

Parietal cortex activation predicts memory decline in *apolipoprotein E-ε4* carriers

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Apolipoprotein E-ε4 is the main known genetic risk factor for Alzheimer's disease. Functional abnormalities in the parietal cortex have been reported for Alzheimer's disease patients and also for those at risk. Hence, a critical question is whether measurements of parietal cortex integrity may predict negative outcome among at-risk persons. We studied nondemented *apolipoprotein E-ε4* carriers and found a significant relationship between

parietal blood-oxygen-level-dependent functional magnetic resonance imaging response during a word categorization task and subsequent episodic memory performance. Thus, the results show that parietal cortex alterations predict memory decline in nondemented *apolipoprotein E-ε4* carriers, and hence likely progression to Alzheimer's disease. *NeuroReport* 17:1683-1686 © 2006 Lippincott Williams & Wilkins.

Keywords: Alzheimer's disease, *apolipoprotein E*, functional magnetic resonance imaging, memory, parietal cortex

Introduction

A robust finding in brain imaging studies of Alzheimer's disease is abnormally low rates of cerebral glucose metabolism, especially in the parietal cortex [1,2]. Findings of a similar pattern in nondemented individuals at risk for the Alzheimer's disease have provided further evidence for disease-related alterations of parietal cortex functioning [3,4]. The *apolipoprotein E-ε4* (*APOE-ε4*) is the main known genetic risk factor for Alzheimer's disease [5]. Reiman and colleagues [3] observed reduced parietal glucose metabolism in healthy *APOE-ε4* carriers. Furthermore, we recently reported reduced blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD-fMRI) response in a left-sided inferior parietal area among cognitively intact carriers of the *APOE-ε4* allele [6]. A critical question in this context is whether measures of parietal cortex integrity can reliably predict negative outcome among at-risk persons. Support for this notion was reported by Small and colleagues [7]. They used positron emission tomography and found that reduced cerebral glucose metabolism in inferior parietal, lateral temporal and posterior cingulate regions predicted memory performance decline 2 years

later. It has been established that a declining level of episodic memory precedes Alzheimer's disease diagnosis [8].

The purpose of the present fMRI study was to examine whether a diminished BOLD-fMRI response in the same parietal area that differentiated among healthy carriers and noncarriers of the *APOE-ε4* allele [6] longitudinally predicted episodic memory decline within the group of *APOE-ε4* carriers.

Methods

Participants

Eighteen *APOE-ε4* carriers were included (Table 1). *APOE* genotyping was performed as described previously [6]. All participants were recruited from the longitudinal Betula prospective cohort study: memory, health and aging [9] as part of a previous study sample [6]. Here, the participants were divided into two groups ('decline' vs. 'nondecline') on the basis of their longitudinal episodic memory performance, measured at two test occasions (T1 and T2) approximately 5 years apart (Table 1 and Fig. 1a). Three

Table 1 Group characteristics

	Nondecline	Decline
N	9	9
Homozygous ($\epsilon 44$)/heterozygous ($\epsilon 34$)	1/8	2/7
Female/male	6/3	4/5
Age	66.7 (5.9)	68.0 (4.1)
Education (years)	10.9 (3.7)	10.1 (3.9)
AD in family (N)	1	1
MMSE ^a		
T1	28.7 (1.3)	28.2 (1.0)
T2	28.1 (1.5)	28.3 (1.0)
Episodic memory performance ^b		
T1	21.6 (1.7)	21.8 (5.3)
T2*	23.3 (2.3)	15.0 (4.7)
$\Delta T2-T1^*$	1.8 (2.5)	-6.8 (2.0)
$\Delta T2-T1$ range	-2 to +5	-10 to -4
Functional magnetic resonance imaging performance		
Word classification accuracy ^c	156.3 (1.7)	155.9 (5.0)
Response time (ms)	2232 (189)	2216 (295)
Recognition test ^c	101.1 (16.9)	92.6 (19.1)

Note: Means and standard deviations (in parentheses).

AD in family, first-degree family history of Alzheimer's disease; MMSE, mini mental state examination; T1 and T2, the two test occasions.

^aMax, 30.

^bMax, 44.

^cMax, 160.

*Group difference; $P < 0.001$, Student's *t*-test, two-tailed.

episodic-memory tasks were used to determine memory performance: (i) yes/no face recognition; (ii) recall of participant-performed tasks; (iii) verbal recall (for detailed description of the tests, see [9]). To be assigned to the declining group, participants had to show a drop of at least four points between T1 and T2, whereas those in the nondeclining group were allowed a maximum drop of two points (Table 1). All participants were diagnosed as nondemented at both test occasions, and there was no difference in mean Mini Mental State Examination scores between the groups (Table 1). They were right-handed, native Swedish speakers and had no reported neurological problems. Structural information was available for the hippocampus volume (cf. [10]) and there was no difference between decliners and nondecliners ($P > 0.5$, Student's *t*-test, two-tailed). The study was approved by the Ethics Committee of Umeå University. Participants were paid for participating and a written informed consent was obtained in accordance to the Declaration of Human Rights of Helsinki, 1975.

