Altered PET Functional Brain Responses in Cognitively Intact Elderly Persons at Risk for Alzheimer Disease (Carriers of the ϵ4 Allele)

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Objective: *Few previous studies have investigated the association between APOE genotype and brain activation during performance of cognitive tasks in healthy middle-aged and elderly subjects, and the results have been mixed. The authors investigated APOE-mediated differential brain activation in a group of healthy elderly subjects.* **Methods:** *Using $H_2{}^{15}O$ positron emission tomography (PET), they imaged 32 healthy subjects (26 non-ϵ4 carriers and 6 ϵ4 carriers) performing a serial shape-recognition memory task under two conditions: Simple Demand (SD), in which one shape was presented in each study trial, and Titrated Demand (TD), in which study list length was adjusted so that each subject recognized words at approximately 75% accuracy. Multiple-regression analyses were performed, with the "activation" difference (TD–SD PET counts) as the dependent variable and the APOE genotype (presence versus absence of the ϵ4 allele) as the independent variable.* **Results:** *Compared with non-carriers, ϵ4 carriers exhibited significantly decreased TD–SD activation differences in the left superior temporal, right superior frontal, left postcental, left precuneus, and posterior cingulate gyrus because ϵ4 carriers (versus non-carriers) showed increased activation during the SD and decreased activation during the TD condition.* **Conclusion:** *Patterns of brain activation during a nonverbal memory task differed as a function of APOE genotype and, therefore, of genetic risk for Alzheimer disease (AD). Differences in activation were not a reflection of task difficulty, but indicate memory-related altered cognitive processing. Brain regions with decreased activation in the ϵ4 subjects may result from subclinical incipient AD pathology and/or APOE-related neurophysiologic heterogeneity.* (Am J Geriatr Psychiatry 2004; 12:596–605)

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In resting brain imaging studies, the inheritance of the ϵ4 allele has been associated with an Alzheimer disease (AD)-like positron emission tomography (PET) pattern in middle-aged and elderly adults with a family history of AD.[1,2] These PET results suggest that, in genetically at-risk individuals, subtle changes in resting cerebral glucose metabolism occur before the onset of clinical manifestations of disease. We recently reported APOE-related differences in cerebral blood flow even for young, college-age subjects.[3]

Imaging during performance of cognitive tasks may be more sensitive in revealing earlier and subtler changes in cognitive functioning in subjects at risk for AD. Only three functional magnetic resonance imaging (fMRI) studies (and no activation PET studies) have investigated the association between APOE and patterns of brain activation.[4–6] Smith et al.[4] reported that cognitively normal women ϵ4 carriers demonstrated decreased fMRI brain activation in bilateral mid- and posterior inferotemporal regions during naming and fluency tasks.[4] On the contrary, in the study by Bookheimer et al.,[5] the magnitude and the extent of fMRI activation during a verbal memory task were greater among healthy carriers of the ϵ4 allele. The latter results were interpreted as evidence of compensatory processing in subjects at risk for AD; that is, the APOE ϵ4 subjects use additional cognitive resources to bring their performance to a normal level.

No APOE-related differences were detected when the same group of investigators used a verbal working memory task at various levels of task difficulty.[6] The authors concluded that the effect of APOE is specific to memory, and not related to general task difficulty. However, the finding of no association between brain activation and APOE genotype for various levels of difficulty in a working memory task does not necessarily exclude the possibility that degree of difficulty may play a role in the association between APOE and brain activation in an episodic memory task.

We sought to investigate the association between APOE genotype and neurophysiological functioning in a group of healthy elderly subjects during performance of a nonverbal episodic memory task when performance on the memory task was titrated to yield accuracy close to 75% for each subject (in an attempt to equate subjective task difficulty across subjects). We hypothesized that even when demands of cognitive task were equated across subjects, healthy elderly subjects carrying the ϵ4 allele (compared with non-ϵ4 allele carriers) would still demonstrate different patterns of activation.

METHODS

Participants

Subjects were recruited from two sources. Eighteen participants were recruited through the community via posted flyers and advertisements in newspapers (requesting healthy elderly persons for participation in a PET study), and 14 participants were outpatients who presented to the Alzheimer's Disease Research Center at Columbia University with minor cognitive or functional complaints. Because these 14 participants showed no deficits on neuropsychological testing and were judged to be healthy (i.e., not to suffer from any neurological or psychiatric disease) after thorough evaluation (described below), we combined them with the 18 participants recruited through flyers and advertisements, for the purposes of this analysis. The two different recruitment-method groups did not differ in APOE genotype distribution (three ϵ4 carriers in each group), gender, age, education, or any neuropsychological measure of performance.

All potential subjects were carefully screened with medical, neurological, psychiatric, and neuropsychological evaluations, to exclude those with dementia or possible dementia, or cognitive impairment, or other neurological or psychiatric disorders and severe medical illnesses. A brain MRI was evaluated as normal by a neuroradiologist. All subjects were rated as Clinical Dementia Rating: 0. No subject was receiving central nervous system-acting medications prescribed for neurologic or psychiatric diseases or herbal supplements, such as ginkgo biloba, that may have central nervous system effects.

