4 carriers and seven non-e4 carriers were male ($p = 0.09$, Fisher’s exact test). Neither shape recognition accuracy nor shape list length were related to the APOE genotype.

In comparison with the subjects without the e4 allele, e4 carriers showed significant deactivation in right superior temporal and left fusiform gyri (table 2, fig 2, fig 3). E4 carriers showed significantly higher activation in the left middle temporal and right transverse temporal gyri (table 2, fig 2, fig 3). The results were also significant in the non-parametric test. Because of the slight (although non-significant) imbalance in sex distribution, we conducted supplementary analyses including sex as a covariate; the results were essentially unchanged.

For all 20 subjects combined there were significant activations ($t$ values ranging from 4.51 to 8.11) during the TD as compared to the SD condition in bilateral occipital-parietal areas (Brodmann areas (BA) 18, 19; middle occipital gyri, cuneus and fusiform gyri), right inferior parietal lobule (BA 40), right inferior (BA 9), and left superior (BA 10) and middle frontal (BA 9) gyri. Significant deactivations ($t$ values

Table 1 Demographic and neuropsychological performance information by APOE group

<table>
<thead>
<tr>
<th></th>
<th>No e4 allele c2/c3 (n = 2), c3/c3 (n = 14)</th>
<th>Presence of e4 allele c3/c4 (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) Range</td>
<td>Mean (SD) Range</td>
</tr>
<tr>
<td>Age (years)</td>
<td>23.1 (2.25) 19 to 28</td>
<td>25.3 (1.23) 24 to 27</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.8 (1.83) 13 to 20</td>
<td>17.0 (2.45) 14 to 19</td>
</tr>
<tr>
<td>mMMS</td>
<td>55.6 (1.03) 53 to 57</td>
<td>56.0 (1.41) 54 to 57</td>
</tr>
<tr>
<td>NART IQ</td>
<td>120.8 (3.19) 115.2 to 126.6</td>
<td>122.3 (4.64) 115.8 to 125.7</td>
</tr>
<tr>
<td>WAIS-R vocabulary</td>
<td>13.6 (1.37) 10 to 15</td>
<td>12.5 (2.38) 9 to 14</td>
</tr>
<tr>
<td>SRT total recall</td>
<td>59.1 (6.31) 49 to 69</td>
<td>55.0 (8.83) 43 to 63</td>
</tr>
<tr>
<td>SRT delayed recall</td>
<td>10.4 (1.50) 7 to 12</td>
<td>9.5 (1.73) 8 to 11</td>
</tr>
<tr>
<td>WAIS-R digit symbol</td>
<td>12.5 (2.94) 6 to 19</td>
<td>10.8 (4.27) 5 to 14</td>
</tr>
<tr>
<td>Recognition accuracy (% of shapes)</td>
<td>0.81 (0.11) 0.55 to 0.95</td>
<td>0.79 (0.13) 0.61 to 0.92</td>
</tr>
<tr>
<td>TD shape list length</td>
<td>14.9 (6.69) 5 to 35</td>
<td>14.8 (4.92) 10 to 19</td>
</tr>
</tbody>
</table>

Student’s $t$ test was used for $p$ value calculations.

mMMS, modified mini-mental state examination; NART IQ, Nelson adult reading test IQ; SRT, selective reminding test; TD, titrated demand; WAIS-R, Wechsler adult intelligence scale-revised.
4.69 to 14.15) during the TD (as compared to SD) condition were noted in the anterior cingulate area (BA 32), bilateral temporal areas (BA 21, 22, 39; superior and middle temporal gyri), bilateral parietal areas (BA 40, 39; inferior parietal lobule and angular gyrus), bilateral insula (BA 13), bilateral frontal (BA 11, 9, 47; medial, middle and inferior frontal gyri), left fusiform, and lingual gyri (BA 20, 18), and putamen. There was no overlap between the above areas and regions where the cognitive task condition × APOE interaction was significant.

### Table 2
Areas where significant associations between brain activation differences (TD – SD) and APOE (presence versus absence of e4) were detected (p<0.05 Bonferroni corrected) in the SPM analyses

<table>
<thead>
<tr>
<th>Talairach Coordinates</th>
<th>t Values (df = 18)</th>
<th>Cluster size</th>
<th>Location (Brodmann’s area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Areas where e4 carriers showed lower rCBF activation</td>
<td>53 10 -10</td>
<td>5.5</td>
<td>24</td>
</tr>
<tr>
<td>Areas where e4 carriers showed higher rCBF activation</td>
<td>-53 -36 -27</td>
<td>5.3</td>
<td>20</td>
</tr>
<tr>
<td>Areas where e4 carriers showed areas of significantly different activation (either higher or lower) during the non-verbal memory task. These differences were not a reflection of task difficulty (which was equated in our experimental design) but indicate memory related altered cerebral physiology in young subjects with the e4 allele.</td>
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</table>

**DISCUSSION**

We observed differences in brain activation in healthy young subjects with different APOE genotypes. College age healthy e4 carriers, although cognitively indistinguishable from non-e4 carriers, showed areas of significantly different activation (either higher or lower) during the non-verbal memory task. These differences were not a reflection of task difficulty (which was equated in our experimental design) but indicate memory related altered cerebral physiology in young subjects with the e4 allele.

