PAPER

Hippocampal activation in patients with mild cognitive impairment is necessary for successful memory encoding

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Background: Episodic memory enables us to consciously recollect personally experienced past events. Memory performance is reduced in patients with mild cognitive impairment (MCI), an at-risk condition for Alzheimer's disease (AD).
Patients and methods: We used functional MRI (fMRI) to compare brain activity during memory encoding in 29 healthy elderly subjects (mean age 67.7 (SD 5.4) years) and 21 patients with MCI (mean age 69.7 (SD 7.0) years). Subjects remembered a list of words while fMRI data were acquired. Later, they had to recognise these words among a list of distractor words. The use of an event related paradigm made it possible to selectively analyse successfully encoded items in each individual. We compared activation for successfully encoded words between healthy elderly subjects and patients with MCI.
Results: The main intergroup difference was found in the left hippocampus and surrounding medial temporal lobe (MTL) regions for the patients with MCI compared with healthy subjects during successful encoding.
Conclusion: These results suggest that in patients with MCI, an increase in MTL activation is necessary for successful memory encoding. Hippocampal activation may help to link newly learned information to items already stored in memory. Increased activation in MTL regions in MCI may reflect a compensatory response to the beginning of AD pathology.

Episodic memory, which enables humans to consciously recollect personally experienced past events, is based on at least two fundamental mnemonic operations: memory formation and retrieval. Event related functional MRI (fMRI) provides a unique opportunity to study the neural correlates of these processes and their subcomponents, such as successful and failed encoding.[1]

Studies in young healthy subjects have shown that successful declarative memory formation, measured as the difference in brain activity during encoding between subsequently remembered and forgotten items, is accompanied by increases in activity in medial temporal and inferior prefrontal areas.[2–10] Structures within the medial temporal lobe (MTL) region, especially hippocampal formation,[7 11] are believed to be essential in establishing new memories.

Patients with mild cognitive impairment (MCI)[12] are characterised by significant memory impairment, which is not severe enough to interfere with usual activities of daily living.[13] The majority of patients with MCI go on to develop Alzheimer's disease (AD).

Patients with AD, in comparison with older controls, show consistently decreased MTL activation during encoding of new materials.[14–17] Fewer fMRI studies have investigated MTL encoding activation in patients with MCI,[15 16 18] showing inconsistent results. A recent fMRI study showed decreased MTL activation during a memory encoding task.[15] However, another study[16] found that only a subgroup of subjects with ''isolated memory decline'' demonstrated decreased hippocampal activation during encoding, whereas still another study[19] reported increased MTL activation in cognitively intact individuals genetically at risk for AD. The variability in these fMRI results may be because the groups differed in the degree of impairment and underlying neural pathology.

The degree of activation detected by fMRI within MTL regions during encoding strongly correlates with subjects' subsequent ability to remember the items encoded.[2 8] Decreased MTL activation in patients with MCI and AD has been associated with relatively poor performance on post scan memory testing.[14 15 17] In contrast, subjects who were genetically at risk for AD, but could successfully perform the fMRI encoding task, showed increased MTL activation. It has been hypothesised that increased MTL activation during successful encoding may represent a compensatory response that allows for relatively normal memory function in the face of developing pathological change[19] There is first evidence that elderly subjects with MCI and with a relatively preserved performance in the fMRI memory task show such a compensatory increased hippocampal response in comparison with healthy subjects, while patients with AD who exhibited poorer performance in the task had lower hippocampal activation.[20]

To further examine this question, it is not sufficient to compare general encoding related activation between patients with MCI and healthy subjects as this comparison would be confounded by task performance. Therefore, we used an event related fMRI paradigm, where subjects are instructed to remember visually presented words. According to task performance in subsequent recognition memory tests, all learned items can then be separated into those that are later remembered (subsequent hits) and those that are later forgotten (subsequent misses), individually for each subject. By comparing brain activation between healthy subjects and patients with MCI only for subsequent hits, brain regions can be identified that differ between groups during successful encoding into episodic memory. It has been shown previously that the degree of neural activity increases with the demands of the cognitive task and that the magnitude and spatial extent of brain activation increases with cognitive effort.[21–23] We