In all, 6 ϵ4 carriers (5 ϵ3/ϵ4 and 1 ϵ4/ϵ4) and 26 non-ϵ4 carriers (25 ϵ3/ϵ3 and 1 ϵ3/ϵ2) (all right-handed) participated in the study. The study complied with the ethical rules for human experimentation and was approved by the Columbia Presbyterian Medical Center Institutional Review Board.

Neuropsychological Evaluation and Cognitive Tasks

In addition to neurological and psychiatric evaluation, subjects also received the modified Mini-

Mental State Exam,[7] WAIS–R Vocabulary subtest, WAIS–R Digit Symbol, and the Selective Reminding Test.[8]

We chose a non-verbal episodic memory task for the neuroimaging component of this study; further details of the task can be found in previous publications.[9,10] Briefly, the task comprised two conditions (Figure 1). In each condition, a trial comprised an encoding phase followed by a recognition phase. During each recognition phase, subjects made decisions about whether the current shape had been presented in the encoding phase of that trial. Recognition probes were distinguished from study items by a rectangular frame.

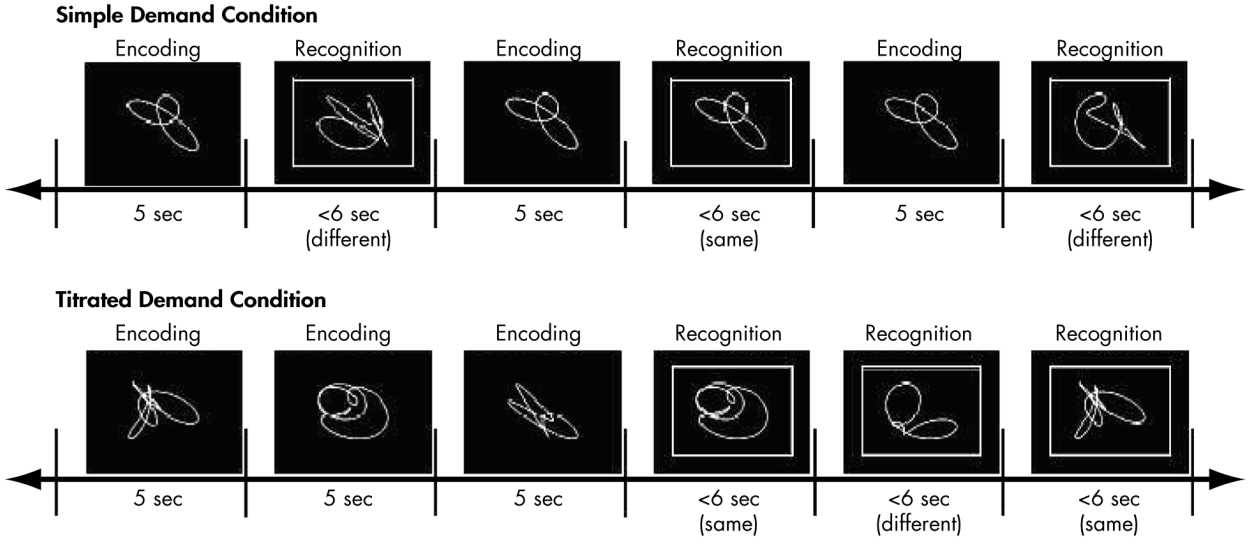
The two conditions were 1) A "simple demand" condition (SD), in which a single shape (the same each time) presented during the encoding phase was followed by one shape during the recognition phase (which was either the same or different from the encoding-phase shape); and 2) A "titrated demand" (TD) condition that involved serial presentation of a sequence of shapes during the encoding phase, the length of which was determined in a training session on the day preceding the PET scan. During the training session, study list size was adjusted in a staircase manner such that a recognition accuracy of about 75% for each individual subject was attained. The recognition phase of the TD condition involved presentation of shapes studied during the preceding study phase intermixed with foils. The total number of shapes presented in each trial during the recognition phase was equal to each subject's study-list size during encoding.

PET Scans

One PET scan per condition was acquired (encompassing both the encoding and recognition phases). Multiple trials of each condition were acquired during each scan: on average 18 trials for SD (each trial consisting of one shape during encoding and one shape during recognition) and two trials for TD (each trial consisting of 8.5 shapes during encoding and 8.5 shapes during recognition). Subjects viewed the shape stimuli on an overhead monochrome monitor while lying in a supine position. Scans were separated by 10 minutes and were obtained in the following order: resting scan (eyes closed), SD, and TD. Because AD patients were also subjected to this experimental design[10] and in order to minimize possible subject confusion, we elected to fix the order of the conditions in this study (as opposed to randomization or counterbalancing). The consequence of using a fixed task order is the possibility of confounding between condition and position in the task sequence.

