Alzheimer's Patients Engage an Alternative Network during a Memory Task

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We conducted an event-related functional magnetic resonance imaging experiment to better understand the potentially compensatory alternative brain networks activated by a clinically relevant face-name association task in Alzheimer's disease (AD) patients and matched control subjects. We recruited 17 healthy subjects and 12 AD patients at an early stage of the disease. They underwent functional magnetic resonance imaging scanning in four sessions. Each of the sessions combined a "study" phase and a "test" phase. Face/name pairs were presented in each study phase, and subjects were asked to associate faces with names. In the test phase, a recognition task, faces seen in the study phase were presented each with four different names. The task required selection of appropriate previously associated names from the study phase. Responses were recorded for post hoc classification into those successfully or unsuccessfully encoded. There were significant differences between the groups in accuracy and reaction time. Comparison of correctly versus incorrectly encoded and recognized pairs in the two groups indicated bilateral hippocampal hypoactivation both when encoding and recognizing in the AD group. Moreover, patients showed bilateral hyperactivation of parts of the parietal and frontal lobes. We discuss whether hyperactivation of a frontoparietal network reflects compensatory strategies for failing associative memory in AD patients.

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Patients with early Alzheimer disease (AD) frequently report difficulties remembering names of persons they know; a problem that may lead to significant social withdrawal. It has been shown that this specific cognitive-perceptual ability in general and paired associative learning in particular is affected early in the course of AD.[1] Face-name association is therefore an ecologically valid and sensitive task of altered function in AD patients at an early stage of the disease.

The neuronal correlates of encoding a face-name association have been investigated in recent neuroimaging studies of healthy volunteers.[2–5] This task engages the medial temporal lobe and the prefrontal cortex. More specifically, the CA2, CA3, and DG regions of the hippocampus are activated when subjects first study a block of face-name pairs, and this activation decreases when the pairs are repeated.[4] Moreover, event-related functional magnetic resonance imaging (fMRI) studies have shown that activation of this temporofrontal network, particularly the hippocampus, predicts memory for individual face-name pairs.[6]

Concomitantly, several MRI morphometric studies[7,8] have confirmed anatomopathological data[9] that show early susceptibility of the hippocampal complex to neurodegeneration in AD. Recent functional neuroimaging studies have investigated neuronal networks associated with paired associative learning task in subjects with a genetic risk for development of AD[10] or patients at an early stage of the disease.[11] Compared with healthy volunteers, AD patients and subjects at risk for AD show relative hypoactivation of hippocampal complex, in keeping with the morphological evidence. Furthermore, a large cortical network is hyperactivated. These activations include the prefrontal cortex and have been described as compensatory.

All previous positron emission tomography or fMRI studies in AD patients have used "block-design" experiments. A relative weakness of this design is the ques-

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tion of suitable control subjects with whom to isolate memory-related activity. For example, presenting a block of face-name pairs and asking subjects to remember them may engage several processes in addition to memory encoding relative to control tasks of passive viewing or fixation on a crosshair. Moreover, memory performance is likely to differ between AD patients and control subjects such that different numbers of face-name pairs will be remembered within each block. If the brain's response to correct and incorrect pairs differs in ways other than those associated with memory, this will confound comparisons between patients and control subjects.

Event-related designs,[12] in contrast, allow the brain's responses to remembered and forgotten pairs to be separated. Thus, one can examine differences between pairs within a "study block" as a function of whether they are remembered or forgotten in a later "test block" (the so-called difference in memory (DM) effect[13]). One can therefore compare the mean activity associated with remembered and forgotten pairs, whereas allowing for differences in the total number of such pairs. Such designs have been used successfully to compare memory encoding in healthy young and older volunteers.[14]

We therefore conducted an event-related fMRI experiment to better understand both the dysfunction of the temporal frontal network normally involved in paired-associate learning and the potentially compensatory, alternative brain networks activated by a clinically relevant, everyday, face-name association task in early AD patients. We designed a simple face-name association task realizable by patients and matched control subjects for this purpose. We used event-related analyses to directly compare remembered and forgotten associations in patients and control subjects, controlling for differences in overall performance levels.

We had several hypotheses. First, the paired associative learning task is realizable by patients with AD in an MRI environment, and a behavioral difference exists between patients and matched healthy volunteers. Second, this design for face-name learning will allow us to demonstrate lack of activation in the hippocampus in patients relative to healthy volunteers during the encoding and recognition phases. Third, when the task is performed correctly by patients, they engage an alternative compensatory brain network that involves, at least partially, the prefrontal cortex.

