



Published in final edited form as:

JAMA. 2003 September 24; 290(12): 1581–1582. doi:10.1001/jama.290.12.1581.

## APOE Genotype and Cerebral Blood Flow in Healthy Young Individuals

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### To the Editor

Several epidemiologic studies have found an association between the presence of an apolipoprotein E (*APOE*)  $\epsilon 4$  allele and increased risk for Alzheimer disease (AD). Although 2 brain imaging studies of middle-aged and elderly individuals have found that the  $\epsilon 4$  allele is associated with an AD-like pattern on positron emission tomography (PET) brain scans,<sup>1,2</sup> we are not aware of any study that has examined this association in young individuals.

### Methods

We recruited 18 college-age individuals who were without significant medical problems, as determined by medical, neurologic, psychiatric, and neuropsychological evaluations, as well as by magnetic resonance imaging of the brain. After obtaining informed consent, we determined the  $\epsilon 4$  allele status of each individual. After providing informed consent, all participants waived their right to be informed of these results. Participants then underwent resting  $H_2^{15}O$  PET scans of the brain to determine resting relative cerebral blood flow (rCBF). The Statistical Parametric Mapping 1999 program was used to implement standard steps for the PET images of each participant. PET counts, proportionally scaled by the global mean, were used as a surrogate of resting rCBF. Voxel-wise *t* statistics for between-group comparisons were computed, with *P* values for multiple comparisons adjusted by the Bonferroni correction.

### Results

Three of the 18 participants were found to be carriers of the  $\epsilon 4$  allele, while the other 15 did not have the allele. Carriers were of similar age than noncarriers (26 vs 23 years,  $P=.07$ ), education (17.3 vs 16.5,  $P=.56$ ) and sex ( $P=.13$ ). Neuropsychological performance did not differ between the groups for the Mini-Mental State Examination (29.2 vs 28.9,  $P=.46$ ), Nelson Adult Reading Test intelligence quotient (121.3 vs 119.9,  $P=.60$ ), Wechsler Adult Intelligence Scale-Revised vocabulary subtest (12.0 vs 12.8,  $P=.51$ ), digit symbol subtest (11.7 vs 12.7,  $P=.62$ ), and Selective Reminding Test delayed recall score (9.7 vs 10.5,  $P=.35$ ).

Compared with individuals without the  $\epsilon 4$  allele,  $\epsilon 4$  carriers exhibited significantly lower resting rCBF in the left and right inferior temporal gyri, while resting rCBF was higher in the left insula, right supramarginal gyrus, and the inferior occipital gyrus (Figure). The results were unchanged after controlling for age.

## Comment

Reiman et al<sup>2</sup> found that the left and right inferior temporal regions were among the 7 regions with the greatest reductions in cerebral glucose metabolism among adults with the  $\epsilon 4$  allele. These bilateral inferior temporal regions that they noted in the older individuals overlap with the areas of reduced rCBF in our younger individuals. The significant associations in our data indicate that despite the small number of individuals in the  $\epsilon 4$  group (which is consistent with the proportions of the *APOE* polymorphisms in the population) the effects were strong enough to be demonstrable.

The  $\epsilon 4$  allele has been implicated in impaired brain repair mechanisms<sup>3</sup> that place individuals at risk for either AD or other brain diseases (eg, worse cognitive sequelae after traumatic brain injury). The observed rCBF pattern of  $\epsilon 4$  carriers (which were cognitively indistinguishable from the non- $\epsilon 4$  carriers) may be the early signature of an *APOE*-dependent alteration in brain function. This might result in greater vulnerability to genetic or environmental effects later in life. Therefore it is conceivable that some of these young participants carrying the  $\epsilon 4$  allele may be more susceptible to AD, traumatic brain injury, or other brain insult.

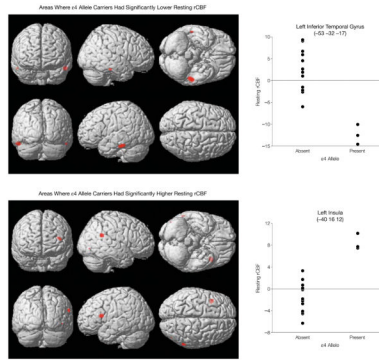
Alternatively, it is conceivable that brain regions where significant hypoperfusion was detected already may have been affected by AD pathology. Abnormally high levels of A $\beta$  in the brain have been reported among carriers of the  $\epsilon 4$  allele as young as 40 years,<sup>4</sup> and neurofibrillary tangles have been found in carriers as young as 22 years.<sup>5</sup> The more spatially extended PET deficits that have been noted in elderly carriers of the  $\epsilon 4$  allele<sup>1,2</sup> may suggest a progressive pattern.

It also is possible that methodological differences between the studies may account for the somewhat inconsistent pattern of brain findings between our study and previous imaging studies of older  $\epsilon 4$  carriers. These might include different imaging modalities, different methods of analysis (region of interest vs voxel-wise), differences in sample size, and differences other than age among the studied populations (eg, demographic factors, neuropsychological performance, recruitment methods). In addition to hypoperfusion in some areas, we found that the presence of an  $\epsilon 4$  allele was associated with increased rCBF in other areas. Although we studied rCBF at rest, this hyperperfusion may be compensatory, similar to the hyperperfusion noted in a functional study of healthy middle-aged and elderly carriers of the  $\epsilon 4$  allele during performance of a memory task.<sup>6</sup>

## References

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**Figure.**  
 Resting Relative Cerebral Blood Flow (rCBF) in Individuals With and Without an Apolipoprotein ε4 Allele  
 Three-dimensional brain-rendering representation of statistical parametric mapping. Areas of red depict areas in which mean resting rCBF is significantly ( $P < .05$ , Bonferroni corrected) different between individuals with and without an ε4 allele. The graphs plot the rCBF values for the 2 groups in regions in which differences were most significant—the left inferior temporal gyrus and the left insula. The values in parentheses in the graph panel labels are Talairach coordinates denoting the exact brain locations of the statistically significant areas.