For each scan, a bolus of 30 mCi $H_2{}^{15}O$ was injected

FIGURE 1. Non-verbal Memory Task



Note: List length varied for the titrated demand (TD) condition, so that each subject's performance was approximately 75% accurate. For presentation purposes, a list length of three shapes during the TD condition is illustrated here.

intravenously. Using a Siemens EXACT 47 PET camera (Knoxville, TN), we acquired two 30-sec. scan frames (which were subsequently averaged) in 2-D mode. After measured attenuation correction (15-min. transmission scan) and reconstruction by filtered back-projection, image resolution was 4.6 mm full width at half-maximum (FWHM). Arterial blood sampling was not conducted; thus, only non-quantitative relative cerebral blood flow count images (referred to as "rCBF") could be obtained.

PET data processing. We used the SPM99 program to implement standard steps (realignment, spatial transformation, smoothing with isotropic, Gaussian kernel [FWHM = 12 mm], and proportional scaling by global means). Significance thresholds for the *t*-statistics were calculated at $\alpha = 0.05$ per map, after Bonferroni correction, for the number of statistically independent resolution elements (resels) across which regressions were calculated.

General linear model design. We performed voxel-wise, multiple-regression analyses with rCBF as the dependent variable. Condition (TD versus SD) and APOE genotype in a dichotomous form (presence [either ϵ3/ϵ4 or ϵ4/ϵ4] versus absence [either ϵ3/ϵ3 or ϵ3/ϵ2] of an ϵ4 allele) as independent variables.

The regressions modeled the following effects: 1) the Condition × APOE interaction effect. This represents the relationship between APOE genotype and task-related activation, and it addresses the hypothesis that APOE genotype plays a role in the neurophysiology of memory in healthy elderly populations; 2) the Condition effect (the difference between TD and SD rCBF). This is meant to represent the functional activation related to titrated memory performance, while subtracting out activity related to basic sensory and motor processing. In particular, we report the Condition effects in voxels selected for having high interaction values (still using a map-wise threshold [$\alpha = 0.05$ per map after Bonferroni correction for the number of resels]). In order to appropriately interpret the above results, we also estimated the correlation between the estimators of the Condition effect and the estimators of the interaction.

In order to further explore whether among-APOE group differences in activation were related to changes in the SD or the TD conditions, we calculated separately for each APOE group the activation values of the SD and TD conditions as compared with resting rCBF. These analyses were performed on 30 (rather than 32) subjects because resting scans were not available for two non-ϵ4 carriers.

After testing our data, we detected no deviations from assumptions required for application of parametric statistics (although we cannot completely exclude the possibility that such assumptions may be still violated in studies with small and unequal sample sizes).

RESULTS

Demographic/Behavioral

Thirteen of our subjects were female (three were ϵ4 carriers), and 19 were male (three ϵ4 carriers). There was no significant association between gender and APOE genotype (Fisher's exact test, $p = 0.66$). Twenty-eight of our subjects were white (five ϵ4 carriers), two were African American (one ϵ4 carrier) and one was Asian. There was no significant association between APOE genotype and ethnicity (Fisher's exact test, $p = 0.49$). Demographic characteristics and neuropsychological performance did not differ among the groups (Table 1). Neither accuracy nor study-list length (the number of shapes attained by each subject during the TD condition) were related to the APOE genotype.

PET Data

In comparison to the subjects without the ϵ4 allele, ϵ4 carriers exhibited decreased TD–SD activation in the left superior temporal gyrus, right superior frontal, left postcentral, posterior cingulate gyrus, and left precuneus (Table 2, Figure 2, and Figure 3). We identified no brain regions where ϵ4 carriers manifested significantly higher (versus non-ϵ4 carriers) TD–SD activation.

Averaged over both APOE groups, from the brain areas where a significant interaction effect was noted, significant Condition effects were detected for the left superior temporal gyrus ($T = -4.29$) and the posterior cingulate ($T = -4.83$). The negative signs of the T values indicate that, averaged over both APOE groups, rCBF in the TD was lower as compared with the SD condition. When the Condition effect was examined in the non-ϵ4 carrier group alone, from the brain areas where a significant interaction effect was

noted, the post-central gyrus data approached a significant condition effect (T = 4.04, with T threshold [for $\alpha_{corrected}$: 0.05] = 4.06). When the Condition effect was examined in the ϵ4 carrier group alone, from the brain areas where a significant interaction effect was noted, the left superior temporal gyrus (T = –5.65), the right superior frontal gyrus (T = –4.64), and the posterior cingulate (T = –5.02) manifested significant Condition effects.

There was a positive correlation between the estimators of the Condition effect and the estimators of the interaction (i.e., Condition effect in APOE-0 – Condition effect in APOE-1): $R_{interaction,\ Condition\ effect\ in\ APOE\text{-}0} = 0.43$; $R_{interaction,\ Condition\ effect\ in\ APOE\text{-}1} = -0.90$. This is an important caveat, suggesting caution in interpreting the Condition effects when selecting voxels based on their value for the interaction. However, we can use the results calculated with mapwise-corrected thresholds to report presence of a Condition effect (as the specification of this mapwise threshold does not depend on selection of voxels satisfying some condition for another contrast).