Subjects and Methods

Subject Recruitment

PATIENT RECRUITMENT. Patients with probable AD were recruited from the Dementia Research Group, National Hospital for Neurology and Neurosurgery (London, United Kingdom) and the Cognitive Disorder Clinic, Chelsea and Westminster Hospital (London, United Kingdom). Patients had to fulfill the following inclusion criteria to be recruited in the study: (1) probable AD according to international criteria (National Institute of Neurological and Communication Disorders/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[15] and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV); (2) Mini-Mental State Examination (MMSE) score greater than 20[16]; (3) no major visuospatial or visuoperceptual impairment or severe apraxia; (4) receiving no psychoactive drugs, including anticholinesterase inhibitors or *N*-methyl-D-aspartate antagonist; (5) white matter changes in a T2-weighted MRI scan rated 2 or less on the modified Hachinski ischemic score[17]; (6) able to perform the paired associative learning task described later in this section at above chance; and (7) able to sign informed consent. All patients underwent a full neuropsychological assessment and a neurological and a general clinical examination. Twelve patients (8 women; mean age, 70.9 years; range, 58–79 years) meeting the inclusion criteria were recruited. The mean MMSE was 25.1 of 30 (range, 23–28). Table 1 lists the characteristics of the patients recruited.

VOLUNTEER RECRUITMENT. Healthy volunteers were recruited to match the patient group by advertisement in a local community center. Volunteers were screened for major neurological and psychiatric conditions and use of psychoactive drugs. All healthy volunteers underwent the following examinations: (1) a neurological and a general clinical examination; (2) a neuropsychological assessment; and (3) a structural MRI scan. If results from any of these tests were found to be abnormal, exclusion from the study ensued. A total of 17 healthy volunteers aged between 65 and 82 years (13 women; mean age, 70.6 years) with a mean MMSE score of

Table 1. Demography and Relevant Neuropsychological Evaluation of Healthy Volunteers and Patients

Characteristic	Healthy Volunteers	Patients
No. of subjects	17	12
Mean age, yr (+SD)	70.6 (5.6)	70.9 (6.4)
Women, %	76.5	66.6
Education, yr (+SD)	13.2 (3.8)	12.9 (2.3)
Mean MMSE (+SD)	29 (1)	25.1 (1.8)[a]
RMT faces/50	—	31.7 (8.1)
RMT word/50	—	32.5 (11.1)
DP-PT delayed/12	—	3.6 (4.1)
DP-ST/12	—	5 (3.3)
Famous faces/12	—	5 (2.6)
Face recognition/12	—	8.7 (2.6)

[a]Statistically significant, independent t test, $p < 0.05$.

SD = standard deviation; MMSE = Mini-Mental State Examination; RMT = Recognition Memory Test; DP-PT = Doors and People—People Test; DP-ST = Door and People—Shape Test.

29 of 30 (range, 27–30) were recruited. Table 1 provides characteristics of the recruited healthy volunteers.

Informed consent was obtained for every healthy volunteer and patient before participation in the study. The study was approved by the National Hospital for Neurology and Neurosurgery (University College London Hospitals National Health Service Trust) and the Institute of Neurology (University College London) Joint Research Ethics committee (London, United Kingdom) and by Riverside Research Ethics Committee (London, United Kingdom).

Functional Magnetic Resonance Imaging Paired Associative Learning Task

The fMRI paired associative learning task was adapted from the one that Sperling and colleagues[6] had developed to accommodate patient requirements for length, difficulty, and memory load. The parameters of the task were adapted after behavioral pilot studies with a group of AD patients not involved in this imaging study.

The task was explained to subjects outside the scanner, and a practice session of 20 minutes before scanning was given with different material from that used during experimental scanning. A practice session of a further 10 minutes was repeated inside the scanner to ensure that the task was well understood by both healthy volunteers and patients.

During functional image acquisition, healthy volunteers and patients performed an associative encoding task (study phase) followed by a recognition task (test phase). Twelve face-name pairs were presented in each study phase and subjects were asked to associate faces with names. They were told to press a key on a response box as soon as a new association appeared on the screen. This phase was followed by the test phase in which a face seen in the study phase was presented with four different names including one corresponding to a previously seen association (all the names were seen in the study phase). Subjects were asked to select the name previously associated with a given face in the study phase with a four-key response box. The same material was presented to patients and healthy volunteers. A distraction task was inserted between the study and test phases to prevent rehearsal.

The 48 face-name pair associations were stored digitally in color on a computer and presented in random order onto a projection screen located at the head of the MRI machine. Subjects viewed the screen through a mirror located in the head coil. None of the subjects scored at chance level during the test phase (see inclusion criteria earlier in article). The length of stimulus presentation during study and test phases was 6.4 seconds with an interstimulus interval of 0.1 second. Null events of the same length (6.4 seconds) were added in the test phase (12/phase). The two phases were each repeated four times during image acquisition, each time with different faces and names (giving a total of 20.4 minutes of scanning time). Reaction times and responses were recorded to allow subsequent classification of pairs as successfully or unsuccessfully encoded and recognized.

Scanning Procedure

DATA ACQUISITION. Both T1-weighted anatomical volume images (MPRAGE sequence) and T2*-weighted echo planar (EPI) images with blood oxygenation level dependent contrast were acquired with a 3-Tesla Siemens Allegra system (Siemens, Erlangen, Germany). Each EPI volume comprised forty 2.5mm-thick axial slices separated by 1.5mm, positioned for full coverage of the brain. Data were acquired continuously during a single session and comprised 410 volumes with a repetition time of 2.6sec/vol. The first five volumes were discarded to allow for T1 equilibration effects.