There are known early biochemical changes in neuronal processes and synapses, long before structural Alzheimer’s disease pathology is detected. It is conceivable that these changes may be manifested in rCBF activation studies. It is also known that symptoms of Alzheimer’s disease are preceded by a period of unknown duration during which neuropathological alterations accumulate in the brain without associated memory loss or other detectable cognitive change. In a neuropathological study of 105 necropsy cases who showed no signs of dementia, abnormally high brain β amyloid levels were reported for e4 carriers as young as 40 years of age. That study concluded that the e4 allele predisposes the carriers to begin accumulating β amyloid earlier in life than non-carriers. In another study, the e4 allele was associated with the presence of neurofibrillary tangle changes in 44 necropsy cases of young subjects (mean age 38 years, range 22 to 46). The usual pattern seen in PET imaging of Alzheimer patients includes parietal, temporal, cingulate, and sometimes prefrontal hypometabolism or hypoperfusion. The e4 related differences in activation were localised in the temporal areas in our study. Thus incipient Alzheimer’s disease type pathology may be present in e4 carriers even from a very young age, while the brain preserves enough redundancy/efficiency to avoid failure in clinical cognitive performance.

However, several considerations make this possibility less plausible. The fact that the APOE related differences in activation are detected at such a young age (four to five decades before the possible onset of dementia) weakens the hypothesised link with Alzheimer’s disease. The spatial extend of differences in activation between e4 carriers and non-carriers is small and both increased and decreased activation was noted for e4 carriers. Most resting flow or metabolism studies have reported decreased signal at parietal association areas but we did not detect differences in this location. The e4 allele’s presence is not equivalent to early Alzheimer’s disease, and a significant proportion of e4 heterozygotes will never develop Alzheimer’s disease. It has been proposed that e4 facilitates rather than causes the disorder and e4 has been implicated in impaired brain repair mechanisms which may place subjects at risk for either Alzheimer’s disease or other brain diseases. Important direct effects of the e4 allele on the nervous system include impaired neuroregeneration within the dentate gyrus and increased vulnerability to exogenous neurotoxins.

![Figure 2](https://www.jnnp.com)
observed activation pattern of ε4 carriers in their twenties may be the early signature of an APOE dependent alteration in brain physiology which could result in greater vulnerability to environmental effects (such as traumatic brain injury or other insult) later in life. It is also conceivable that differences in cerebral activation may not be strictly APOE related but may be present as a function of many neurally expressed genes other than APOE. Thus the detected activation differences may reflect an APOE dependent physiological heterogeneity which may not necessarily lead to disease.

In PET studies during rest, the inheritance of the ε4 allele has been associated with decreased parietal, temporal, cingulate, and prefrontal metabolism (as with the PET pattern seen in Alzheimer’s disease) in middle aged adults with a family history of Alzheimer’s disease. Resting imaging studies in young people have revealed decreased temporal, parietal, cingulate, and prefrontal metabolism or perfusion for the ε4 carriers. All detected differences in activation in our study were localised to the temporal regions where alterations in resting metabolism or flow have been noted for both middle aged and young ε4 carriers.

Only four previous studies have investigated APOE related brain activation, with mixed results. One study reported increases in the extent and intensity of activation during learning and recall periods in (among other regions) temporal areas in middle aged and elderly ε4 allele carriers, which was interpreted as an attempt to ameliorate the effects of reduced function in the networks that normally operate during the task. We also noted increased activation for the ε4 carriers in temporal areas. However, unlike the above study, we also found areas of decreased activation for the ε4 carriers. Decreased activation for ε4 carriers has been reported in two other studies—one of middle aged women with at least one first degree relative with Alzheimer’s disease during a letter fluency task and one of cognitively intact elderly people while performing the same non-verbal memory task. As compared with the above two studies, the locations of decreased activation in the present study were less extended and spatially close (but not identical). Previously reported increased activations for ε4 carriers in prefrontal or parietal areas were not noted in our study. In contrast to previous reports, no APOE related differences were detected in another study of elderly subjects using a verbal working memory task at various levels of task difficulty. The investigators concluded that the effect of APOE is specific to episodic encoding and not related to general task difficulty. We detected APOE related differences in our study despite having titrated shape list length, which supports the above notion that the association between APOE genotype and cerebral activation does not seem to be equated to task difficulty.

Many factors may account for discrepancies in the findings between the present and previous activation studies: different imaging modes (all but one previous studies used BOLD-fMRI, where the signal is the result of a complex interaction between changes not only of blood flow but also of blood volume and oxygen consumption accompanying neural activity), differences in power (more spatially restricted activations or deactivations in the current study may be the result of fewer subjects or different relative proportions of homozygotes to heterozygotes), and differences among the
This is the first report indicating that e4 allele carriers have alterations in brain activation even at very young age when behavioural, cognitive, or clinical evidence of disease is absent. Although the results were similar in a sex adjusted model, the absence of sex matching could be a confounding factor. Because of the relatively small number of participants (in particular for the e4 group) the results can only be viewed as preliminary and they should be confirmed in a larger study. However, the significant associations noted indicate that there were effects strong enough to be demonstrable even with our conservative approach to type I error.

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Competing interests: none declared

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