The activation values of the SD and TD conditions (versus rest) were as follows: left superior temporal gyrus, SD (non-ϵ4 carriers: –3.58/ϵ4 carriers: 0.26), TD (non-ϵ4 carriers: –2.76/ϵ4: –4.73); right superior frontal gyrus, SD (non-ϵ4 carriers: –0.18/ϵ4: 1.47), TD (non-ϵ4 carriers: 0.58/ϵ4: –3.01); left postcentral gyrus, SD (non-ϵ4 carriers: –2.47/ϵ4 carriers: 1.80), TD (non-ϵ4 carriers: –0.79/ϵ4 carriers: –0.74); left precuneus, SD (non-ϵ4 carriers: 0.26/ϵ4: 2.15), TD (non-ϵ4 carriers: 1.68/ϵ4 carriers: –0.42); posterior cingulate gyrus, SD (non-ϵ4 carriers: –0.15/ϵ4 carriers: 3.16), TD (non-ϵ4 carriers: –0.58/ϵ4 carriers: –3.08). Inspection of the above activation values indicates that, as compared with non-ϵ4 carriers, ϵ4 carriers seemed to exhibit both increased activation in the SD condition and decreased activation in the TD condition. The left postcentral gy-

TABLE 1. Demographic and neuropsychological performance, by APOE group

	No ε4 Allele[a]	Presence of ε4 Allele[b]	T (df: 30)	p
Age, years	68.5 (8.87)	65.8 (8.59)	0.66	0.52
Education, years	15.5 (3.63)	17.0 (1.55)	−1.62	0.12
mMMSE	54.8 (1.75)	54.5 (3.56)	0.18	0.86
WAIS-R Vocabulary	14.1 (2.15)[c]	13.7 (2.07)	0.47	0.64
SRT Total Recall	50.5 (7.49)	48.0 (8.88)	0.70	0.49
SRT Delayed Recall	8.1 (2.91)	6.8 (3.31)	0.92	0.36
WAIS-R Digit Symbol[b]	13.4 (2.76)	11.5 (2.07)	1.60	0.12
Accuracy, % correct	0.77 (0.11)	0.81 (0.16)	−0.74	0.46
TD list length	8.8 (5.18)	7.3 (4.23)	0.65	0.52

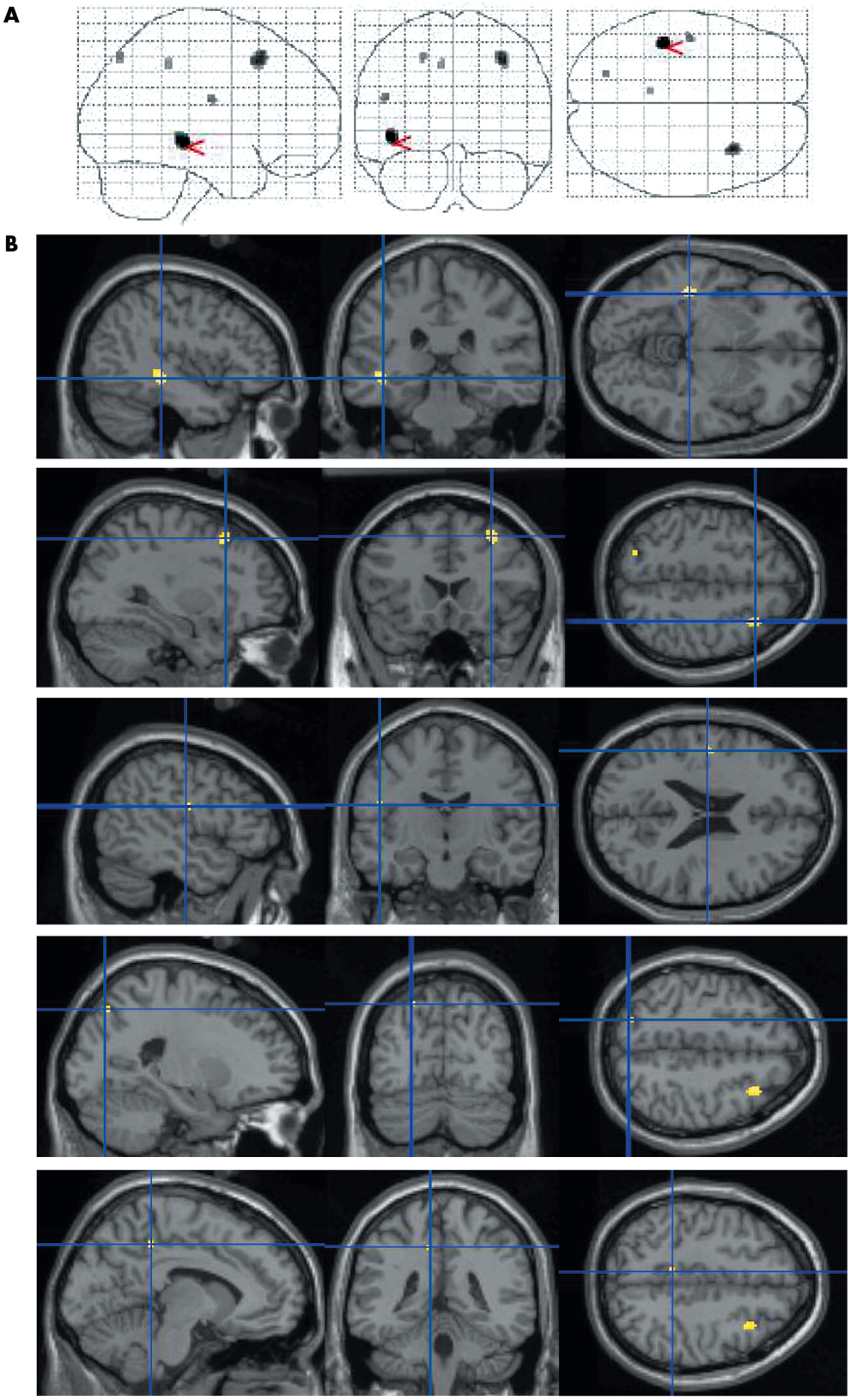
Note: Values are mean (standard deviation), unless otherwise noted. Student *t*-test was used for p calculations.
mMMSE: modified Mini-Mental State Exam; WAIS-R: Wechsler Adult Intelligence Scale–Revised; SRT: Selective Reminding Test.
[a] ε3/ε3 (N = 25); ε3/ε2 (N = 1).
[b] ε3/ε4 (N = 5); ε4/ε4 (N = 1).
[c] Information was available for 25/26 subjects without the ε4 allele (df: 29).