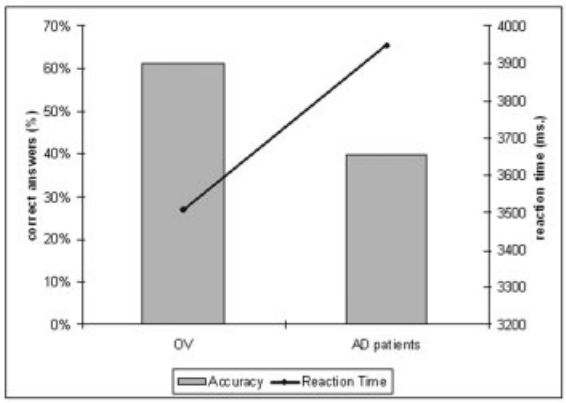
PREPROCESSING. Preprocessing and data analysis were performed using Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology, London, United Kingdom).[18] For each subject, all volumes in a session were realigned spatially to the first volume and resliced using a sync interpolation in anatomical space. To correct for different acquisition times, we shifted the signal measured in each slice relative to the acquisition of the middle slice using a sync interpolation in time. Each volume was then normalized to a standard EPI template in the space of Talairach and Tournoux[19] using nonlinear basis functions. The EPI volumes were smoothed with an 8mm full-width at half-maximum isotropic Gaussian kernel. The T1 structural volume was coregistered with the mean realigned EPI volume and normalized with the same deformation parameters.

Data Analysis

Face-name pairs were classified as "test correct" (TC) or "test incorrect" (TI) by recognition decisions in the test phases. By inferring that pairs correctly recognized at test were successfully encoded at study, we also used these decisions to define each pair as "study correct" (SC) and "study incorrect" (SI) during the study phases.

The volumes acquired for each subject were modeled as a continuous time series. The hemodynamic response to each event type of interest (SC, SI, TC, TI) was modeled as a "boxcar" encompassing the whole period of the event (ie, 2.5sec/vol repetition time), convolved with a canonical impulse response function. Also included for each subject were six rigid-body realignment parameters for each scan, to capture residual movement-related artifacts. Parameter estimates for each condition and covariate were calculated from the least mean squares fit of the model to the data. In the second stage of analysis, parameter estimates were tested using planned contrasts (see Results). The linear combinations of parameter estimates for each contrast were stored as separate images for each subject. These contrast images were entered into one- and two-sample t tests, to permit inferences about condition-specific effects within and across groups that generalize to the control and patient populations (ie, a random-effects analysis). These contrasts produced statistical parametric maps of the t statistics at each voxel, which were subsequently transformed to the unit normal Z-distribution. The thresholds for contrasts of five contiguous voxels were at p less than 0.001, uncorrected. We concentrated on regions that survived p less than 0.05 at the voxel level, corrected using false discovery rate[20] for the whole brain. The locations of maxima of suprathreshold regions were established by rendering them onto subjects' normalized structural scans. They were labeled using the nomenclature of Talairach and Tournoux.[19]

Correlation analyses were performed by linear regression.



	Accuracy	Reaction time
V and AD patients	p<0.0005	p<0.02

Fig 1. Reaction time and accuracy during the recognition task (test phase) and statistical difference. Alzheimer's disease (AD) patients had significantly poorer results than healthy volunteers (V) in both accuracy and reaction times.

These data are reported if statistically significant at the voxel level (false discovery rate whole-brain corrected, $p < 0.05$).

Results

Behavioural Results

Significant differences were found between the two groups in accuracy and reaction time. Accuracy in the forced choice recognition task was greater in the healthy volunteer (61.5%; range remembered, 18–38; range forgotten, 30–10) than in the AD patient group (39.5%; range remembered, 15–22; range forgotten, 33–26); the random response rate was 25%. Patient accuracy was significantly above chance ($p < 0.05$). Healthy volunteers were faster in answering (mean, 3,506 milliseconds; range, 2,278–4,522 milliseconds) than AD patients (mean, 3,946 milliseconds; range, 3,309–4,649 milliseconds). All differences are significant (independent sample test, $p < 0.05$) (Fig 1).

Functional Magnetic Resonnance Imaging Results

Table 2 lists coordinates of the peak of activation within clusters, its statistical significance, and the related *Z*-scores.

WITHIN-GROUP COMPARISONS.

We compared pairs at study that were later remembered (SC) with pairs that were later forgotten (SI) within each group. In normal volunteers, differential activation was found in several regions, including the right hippocampus. No differences were found for the same comparison in the patient group (Fig 2).

We compared remembered versus forgotton pairs at test within each group. In the volunteers differential activation was revealed in several structures, again including the left and right medial temporal gyrus and the right hippocampus. No difference was found in the patient group.

COMPARISONS BETWEEN GROUPS.