Functional neuroimaging

The fMRI data collection was performed on a Philips Intera 1.5T scanner (Philips Medical Systems, The Netherlands) and completed approximately 2 years before T2. The scanning details have been reported elsewhere [6]. In brief, in a block design, participants performed a word categorization task (abstract/concrete) that promoted incidental encoding of a word list. Participants' behavioral performance was recorded for response reaction times and categorization accuracy. About 15 min after the scanning session ended, a self-paced surprise recognition test was administered during which participants made yes/no recognition decisions on 240 words: 80 new (not presented during the categorization task) and 160 previously studied words. No significant ($P > 0.3$; Student's *t*-test, two-tailed)

between-group differences were seen in behavioral performance (Table 1).

Data analysis

The imaging data were sent to a PC and converted to analyze format. Functional images were preprocessed and analyzed using SPM99 (Wellcome Department of Cognitive Neurology, UK, <http://www.fil.ion.ucl.ac.uk>) implemented in Matlab 6.1 (Mathworks Inc., Natick, Massachusetts, USA). Before analysis, all images were realigned to the first image volume acquired, and also spatially normalized and transformed into a standard anatomic space as defined by the SPM99 MNI EPI template. The images were spatially smoothed using a 6.0 mm full-width at half-maximum Gaussian filter kernel. First-level contrast images (categorization vs. fixation baseline) were created for each participant using the general linear model. The task condition was modeled as a fixed response (box-car) waveform convolved with the hemodynamic response function. In second-level (random-effects) analyses, *t* statistics were applied to identify regions activated according to the model. On the basis of previous findings of altered regional activity in *APOE-ε4* carriers, the left inferior parietal cortex was predefined to be of interest. Statistical thresholding for the contrast (nondecline > decline) used a small volume correction based upon the area (10 mm sphere) encompassing the left inferior parietal cortex identified in our previous study [6]. The activation discussed below survived a small-volume false-discovery rate correction at $P < 0.05$. Activation outside this region of interest was considered significant at $P < 0.05$ corrected for multiple comparisons. Peak locations are expressed in coordinates according to MNI space (SPM99). The activation magnitudes used in the correlation analyses were calculated using the SPM region-of-interest toolbox.

Results

The group contrast showed a significant difference (nondecline > decline) in a left inferior parietal region [BA 39; peak voxel at ($x, y, z = -48, -54, 42$); $k = 27$, $Z = 3.16$, $P = 0.008$, small-volume correction false discovery rate corrected; Fig. 1c]. The location of this region overlapped with that of a region [peak voxel at ($-44, -56, 36$); Fig. 1b] in which activity previously was found to differentiate cognitively intact *APOE-ε4* carriers from noncarriers [6].

Further analyses revealed that the parietal BOLD-fMRI response correlated significantly ($R = 0.65$; $P = 0.002$) with the relative change in episodic memory performance over time ($\Delta T2 - T1$) (Fig. 1d). In other words, lower BOLD-fMRI response in the left parietal area was related to poorer subsequent memory performance.

Discussion

We recently reported that reduced BOLD-fMRI response in the left inferior parietal cortex differentiated healthy *APOE-ε4* carriers from noncarriers [6]. In this study, we analyzed follow-up behavioral data and found that diminished BOLD-fMRI response in the same parietal area predicted episodic memory decline within the *APOE-ε4* group. Previous studies have found that functional abnormalities in the parietal area correlate with cognitive impairment in early Alzheimer's disease patients [11,12],