TABLE 2. Areas where significant[a] TD–SD activation differences were detected in the statistical parametric map analyses

	Talairach Coordinates					
	x	y	z	T (df: 30)	Cluster Size[b]	Location (Brodmann's Area)
Areas where ε4 carriers exhibit lower TD–SD activation differences	−42	−29	−4	5.9	70	Left superior temporal gyrus (22)
	32	22	50	4.9	67	Right superior frontal gyrus (8)
	−48	−13	21	4.5	11	Left postcentral gyrus (43)
	−22	−69	50	4.3	10	Left precuneus (7)
	−8	−37	44	4.2	10	Posterior cingulate gyrus (31)
Areas where ε4 carriers exhibited higher TD–SD activation differences	—	—	—	—	—	—

Note: TD: Titrated Demand condition; SD: Simple Demand condition.
[a] $p < 0.05$ Bonferroni-corrected; critical value threshold $t = 4.06$.
[b] (number of voxels); each voxel = 8 mm^3.

FIGURE 2. Areas of Lower TD–SD Activation Differences in ϵ4 Carriers



Note: TD: titrated demand condition; SD: simple demand condition.

A. Two-dimensional projections (glass brain) of statistical parametric map, depicting areas where significantly ($p < 0.05$, Bonferroni-corrected) lower TD–SD activation differences were noted for ϵ4 carriers.

B. Two-dimensional brain sections indicating the exact localization of the areas where significantly ($p < 0.05$, Bonferroni-corrected) lower TD–SD activation differences were noted for ϵ4 carriers. Each row corresponds to one single location (indicated by the point where the two axes cut), presented from three different sections (sagittal, coronal, and axial). The order of presentation follows that of Table 2: left superior temporal, right superior frontal, left postcentral, left precuneus, and posterior cingulate gyri.

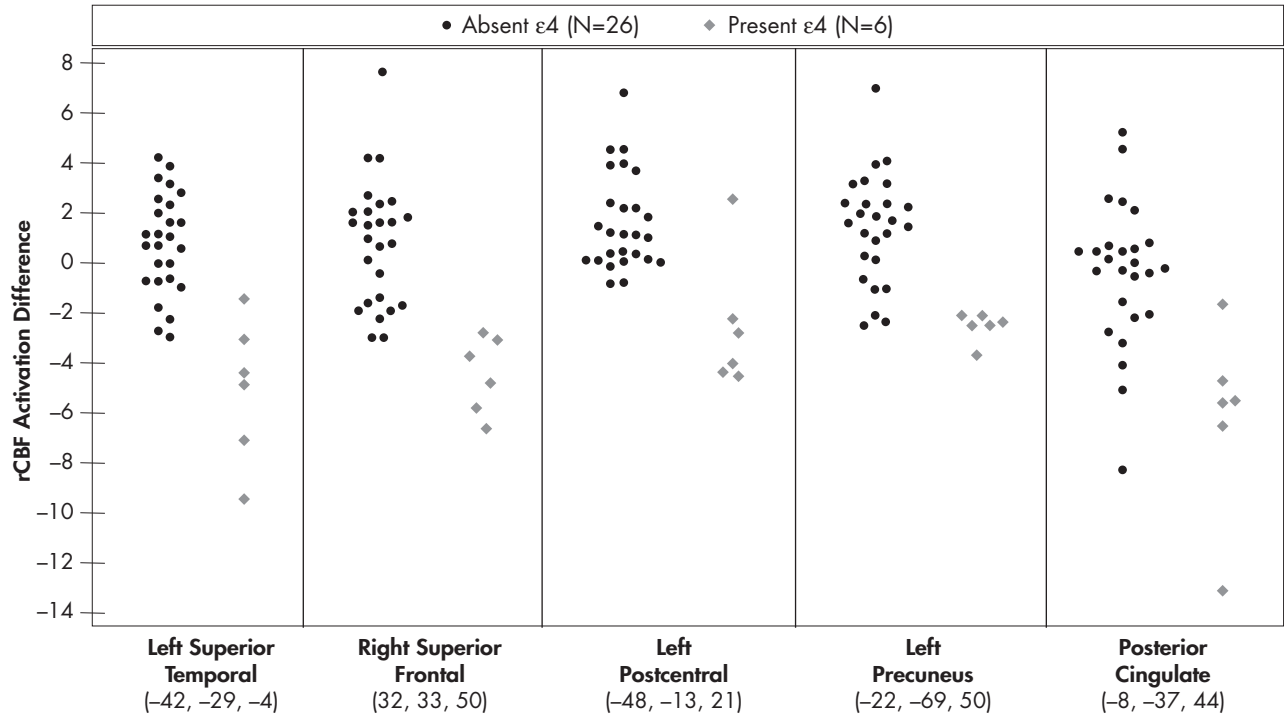
rus constitutes a relative exception to this in that only increased activation in the SD condition was noted for the ϵ4 carriers, whereas the values for the TD condition were similar among ϵ4 and non-ϵ4 carriers in this region.