Interactions between Correct and Incorrect Responses and Group. For the $(SC\text{-}SI)_C > (SC\text{-}SI)_P$ interaction, contrast tested for greater activation at study for subsequently remembered than subsequently forgotten pairs in the control subjects than in the patients. A region within the right hippocampus (30, −20, −12) was significant. At an uncorrected ($p < 0.001$) threshold, we also found a region in the left hippocampus that showed the same pattern of hypoactivation in patients relative to control subjects (Fig 3).

For the $(SC\text{-}SI)_P > (SC\text{-}SI)_C$ reverse interaction, no regions survived correction, though at the p less than 0.001 uncorrected threshold, hyperactivation was found in the precuneus bilaterally and in the superior parietal lobule for patients relative to control subjects.

For the $(TC\text{-}SI)_C > (TC\text{-}SI)_P$ interaction, contrast tested for greater activation at test for remembered than forgotten pairs in the control subjects compared with patients. A region in the right hippocampus (26, −16, −16) was significant. Activations also were found in the middle and inferior temporal gyrus at an uncorrected threshold of p less than 0.001.

For the $(TC\text{-}TI)_P > (TC\text{-}TI)_C$ reverse interaction, activation in right fusiform gyrus was observed only at the uncorrected threshold of p less than 0.001.

Comparison of Correct Responses between Groups. We then compared activations in patients and control subjects in response to remembered pairs alone, at study and test (Fig 4). Results given in the following sections are at p greater than 0.05 false discovery rate, corrected.

For SC_C versus SC_P, no differences were found in the contrast ($SC_C > SC_P$). In the reverse contrast ($SC_P > SC_C$), a large, bilateral, parietofrontal network was hyperactivated by patients compared with control subjects. This area included the inferior parietal lobule bilaterally, the medial frontal gyrus bilaterally, and the left inferior frontal gyrus. Interestingly, the Z values and number of suprathreshold voxels were greater on the right than left (see Fig 4A).

For TC_C versus TC_P, in the contrast $TC_C > TC_P$, a right hippocampal region (26, −18, −18) survived correction for a 5mm-radius sphere centered on the maximum of the right hippocampal activation (24, −16, −14) found for the same contrast in the control group (see earlier). In the reverse contrast ($TC_P > TC_C$), regions in the left inferior parietal lobule and

Table 2. Coordinates of the Activation: Intragroup, Intergroup, and Correlation Analyses

Comparisons	Structure	*x*	*y*	*z*	*Z*-scores	*p*
Intragroup comparisons						
Healthy volunteers						
SC > SI	Right hippocampus	32	−16	−10	4.60	<0.0001[a]
	Right cerebellum	8	−44	−16	4.90	<0.0001[a]
	Left inferior temporal pole	−35	14	−28	4.94	<0.05[a]
	Left fusiform gyrus	−36	−60	−10	3.91	<0.05[a]
TC > TI	Right hippocampus	24	−16	−14	3.85	<0.0001[a]
	Right medial temporal gyrus	60	4	−20	4.73	<0.0001[a]
	Left medial temporal gyrus	54	−60	12	4.22	<0.0001[a]
	Left precuneus	−10	−40	48	4.30	<0.0001[a]
	Lingual gyrus	6	−78	2	4.03	<0.0001[a]
	Right cerebellum	30	−60	−20	4.26	<0.0001[a]
AD patients						
SC > SI	No difference					
TC > TI	No difference					
Intergroup comparisons						
Encoding						
$(SC - SI)_C - (SC - SI)_P$						
	Right hippocampus	30	−20	−12	3.18	<0.05[a]
	Left hippocampus	−24	−32	0	3.77	<0.001[b]
$(SC - SI)_P - (SC - SI)_C$						
	Right precuneus	16	−62	34	3.03	<0.001[b]
	Left precuneus	−12	−58	40	3.06	<0.001[b]
	Right superior parietal lobule	22	−62	62	3.06	<0.001[b]
	Left superior parietal lobule	−18	−60	58	2.86	<0.001[b]
$SC_C > SC_P$	No difference					
$SC_P > SC_C$	Right medial frontal gyrus	46	16	46	4.63	<0.05[a]
	Right medial frontal gyrus	46	48	−8	5.11	<0.001[a]
	Left inferior frontal cortex	−24	58	−8	4.55	<0.05[a]
	Right inferior parietal lobule	44	−66	42	5.49	<0.0001[a]
	Left inferior parietal lobule	−48	−58	48	4.92	<0.001[a]
	Left cerebellum	−10	−80	−30	3.92	<0.05[a]
Recognition						
$(TC - TI)_C - (TC - TI)_P$						
	Right hippocampus	26	−16	−16	3.83	<0.05[a]
	Right middle temporal gyrus	58	4	−22	3.76	<0.001[b]
	Right inferior temporal gyrus	38	22	−34	3.63	<0.001[b]
	Left inferior temporal gyrus	−32	12	−36	3.22	<0.001[b]
$(TC - TI)_P - (TC - TI)_C$						
	Right fusiform gyrus	42	−56	−8	3.06	<0.001[b]
$TC_C > TC_P$	Right hippocampus	26	−18	−18	3.09	<0.05[a]
$TC_P > TC_C$	Left inferior frontal gyrus	−58	18	0	5.04	<0.05[a]
	Left inferior parietal lobule	−48	−56	44	5.05	<0.05[a]
Correction analysis						
MMSE and BOLD signal during SC						
Patients	Right inferior parietal lobule	44	−76	32	4.03	<0.001[a]

[a]*p* values are corrected for multiple comparisons for the whole brain (false discovery rate, $p < 0.05$).
[b]Uncorrected *p* values.