Abbreviations: AD, Alzheimer's disease; BA, Brodmann area; fMRI, functional MRI; HRF, haemodynamic response function; ISI, interstimulus interval; MCI, mild cognitive impairment; MTL, medial temporal lobe; VLMT, Verbal Learning and Memory Test

Table 1 Demographic data and neuropsychological screening results

	Elderly controls (n = 29)	MCI patients (n = 21)	Difference between groups
Sex (F:M)	17:12	12:9	$\chi^2 = 0.157$, p = 0.692, NS
Age (y)	67.8 (5.4; 60–81)	69.7 (7.0; 59–82)	t = −1.189, p = 0.262, NS
SIDAM*	52.1 (2.0; 46–55)	47.9 (3.1; 41–54)	t = 5.665, p<0.001
MMSE†	28.8 (1.2; 27–30)	26.6 (1.4; 24–30)	t = 6.069, p<0.001
Verbal learning/immediate recall‡	48.5 (6.6; 38–60)	42.1 (6.3; 28–59)	t = 3.391, p = 0.001
Delayed recall§	9.9 (2.3; 5–15)	7.1 (2.7; 4–14)	t = 3.601, p = 0.001
Recognition¶	12.0 (2.4; 5–15)	9.6 (3.5; 0–14)	t = 2.593, p = 0.013

MCI, mild cognitive impairment.
*Structured Interview for the Diagnosis of Dementia of the Alzheimer type, multi-infarct dementia and dementia of other aetiology according to the International Classification of Diseases-10 and the Diagnostic and Statistical Manual of Mental Disorders, version IV; scores may range from 0 to 55.
†Mini-Mental State Examination; scores may range from 0 to 30.
‡Immediate recall/sum of five learning trials of 15 words; scores may range from 0 to 75.
§Delayed recall of the 15 word list after 20 minutes; scores may range from 0 to 15.
¶Correct recognitions of the 15 words out of a 50 word list, less the false alarms.
Values are mean (SD; range).

hypothesise that successful memory encoding, which should be more demanding for patients with MCI than for healthy elderly subjects, would result in increased MTL activation in patients with MCI.

MATERIALS AND METHODS

Subjects

Twenty-one participants with MCI (12 female, 9 male) and 29 (17 female, 12 male) elderly control subjects with unimpaired memory participated in the study. They were recruited through newspaper advertisements and from the inpatients and outpatients of the Department of Psychiatry, Tübingen University Hospital. Sociodemographic and clinical characteristics are shown in table 1. All subjects had normal or corrected-to-normal vision and were right-handed, according to the Edinburgh Handedness Index.[24] All subjects were interviewed, tested and given a medical and psychiatric evaluation by an experienced psychiatrist (DL). Subjects were excluded if they had been diagnosed with a psychiatric, neurological or medical disease. Subjects underwent a further neuropsychological screening procedure, including the SIDAM (Structured Interview for the Diagnosis of Dementia of the Alzheimer type, multi-infarct dementia and dementia of other aetiology according to the International Classification of Diseases-10 and the Diagnostic and Statistical Manual of Mental Disorders version IV) and also the Mini-Mental State Examination[25] to exclude the presence of dementia and evaluate global cognitive functioning. Additionally, the Verbal Learning and Memory Test (VLMT)[26] was administered to account for verbal encoding/immediate recall, delayed recall and recognition deficits in all participants. In a consensus conference comprising three psychiatrists and one neuropsychologist, subjects were diagnosed with MCI if they fulfilled the criteria according to Petersen and colleagues,[13] comprising memory complaint, objective memory impairment, normal general cognitive function, intact activities of daily living and not demented. In the consensus conference, overall performance in the tests and clinical impression was evaluated. As a measure of ''objective memory impairment'', an impaired performance on the VLMT (approximately 1 SD or below) was used in our study. Plausibility and homogeneity of the test results were important for the decision. Subjects who showed conflicting results in the memory domain were not included in the study.