DISCUSSION

We observed different patterns of brain activation for healthy elderly subjects with different APOE genotype during a non-verbal memory cognitive task. High-risk-for-AD healthy individuals (ϵ4 carriers), although not clinically affected and cognitively (in terms of neuropsychological performance) indistinguishable from their low-risk counterparts (non-ϵ4 carriers), manifested brain areas of significantly altered activation during the task. These differences are not merely a reflection of task difficulty (which was equated in our experimental design), but they indicate memory-related altered cognitive processing in subjects with the ϵ4 allele.

There are known early biochemical changes in neuronal processes and synapses that may be manifested in rCBF activation studies a long time before structural pathology is detected.[11] It is also known that symptoms of AD are preceded by a period of unknown duration during which neuropathologic alterations accumulate in the brain without associated memory loss or other detectable cognitive change. The increased risk for AD in subjects carrying the ϵ4 allele has been thought to be mediated by the APOE genotype being implicated in β-amyloid deposits and/or neurofibrillary tangles in biochemical pathways.[12,13] In a neuropathological study of 105 autopsies of subjects who showed no signs of dementia, abnormally high brain β-amyloid levels (the deposition of which is the hallmark of AD) were reported for ϵ4 carriers as young as 40 years old.[14] That study concluded that the ϵ4 allele predisposes carriers to begin accumulating β-amyloid earlier in life than non-carriers. In another study, the ϵ4 allele was associated with presence of neurofibrillary tangle changes in 44 autopsy cases of young subjects (mean

FIGURE 3. Plot of TD–SD Activation Differences for Subjects With and Without an ϵ4 allele in All the Areas Where Significant Interactions Were Noted



Note: TD: titrated demand condition; SD: simple demand condition.

Subjects carrying the ϵ4 allele manifest significantly smaller TD–SD activation differences in all these regions. Talaraich coordinates in parentheses.

age 38 years old; range: 22–46).[15] Therefore, brain regions where significant differences were detected may have already been affected by AD pathology although the brain preserved enough redundancy (efficiency) to avoid failure in clinical cognitive performance.

Epsilon-4 carriers exhibited increased activation during the SD condition and (with the exception of left postcentral gyrus) decreased activation during the TD condition. It has been noted that a common response to increasing task difficulty is increased activation of areas involved in an easier version of the task and/or the recruitment of additional brain areas.[16,17] Also, several functional neuroimaging studies that compared task-related activation in patients with AD and control subjects found more marked and extensive activation in AD patients.[18,19] This result has been perceived as an attempt to deal with increased (for the AD) task complexity and therefore counteract disease-related deficits. Therefore, if one assumes that 1) "more is better" and that 2) there is more underlying AD pathology in the ϵ4 carriers, one could be led to the hypothesis that ϵ4 carriers may preserve an ability to compensate for AD-related deficits by increasing activation in the less-demanding versions of cognitive tasks. At the same time, some previous studies have interpreted reduced activation in AD patients as compared to healthy elderly subjects[16,17] as reflecting disease-related less-efficient cognitive processing or processing deficiency either due to irreversible absence of cognitive resources or to inability to engage/recruit them despite their presence.[20] Therefore, the ability to compensate during the easier version of the task (by increasing activation) may be lost when the cognitive process becomes more challenging (leading to reduced activation in the TD condition). However, it should be kept in mind that the interpretation of either increased or decreased activation has been very controversial (i.e., which directionality reflects the optimal response?). For example, decreased activation in certain brain regions has been associated with more efficient processing (higher memory performance) in AD patients.[18] Therefore, decreased activation for the ϵ4 carriers during the difficult version of the cognitive task may not necessarily be an indication of dysfunction, but may constitute a beneficial compensatory strategy (if latent AD pathology is causing the APOE differences).