SC = study correct; SI = study incorrect; TC = test correct; TI = test incorrect; AD = Alzheimer's disease; C = control subject; P = patient; MMSE = Mini-Mental State Examination; BOLD = blood oxygenation level dependent.

the left inferior frontal gyrus were hyperactivated in patients relative to control subjects (see Fig 4B).

CORRELATION ANALYSIS. Finally, we correlated the relative blood oxygenation level dependent signal intensity for remembered pairs at study and test with the patients' scores on the MMSE (range, 23–28). For study (SC pairs), a positive correlation was found in the same right inferior parietal region that was hyperactivated for SC pairs in patients relative to control subjects, correcting for a 15mm sphere centered on 44, −66, 42 (Fig 5). At test, no correlations with MMSE scores were observed.

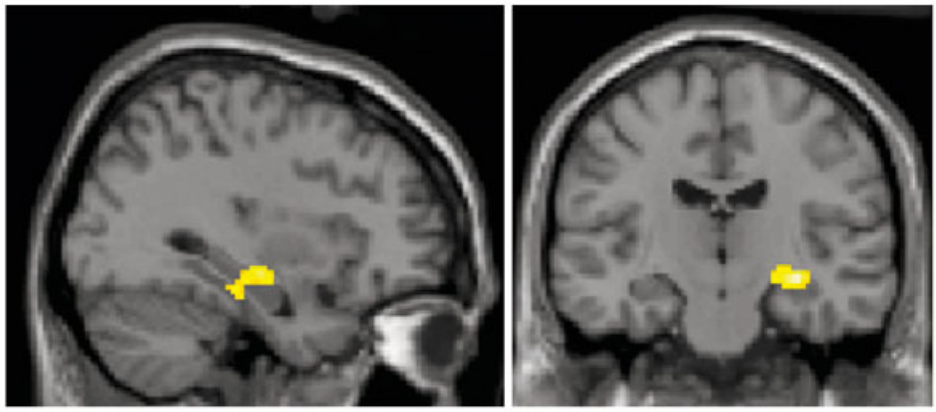


Fig 2. Study correct (SC) > study incorrect (SI) in the group of healthy volunteers: activation of the right hippocampus. $p < 0.05$, *whole-brain corrected (false discovery rate). See Table 2 for statistical significance and peak voxel coordinates. No difference was found for the same contrast in the patient group.*

Discussion

This is the first time to our knowledge that event-related fMRI has been used in a population of AD patients to examine memory-related activity. The behavioral results we report confirm that our face-name paired associative task is sensitive to mild cognitive decline in that AD patients scored significantly worse than matched control subjects. Significantly, patients with AD performed the task according to instructions even in the relatively stressful MRI environment. All patients fulfilling our inclusion criteria were scanned according to plan, and no experiment was discontinued because of patient distress.

The event-related fMRI technique allowed us to classify individual face-name pairs as correctly and incorrectly encoded and recognized. The pattern of brain activations for correctly versus incorrectly encoded and recognized pairs in the control group, particularly in the right hippocampus, was consistent with previous findings. When we compared these activations with those for the AD patients, we found that the right (and probably left) hippocampi were hypoactivated in patients for both encoding and recognition. However, patients also showed hyperactivation of parts of the parietal and frontal lobes bilaterally (though with a right-sided emphasis during encoding and a left-sided emphasis during recognition). We discuss these findings in more detail later, particularly in relation to whether hyperactivation of a frontoparietal network re-