The study was approved by the local ethics committee. All participants signed written informed consent prior to participation and were paid a small fee for participation.

Stimuli and task

Stimuli consisted of 360 German nouns that were matched for imagery, concreteness and meaningfulness.[27]

The experiment consisted of six runs: two encoding and four recognition runs. Each of the encoding runs was followed by two recognition runs so that all words learned during that run were shown in the two subsequent recognition runs.

During each of the encoding runs, 90 randomly selected words were presented for 2000 ms each. Words were presented visually at a randomised interstimulus interval (ISI) of 2–22 s (mean 12 s). The jittering introduced by variable ISIs allowed for a complete mapping of the haemodynamic response function. During the ISI, a string of eight x was presented as a low level baseline. Subjects were instructed to memorise the words for later recognition and to press the right of two response buttons once for every word.

During each of the recognition runs, 45 words from the preceding encoding run (targets) were randomly intermixed with 45 distractors (non-targets). Words were presented visually at the same presentation rate as during the study phase. During the ISI, a string of eight x was presented as a low level baseline. Subjects were required to make an old/new decision for each presented word. By pressing the right button they indicated a previously learned word, while they used the left button for words that were considered new. Button presses were executed with two fingers of the right hand.

In this report, we focus on data from the encoding sessions only; the retrieval data have been reported elsewhere.[28]

Functional MRI data acquisition

All scans were performed on a 1.5 T whole body scanner (Siemens Sonata, Erlangen, Germany) using standard gradients and an eight channel head coil. Subjects lay in the supine position, while head movement was limited by foam padding within the head coil. Words were projected on a transparent screen which could be seen via a mirror attached to the head coil in front of the subject's head. If necessary, participants wore fMRI compatible glasses to ensure optimal visual acuity. For each subject, we acquired six series, two for the study runs and four for the recognition runs, of EPI scans, covering the whole brain, including five initial dummy scans parallel to the AC/PC line with the following parameters: number of slices 25; slice thickness 4.5 mm; interslice gap 1.00 mm; matrix size 64×64; field of view 192 mm×192 mm; repetition time 2 s; echo time 40 ms; flip angle 90°. Each of the six runs comprised 462 scans.

Table 2 Behavioural data

	Elderly controls	MCI patients
% subsequent hits	70.71 (15.72)	63.41 (18.04)
% subsequent misses	28.14 (15.38)	34.44 (17.92)
RT subsequent hits	1299.64 (381.07)	1151.47 (249.07)
RT subsequent misses	1309.89 (423.25)	1137.97 (305.50)

MCI, mild cognitive impairment; RT, reaction time.
Values are mean (SD).

Functional MRI data analysis

MRI images were analysed using Statistical Parametric Mapping (SPM2, www.fil.ion.ucl.ac.uk) implemented in MATLAB 6.5 (Mathworks Inc., Sherborn, Massachusetts, USA). After discarding the first five volumes, all images were realigned to the first image to correct for head movement. Unwarping was used to correct for the interaction of susceptibility artefacts and head movement. After realignment and unwarping, the signal measured in each slice was shifted relative to the acquisition time of the middle slice using a sinc interpolation in time to correct for their different acquisition times. Volumes were then normalised into standard stereotaxic anatomical MNI space by using the transformation matrix calculated from the first EPI scan of each subject and the EPI template. Afterwards, the normalised data with a resliced voxel size of 3×3×3 mm were smoothed with a 10 mm FWHM isotropic Gaussian kernel to accommodate intersubject variation in brain anatomy. The time series data were high pass filtered with a high pass cut-off of 1/128 Hz. The autocorrelation of the data was estimated and corrected for.