Also, it is possible that APOE-related differences may be unrelated to underlying AD-type pathological changes. Despite the APOE-related risk, there is uncertainty about which individuals, in particular, will, in fact, develop AD. Important direct effects of the ϵ4 allele on the nervous system have been reported, including a decrease in the synapse/neuron ratio,[21] impaired neuroregeneration within the dentate gyrus,[22] and increased vulnerability to exogenous neurotoxins.[23] The APOE genotype seems to play a role in regulating synaptic plasticity and long-term potentiation in the hippocampus of young mice.[24] It also seems to affect stress response and spatial-memory performance in young mice.[25] It has been proposed that APOE facilitates rather than causes AD.[26] It is therefore plausible that the detected differences may just reflect an APOE-related cerebral-physiological heterogeneity, rather than being markers of presymptomatic AD.

As compared with non-ϵ4 carriers, ϵ4 carriers exhibited increased activation in the SD condition, an effect similar to that found by Bookheimer et al.,[5] who noted greater magnitude and extent of brain activation for ϵ4 carriers during a verbal memory task. On the contrary, there was decreased activation for the ϵ4 carriers in the TD condition (with the exception of left postcentral gyrus, where the values for the TD condition seemed similar among the two APOE groups). This directionality is in accordance with Smith et al.,[4] who noted reduced activation for ϵ4 carriers in visual naming and letter fluency tasks. However, analogies from other APOE-related activation studies may be confounded by many factors.

First, because PET scanning data-acquisition of the current experimental design encompassed both the encoding and retrieval phases of the tasks, it is not possible to clearly separate the effects of different cognitive processes taking place during the tasks. Like the current study, in the study by Burggren et al.,[6] the obtained fMRI signal reflected both the encoding and testing phase. Therefore, the fact that no APOE-related effect was detected by Burggren et al, whereas APOE-related effects were elicited in the present study, cannot be attributed to the combined scanning of encoding and recognition phases. Bookheimer et al. examined separately the learning and recall aspects of the word-pair task[5] and reported only increases in the extent and intensity of activation for the ϵ4 allele carriers.[5] Notably, the APOE-related ef-

fect was of similar direction (higher activation for the ϵ4 carriers) in both learning and recall. Therefore, most likely, the difference in the APOE-related findings between that study and the present one cannot be attributed to the combined scanning of encoding and recognition phases. However, we cannot completely exclude the possibility that the results might have been different if the two phases were scanned separately.

Second, the discrepant results between the studies by Burggren et al.[6] and Bookheimer et al.[5] and our study may be related to task differences: in contrast to the abstract-shapes task used in this study, the digit-span task that Burggren et al. used is mostly reflective of immediate working memory and involves verbal processes, and the paired word-learning task that Bookheimer et al. used is mostly reflective of verbal processes.

Third, we used a different experimental design: equated task difficulty (by titrating study list size such that recognition accuracy was about 75% for each individual subject) in the present study versus varying degrees of difficulty in previous studies. Several functional-imaging studies suggest that a common response to increasing task difficulty in normal individuals is increased activation of areas involved in an easier version of the task and/or the recruitment of additional brain areas.[16,17] Therefore, areas reportedly associated with compensatory activation that have been identified in experiments with uncontrolled task difficulty may reflect modulation of the same network in response to differential difficulty, rather than APOE-related compensatory recruitment. Overall, our results confirm the conclusion of Burggren et al.,[6] in that the association between APOE genotype and cerebral activation does not seem to be a function of cognitive task difficulty (i.e., not a function of increased memory-related effort).

Fourth, the relative proportions of homozygotes and heterozygotes in different studies may have an impact on power. In our study 1 of 6 (17%) of the ϵ4 carriers was homozygous. In the study by Burggren et al.,[6] the percentage of ϵ4 homozygous subjects was 1 of 13 (8%), and in the study by Bookheimer et al.,[5] it was 2 of 16 (13%). The exact proportion of ϵ4 homozygosity was not provided by Smith et al.[4] Therefore, all three previous activation studies used a mixture of ϵ4 homozygotes and heterozygotes at varying degrees. Hence, it is possible that one of the reasons for the lack of APOE-related effect in the study by Burggren et al. is the relatively lower proportion of ϵ4 homozygotes in that study. Future studies with higher number of subjects should test the hypothesis that a parametric increase (or decrease) in activation may be noted for subjects with no versus one versus two ϵ4 alleles. The relatively higher proportion of ϵ4 homozygotes in our study may have resulted in lower Type II error. Overall, the significant associations noted in our study indicate that, despite the small overall number of subjects in the ϵ4 group, there were effects strong enough to be demonstrable even with our conservative approach to Type I error. The unequal sample sizes of this study may have also resulted in low power to detect the true APOE-related effect, which may, in fact, be more extensive.

Our results indicate that elderly persons with a genetic risk for AD (ϵ4 allele carriers) have alterations in brain functioning even at a point in time when behavioral, cognitive, or clinical evidence of disease is absent. These alterations are not a function of task difficulty or effort invested in task performance. They may be markers of early AD, or they may just reflect an APOE-related cerebral physiological heterogeneity. These results indicate that functional imaging may be a more sensitive tool than behavioral–cognitive tests for measuring early cerebral functional reorganization, possibly in response to incipient pathological processes.