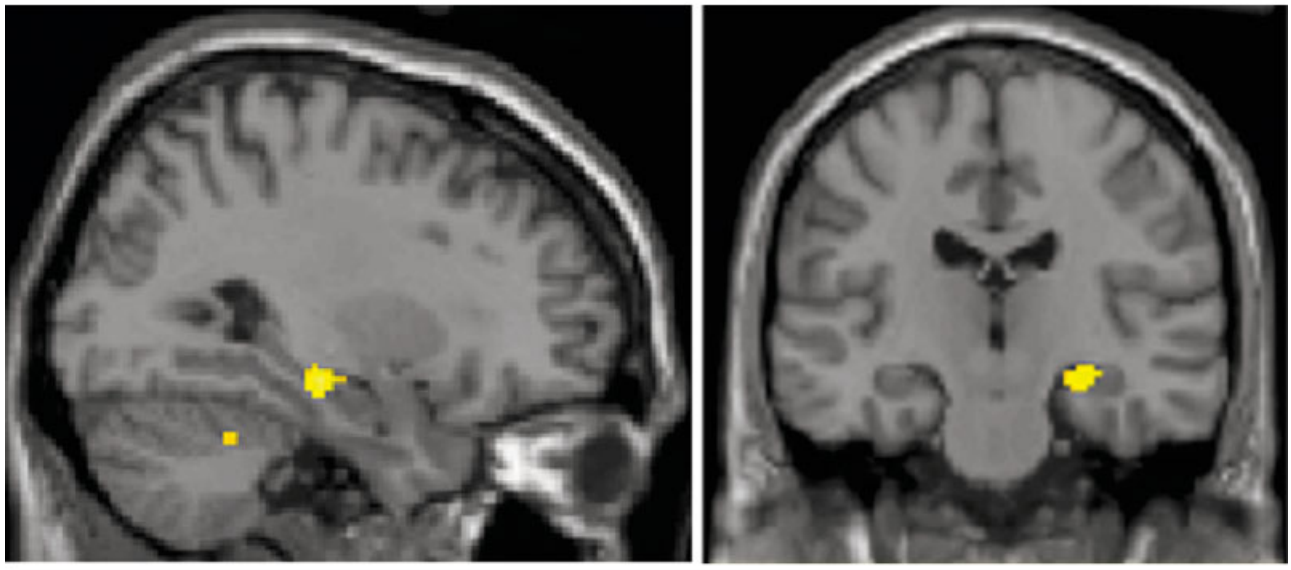


Fig 3. $(SC\text{-}SI)_V > (SC\text{-}SI)_{AD}$*: hypoactivation of the right hippocampus in patients relative to control subjects,* $p < 0.05$, *SVC (false discovery rate). See Table 2 for statistical significance and peak voxel coordinates. AD = Alzheimer's disease; SC = study correct; SI = study incorrect; SVC = small volume correction; V = healthy volunteers.*

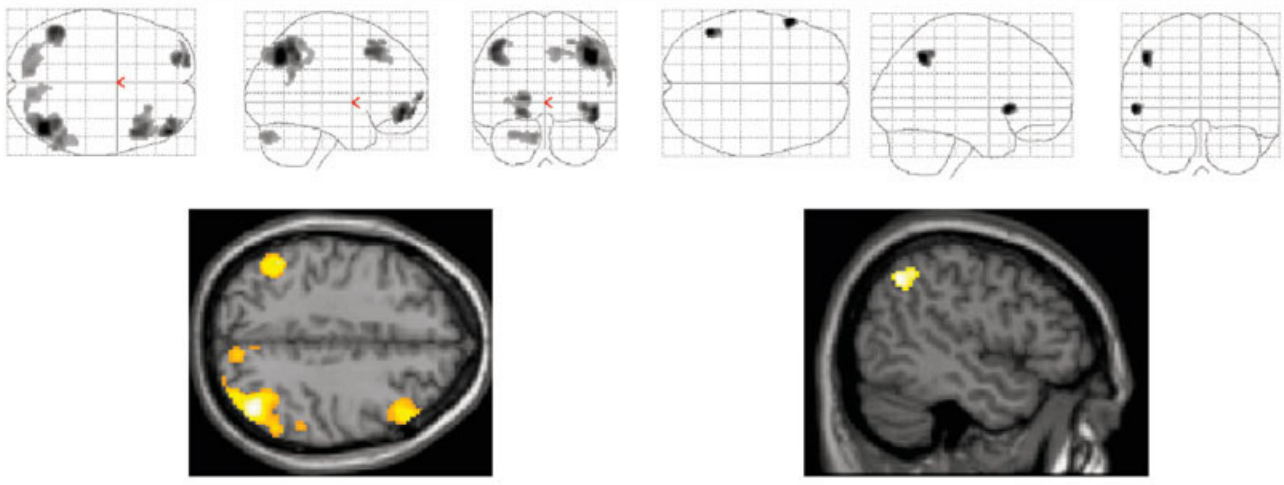


Fig 4. $SC_{AD} > SC_V$ (A) and $TC_{AD} > TC_V$ (B): hyperactivation of frontal and parietal regions in patients relative to control subjects during encoding (A) and recognition (B). p *< 0.05, whole-brain corrected (false discovery rate). See Table 2 for statistical significance and peak voxel coordinates. A parietofrontal cortical network is more activated in the patient group than in control subjects for SC and TC trials, with a right-sided emphasis during encoding and a left-sided emphasis during recognition. AD = Alzheimer's disease; SC = study correct; SI = study incorrect; TC = test correct; TI = test incorrect; V = healthy volunteers.*

flects compensatory strategies in the AD patients for associative memory.