For each subject, stimuli were individually classified into subsequent hits and subsequent misses according to the subject's performance during the recognition phase of the experiment. Words that elicited no reaction were modelled separately but not considered in later analyses.

The expected haemodynamic response at stimulus onset for each event type (subsequent hits and subsequent misses during encoding) was modelled by two response functions, a canonical haemodynamic response function (HRF) and its temporal derivative. The temporal derivative was included in the model to account for the residual variance resulting from small temporal differences in the onset of the haemodynamic response, which is not explained by the canonical HRF alone. The functions were convolved with the event train of stimulus onsets to create covariates in a general linear model. Six movement parameters (three translations, three rotations) were included in the model as covariates of no interest to capture residual movement related artefacts. Subsequently, parameter estimates of the HRF regressor for each of the different conditions were calculated from the least mean squares fit of the model to the time series. Parameter estimates for the temporal derivative were not considered further in any contrast.

Single subject contrast maps were determined for the contrasts of interest according to the general linear model approach of SPM2: (1) subsequent hits versus subsequent misses during the study for healthy subjects; (2) subsequent hits versus subsequent

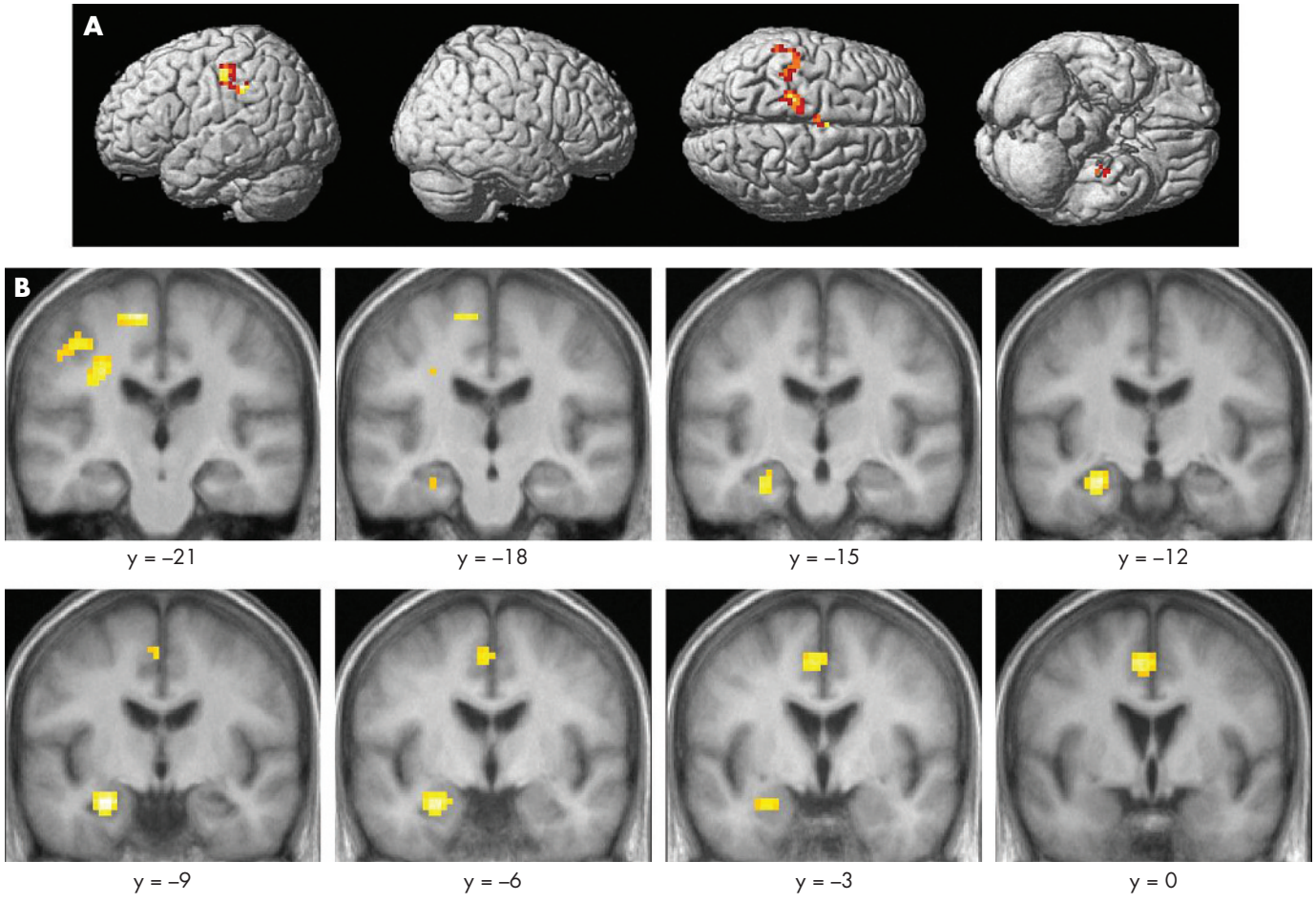

Figure 1 Group difference during the study for subsequent hits. Regions were activated more strongly in patients with mild cognitive impairment than in healthy controls for subsequent hits during the study. The activation map is shown overlaid onto a canonical brain rendered in three dimensions (A) and superimposed onto selected coronal slices of the mean high resolution T1 weighted volume (B) at $p<0.05$, corrected across the whole brain. Slices are numbered according to the coordinates of Talairach and Tournoux.[30]

Table 3 Activation peaks of the intergroup contrast with their localisation. Significance level and the size of the respective activation cluster (number of voxels) at $p<0.05$, corrected