This work was conducted at the Cognitive Neuroscience Division of the Taub Institute for Research in Alzheimer's Disease and the Aging Brain, Division of Aging and Dementia, Department of Neurology, Columbia University Medical Center, New York, NY.

The research was supported by federal grants AG 14671, AG 17761, RR 00645, and the Alzheimer's Association.

References

1. Small GW, Mazziotta JC, Collins MT, et al: Apolipoprotein-E Type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer disease. JAMA 1995; 273:942–947
2. Reiman EM, Caselli RJ, Yun LS, 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
3. Scarmeas N, Habeck CG, Stern Y, et al: APOE genotype and cerebral blood flow in healthy young individuals. JAMA 2003; 290:1581–1582
4. Smith CD, Andersen AH, Kryscio RJ, et al: Altered brain activation in cognitively intact individuals at high risk for Alzheimer's disease. Neurology 1999; 53:1391–1396
5. Bookheimer SY, Strojwas MH, Cohen MS, et al: Patterns of brain activation in people at risk for Alzheimer's disease. N Engl J Med 2000; 343:450–456
6. Burggren AC, Small GW, Sabb FW, et al: Specificity of brain activation patterns in people at genetic risk for Alzheimer disease. Am J Geriatr Psychiatry 2002; 10:44–51
7. Stern Y, Sano M, Paulson J, et al: Modified Mini-Mental State Exam: validity and reliability. Neurology 1987; 37:179
8. Buschke H, Fuld PA: Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology 1974; 24:1019–1025
9. Scarmeas N, Zarahn E, Anderson KE, et al: Cognitive reserve modulates functional brain responses during memory tasks: a PET study in healthy young and elderly subjects. Neuroimage 2003; 19:1215–1227
10. Scarmeas N, Zarahn E, Anderson KE, et al: Cognitive reserve-mediated modulation of positron emission tomographic activations during memory tasks in Alzheimer disease. Arch Neurol 2004; 61:73–78
11. Selkoe DJ: Alzheimer's disease is a synaptic failure. Science 2002; 298:789–791
12. Richey PL, Siedlak SL, Smith MA, et al: Apolipoprotein-E interaction with the neurofibrillary tangles and senile plaques in Alzheimer disease: implications for disease pathogenesis. Biochem Biophys Res Commun 1995; 208:657–663
13. Polvikoski T, Sulkava R, Haltia M, et al: Apolipoprotein-E, dementia, and cortical deposition of beta-amyloid protein. N Engl J Med 1995; 333:1242–1247
14. Morishima-Kawashima M, Oshima N, Ogata H, et al: Effect of apolipoprotein-E allele epsilon-4 on the initial phase of amyloid beta-protein accumulation in the human brain. Am J Pathol 2000; 157:2093–2099
15. Ghebremedhin E, Schultz C, Braak E, et al: High frequency of apolipoprotein-E epsilon-4 allele in young individuals with very mild Alzheimer's disease-related neurofibrillary changes. Exp Neurol 1998; 153:152–155
16. Rypma B, Prabhakaran V, Desmond JE, et al: Load-dependent roles of frontal brain regions in the maintenance of working memory. Neuroimage 1999; 9:216–226
17. Grady CL, Horwitz B, Pietrini P, et al: The effect of task difficulty on cerebral blood flow during perceptual matching of faces. Hum Brain Map 1996; 4:227–239
18. Becker JT, Mintun MA, Aleva K, et al: Compensatory reallocation of brain resources supporting verbal episodic memory in Alzheimer's disease. Neurology 1996; 46:692–700
19. Backman L, Andersson JL, Nyberg L, et al: Brain regions associated with episodic retrieval in normal aging and Alzheimer's disease. Neurology 1999; 52:1861–1870
20. Craik FIM, Byrd M: Aging and cognitive deficits: the role of attentional resources, in Aging and Cognitive Processes. Edited by Craig FIM, Trehub S. New York, Plenum, 1982, pp 191–211
21. Cambon K, Davies HA, Stewart MG: Synaptic loss is accompanied by an increase in synaptic area in the dentate gyrus of aged human apolipoprotein E4 transgenic mice. Neuroscience 2000; 97:685–692
22. Teter B, Xu PT, Gilbert JR, et al: Human apolipoprotein-E isoform-specific differences in neuronal sprouting in organotypic hippocampal culture. J Neurochem 1999; 73:2613–2616
23. Buttini M, Orth M, Bellosta S, et al: Expression of human apolipoprotein E3 or E4 in the brains of Apoe–/– mice: isoform-specific effects on neurodegeneration. J Neurosci 1999; 19:4867–4880
24. Valastro B, Ghribi O, Poirier J, et al: AMPA receptor regulation and LTP in the hippocampus of young and aged apolipoprotein E-deficient mice. Neurobiol Aging 2001; 22:9–15
25. Zhou Y, Elkins PD, Howell LA, et al: Apolipoprotein-E deficiency results in an altered stress responsiveness in addition to an impaired spatial memory in young mice. Brain Res 1998; 788:151–159
26. Meyer MR, Tschanz JT, Norton MC, et al: APOE genotype predicts when—not whether—one is predisposed to develop Alzheimer disease. Nat Genet 1998; 19:321–322