Paired Associative Learning Task (PAL) and Alzheimer's Disease

Recent behavioral studies have shown that paired associative learning abilities are specifically impaired early in the course of the AD at a time when standard cognitive measures are unaffected, and therefore apparently less sensitive to early cognitive decline.[1] The task discriminates AD patients from patients with other neurodegenerative disease such as frontotemporal dementia or semantic dementia.[21,22] PAL performance was found to correlate significantly with subsequent diagnosis of AD in a group of mildly cognitively impaired patients.[23]

In our study, we designed and piloted a face-name paired-associate task to find a suitable compromise between task realizability for patients (patients answering at random were excluded from the study) and a task that was not too easy and consequently without ceiling effect for healthy volunteers (maximum, 91.6% correct answers). This entailed a four-alternative, forced-choice, associative recognition design, which is easier to administer in the scanner than, for example, cued recall of face-names. The behavioral data (both accuracy and reaction times) clearly showed that our task was sensi-

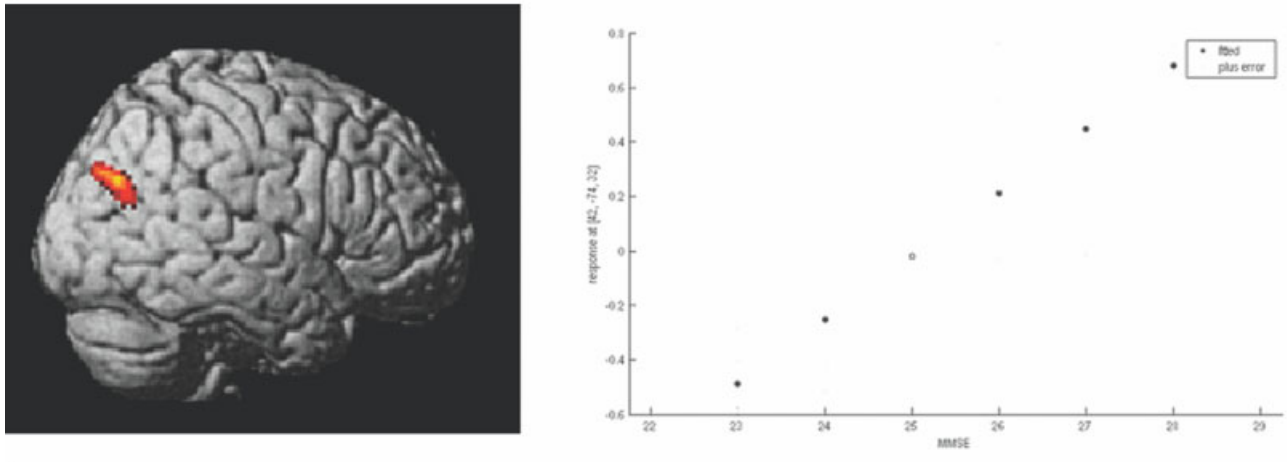


Fig 5. Correlation analysis between hemodynamic response during study correct (SC) and Mini-Mental State Examination in patients with Alzheimer's disease (at voxel 44, −76, 32). Threshold for image at p *less than 0.001, uncorrected for purposes of illustration. See Table 2 for statistical significance and peak voxel coordinates.*

tive enough to discriminate between AD patients and their matched control subjects.

WITHIN-GROUP COMPARISONS. We chose a face-name version of paired associative learning because such a task has been used in previous neuroimaging studies in healthy volunteers,[3,4,6] meaning that the pattern of activation when encoding and retrieving a novel face-name pair has been well characterized. The results from our control group replicated this general pattern, confirming the validity of our task. In particular, the hippocampus was reliably activated for both correct encoding and correct recognition of face-name pairs. The hippocampus appears crucial to this task, and its probable role is to bind together previously unrelated sensory, cognitive, and emotional items to form associations that will make up an episode in memory.[24]

No differential activation was found between remembered and forgotten pairs in the patient group, however, either at study or at test. Whereas lesser activation of these regions in the patients than control subjects might be expected, the absence of significant hippocampal activation in patients for correctly encoded or recognized associations is surprising because they performed the memory task above chance. This negative finding could just reflect a lack of statistical power, or it could be that patients remembered using a different cortical system based on some compensatory strategy (see later). The latter idea would suggest the possibility of a qualitative difference between the type of information encoded and retrieved during task performance by control subjects and AD patients (eg, relational vs unitized memories[25]).

BETWEEN-GROUP COMPARISONS. Direct comparisons of remembered versus forgotten face-name associations across patient and control groups confirmed the following: (1) hypoactivation of the hippocampus in patients relative to control subjects during both encoding and recognition, particularly on the right; and (2) hyperactivation of frontal and parietal regions in patients relative to control subjects. This difference was more extensive on the right during encoding and on the left during recognition. We consider several interpretations of this hyperactivation.