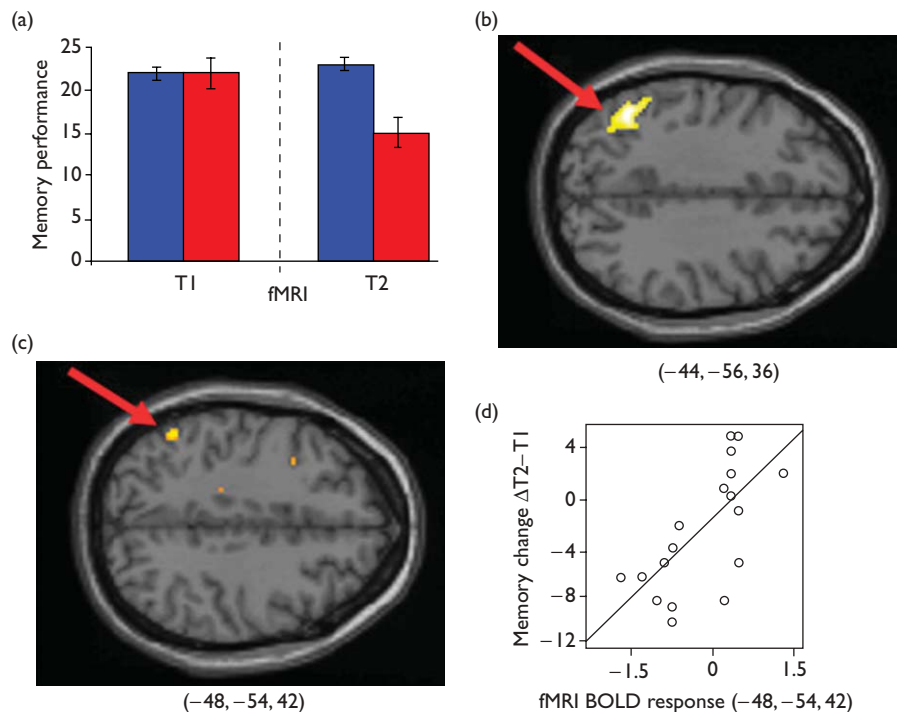


Fig. 1 (a) The two study groups were composed on the basis of the participants' episodic memory performance over time: declining (red column in figure) or nondeclining (blue column), measured at two test occasions (T1 and T2) before and after functional magnetic resonance imaging (fMRI) data collection (indicated by the dashed vertical line). The histogram includes error bars (± 1 standard error of the mean). (b) Reduced blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD-fMRI) response in a left inferior parietal region has previously been observed for nondemented *APOE-ε4* carriers, as compared with noncarriers (Reproduced from [6], with permission from Oxford University Press.) The numbers in square bracket denote MNI coordinates (x, y, z). (c) The SPM results (nondecliners > decliners) showed diminished parietal BOLD-fMRI response for participants who later experienced memory decline. The locus of this effect overlapped with the previously observed region (Fig. 1b; [6]). (d) The parietal BOLD-fMRI response correlated significantly with subsequent episodic memory change, such that lower parietal activity was related to poorer subsequent memory.

especially in *APOE-ε4* carriers [13]. In addition, longitudinal positron emission tomography studies suggest that initial temporoparietal hypometabolism forecasts clinical progression [14], and moreover, that metabolic deficits in the inferior parietal cortex predict future cognitive decline in nondemented *APOE-ε4* carriers [7]. Our study adds to these findings by using longitudinal memory changes to identify subgroups of *APOE-ε4* carriers that initially had comparable levels of performance but subsequently progressed to show either a stable or declining capacity. In that way, parietal activity differences could be revealed at a stage (i.e. during the fMRI session) when no behavioral group differences were apparent.

It is not possible to state at what time exactly during the course of the study the observed memory decline was initialized. However, as the two groups, showed equal behavioral performance at the initial examination as well as at the time for fMRI data collection, it is likely that the drop occurred closer to the final test occasion. Hence, it is reasonable to believe that the observed reduction in parietal BOLD-fMRI response was truly predictive, rather than reflective, of episodic memory impairment.

The altered BOLD-fMRI response in those who later experienced episodic memory decline may reflect different underlying mechanisms. The parietal tissue may locally be affected by neuronal pathology. This is supported by findings of an inverse correlation between density of senile

plaques in Alzheimer's disease and glucose metabolism in the parieto-occipital lobe [15]. The less vigilant response could also reflect impaired synaptic input from connected regions. It has been suggested that hypometabolism in the parietal cortex is induced by damage to the densely interconnected hippocampal region, which is critical for episodic memory function and known to be affected early in the course of Alzheimer's disease [16].

The parietal cortex in conjunction with the hippocampus has been related to memory retrieval success in healthy young adults [17]. In addition, there is much evidence that the parietal cortex plays a role in various attention tasks [18]. An interesting question for future research would thus be whether diminished parietal cortex activation more generally predicts cognitive decline.

Conclusion

In this fMRI study, we report an actual relationship between functional brain alterations and future cognitive decline in persons at genetic risk for Alzheimer's disease. Our results emphasize the value of the parietal cortex for preclinical detection of Alzheimer's disease, and clearly support the notion that a combination of genetic information with neuroimaging and behavioral data represent a promising route for early diagnosis and for monitoring disease progression (cf. [4,11]).

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