

Prefrontal Activation Patterns in Subjects at Risk for Alzheimer Disease

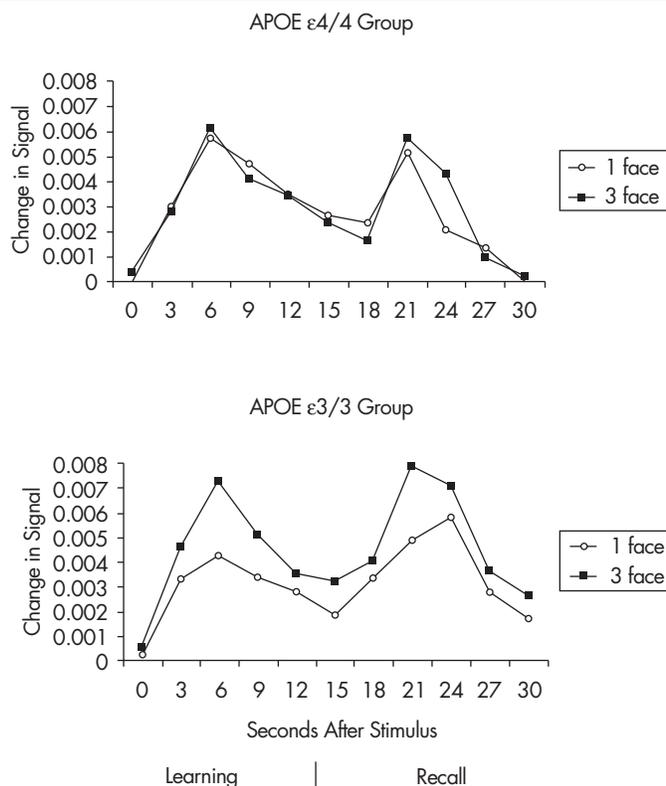
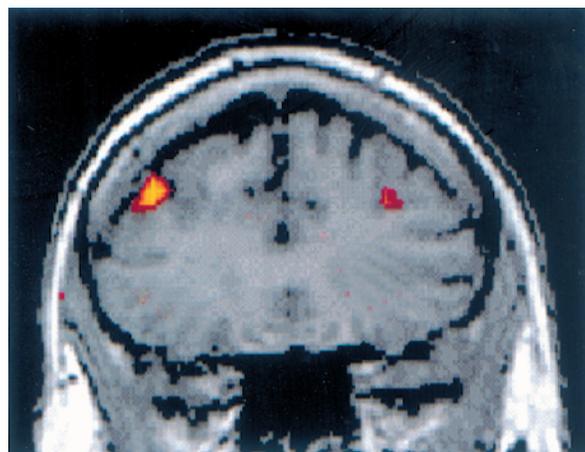
TO THE EDITOR: Event-related functional MRI (fMRI) is a novel technique that can assess activation in discrete brain areas during the component processes of memory tasks (e.g., learning and recall).^{1,2} The dorsolateral prefrontal cortex (DLPFC) is involved in working memory,^{2,3} and previous work in normal young adults suggests that there is a physiological increase in activation in this

region as memory load increases.² This ability may reflect the normal brain reserve capacity to handle memory demands of varying difficulty. The $\epsilon 4$ allele of the ApoE gene is an important genetic risk factor for Alzheimer disease (AD), and subjects homozygous for this allele have a higher risk and earlier onset of AD, compared with those with the $\epsilon 3$ allele, which confers no additional risk.⁴ An earlier report has found that the extent and magnitude of activation responses to memory tasks in subjects carrying the $\epsilon 4$ allele are greater than in those without this allele.⁵ We report here data from a pi-

lot fMRI study examining the effects of varying memory load on DLPFC activation patterns in six elderly subjects grouped into high- and low-risk ApoE genotypes.

A previously described fMRI protocol² was used to study DLPFC activation as a function of memory load in elderly subjects. We selected three normal elderly adults homozygous for the ApoE $\epsilon 4$ allele (mean age: 67.3 years) and three normal adults homozygous for the $\epsilon 3$ allele (mean age: 66.3 years) screened to exclude dementia and neuropsychiatric disorders. MRI analyses were conducted blind to ApoE status. For each trial of

FIGURE 1. Coronal MR image of brain during performance of face memory task, with areas of activation in the dorsolateral prefrontal cortex (DLPFC) depicted as a red–yellow color overlay



Note: Overlay depicts a thresholded correlation map of signal time course with an ideal hemodynamic response function. Graph depicts signal change from baseline (%) during learning and recall at two memory load levels (one and three faces). The ApoE $\epsilon 4/4$ group (top panel) demonstrates a higher level of activation during the easier, one-face condition and thus does not appear to show the same load-related increase in signal amplitude shown by the ApoE $\epsilon 3/3$ group (bottom panel).

the memory task, participants first studied either one face or three faces. After a brief delay, participants were presented with a test face and indicated whether this test face matched the just-studied face or faces. The session consisted of six runs of six trials each, with one-face and three-face trials intermixed within a run. Event-related analyses were used to semi-quantitatively measure brain activation, defined as percentage change in signal over baseline, in the middle frontal gyrus of the DLPFC during the learning and recall phases of each trial.³ Regions of interest were manually drawn on an anatomical T₁-weighted image and superimposed on the corresponding functional data set.² The mean and standard deviation (SD) of signal change during learning and recall were computed for each group. We restricted our fMRI analyses to the DLPFC and did not run statistical comparisons between groups because of small sample size and limited power.

In the one-face condition, the mean (\pm SD) activation during the learning and recall phases in the $\epsilon 4/\epsilon 4$ group tended to be higher ($0.57\% \pm 0.02\%$; $0.51\% \pm 0.12\%$) than in the $\epsilon 3/\epsilon 3$ group ($0.42\% \pm 0.16\%$; $0.48\% \pm 0.35\%$), respectively.

In the three-face condition, during the learning and recall phases, the $\epsilon 4/\epsilon 4$ group ($0.61\% \pm 0.05\%$; $0.57\% \pm 0.23\%$) did not show additional increases in activation, whereas the $\epsilon 3/\epsilon 3$ group ($0.73\% \pm 0.17\%$;

$0.78\% \pm 0.48\%$) showed further increases in activation (Figure 1).

Visual inspection suggests that the magnitude of activation in the DLPFC during learning and recall for the easier, one-face condition may be higher in ApoE $\epsilon 4/\epsilon 4$ subjects. One possible explanation for this finding may be that the at-risk group is applying greater cognitive effort to accomplish this task.⁵ Load-related increases in activation on the more difficult, three-face task also appear to be less consistent in the ApoE $\epsilon 4/\epsilon 4$ group. It is of interest that load-related increases are reported in normal younger subjects² and were also seen in the three ApoE $\epsilon 3/\epsilon 3$ subjects in this sample.

These pilot data were obtained to document the feasibility of using fMRI to study the component processes of working memory as well as the effects of systematically varying memory load in normal elderly subjects. Because of the many limitations (small sample size, examination of a single brain region, vascular risk factors, motion effects, limited behavioral data, etc.) our data should be interpreted with caution and as work in progress. Nevertheless, these data suggest that the impact of task difficulty/complexity on the magnitude and extent of fMRI activation needs to be considered while interpreting studies in patients with memory disorders or at-risk subjects. Moreover, fMRI "memory stress tests," which systematically vary task difficulty,

may offer promise in evaluating brain mechanisms of memory processing in normal aging as well as prodromal dementia.

This work has been funded in part by a seed grant from the Radiological Society of North America Research and Education Fund.

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