Memory Performance: A Possible Confound

As noted in the introduction, results of previous blocked studies may have been confounded by different overall performance levels between patients and their control subjects, and this event-related analysis was designed to overcome this effect. Because event-related analyses measure the average of responses to correct/incorrect trials, they are statistically unbiased by differences in the overall number of such trials. Nonetheless, there are more subtle effects of overall performance that can still affect interpretation of these averages. That is, the overall "difficulty" of a task may still modulate the response to individual trials within that task. One example of this arises in our forced-choice paradigm, for which 25% of trials can be "correct" by guessing alone. This means that a greater proportion of correct trials are likely to be guesses in the patient group (mean, 40% correct) than in control subjects (mean, 62% correct). Because the brain activity associated with guessing is likely to be different from that associated with memory, any difference between correct trials in patients and control subjects (eg, in frontoparietal networks) could reflect differential levels of guessing (a reflection of the greater difficulty patients have with this task), rather than true memory-related effects. One strategy to avoid this possible confound in future studies of AD patients is to match overall memory performance, in addition to using an event-related analyses (eg, see Morcom and colleagues[14]).

General "Difficulty" or "Cognitive Reserve" Effects

Neuroimaging studies have demonstrated correlations between brain activity and cognitive challenge in subjects with normal cognitive functions. The cortical networks engaged by tasks in healthy young volunteers are modulated by task difficulty.[26] That is, more complex stimuli or more demanding cognitive processing result in a greater magnitude and area of activation in regions critical to a task.[27] As performance improves, the signal intensity becomes smaller and more focal.[28] The same observation has been made in the neurodegenerative disease field. Thus, an increase in the number of neurons recruited, in response to greater difficulty or task demands, would produce greater hemodynamic activations in patients with a neurodegenerative process.[10]

One can argue that, in this study, the relative hyperactivation found the patient group may be due to a functional deactivation in the control group as found in previous studies.[29] This is unlikely because we found this parietofrontal cortical network hyperactivated in the patients group in the contrast SC > baseline (38, −68, 48, $Z = 8.93$; −46, −54, 50, $Z = 8.43$; 46, 16, 46, $Z = 7.44$; 46, 48, −8, $Z = 6.49$). Moreover, to assess the difference of relative signal modulation in the SC_p > baseline and SC_c > baseline contrasts, we performed a region of interest analysis centered on the region activated (right medial frontal gyrus: 46, 48, −8; right inferior parietal lobule: 44, −66, 42) in the $SC_p > SC_c$ comparison. We compared the result obtained in the two groups and found a significantly greater increase of the blood oxygenation level dependent signal in the patient group in the two regions (right medial frontal: patient, 1.78, control subjects, 0.42, $p < 0.05$; right inferior parietal lobule: patient, 1.49, control subjects, 0.67, $p < 0.05$). We believe that the AD patients were indeed hyperactivating these

regions during the successful compensation. Thus, the hyperactivations in the group of AD patients could reflect recruitment of additional cognitive resources or greater cognitive effort to maximize task performance. This proposal is similar to the theory of cognitive reserve. Cognitive reserve can be defined as an individual's capacity to compensate for cognitive decline in the face of advancing brain pathology. Stern[30] suggested that the cognitive reserve relies on optimized use of an increased number of residual healthy synapses or neurons ("hardware" compensation) or of alternative brain networks ("software" compensation). Our data suggest a software compensation strategy because the hyperactivated parietal and frontal regions in patients were not associated with task performance in control subjects (though this interpretation is attenuated somewhat by the lack of reliable activation of these regions in the patient group alone). Some further support for our proposal comes from the finding of a positive correlation between albeit a gross global cognitive score (MMSE) and encoding-related activity in the right inferior parietal region. This finding suggests that patients with greater (ie, better preserved) general cognitive abilities were better able to marshal compensatory resources.

Are Compensation Strategies Specific to Memory?

Studies evaluating the neuronal substrates of episodic memory in patients with AD have shown a variety of results. Interpretation has therefore been difficult and has not been facilitated by methodological confounds that have been discussed by several authors (see earlier and Sperling and colleagues,[6] Desgranges and colleagues,[31] Eustache and colleagues,[32] Grady and colleagues,[33] and Stern and colleagues[34]). Of particular interest is the study by Grady and colleagues.[33] It shows that patients with AD performing episodic and semantic memory tasks recruit an additional cortical network comprising the temporoparietal and prefrontal cortices. Activity in the latter correlates with accuracy of task performance.[33]

There are reasons to think that the hyperactivation we observe in patients is not specific to episodic memory. First, frontoparietal activity generally has been associated with visual attention and orienting.[35] Second, the lateralization of this hyperactivity during encoding and retrieval is opposite of the predictions of the influential HERA (hemispheric encoding and retrieval asymmetry) model based on results from healthy volunteers, which states that the left prefrontal cortex is more involved in episodic encoding and the right during episodic retrieval.[36]

The suggestion that frontoparietal hyperactivation is linked to engagement of a general attentional system may be testable with pharmacological manipulation. The acetylcholine deficit in AD has been investigated extensively,[37–39] and it is known that this neurotransmitter is implicated in attention.[40] We therefore suggest that the administration of cholinergic treatment may restore to some as yet undefined extent the attentional competencies in patients with early AD, and thus result in a lesser need for engagement (or hyperactivation) of this system. We are actively investigating this hypothesis with further studies.

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