Anatomical region	BA	Coordinates x	y	z	T value	No of voxels
Study hits: MCI patients > healthy subjects						
Left hippocampus		−27	−10	−16	5.05	59
Left medial frontal gyrus	6	−12	−18	57	4.65	43
Left cingulate gyrus	24	−6	2	45	4.33	41
Left postcentral gyrus	3	−36	−24	44	4.29	156

BA, Brodmann area nearest to the coordinate and should be considered approximate; MCI, mild cognitive impairment. Coordinates are listed in Talairach and Tournoux[30] atlas space.

misses during the study for patients with MCI; (3) subsequent hits versus baseline for healthy subjects; (4) subsequent hits versus baseline for patients with MCI.

An SPM2 group analysis was performed by entering these contrast images into random effects analyses using one sample t tests to determine within group effects and two sample t tests for between group analyses. For all group analyses, we applied a voxel-wise threshold of $p<0.001$. A Monte Carlo simulation of the brain volume in the current study was conducted to establish an appropriate voxel contiguity threshold.[29] Assuming an individual voxel type I error of $p<0.001$, a cluster extent of 20 contiguous resampled voxels was indicated as necessary to correct for multiple voxel comparisons at $p<0.05$. The reported voxel coordinates of activation peaks were transformed from MNI space to Talairach and Tournoux atlas space[30] by non-linear transformations (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

RESULTS

Behavioural results

Table 2 shows the behavioural data of the two groups during the fMRI experiment. The percentage of hits did not differ significantly between elderly controls and patients with MCI ($t = 1.522$; $df = 49$; NS). Furthermore, as can be seen from table 2, accuracy in healthy individuals and in the MCI group was well above chance (elderly controls: $t = 7.093$; $df = 28$; $p<0.001$; patients with MCI: $t = 3.408$; $df = 20$; $p = 0.003$). Also, there was no significant group difference for reaction times between hits ($t = 1.555$; $df = 49$; NS) or misses ($t = 1.612$; $df = 49$; NS).

Imaging results

We intended to examine the between group difference in brain activation during successful encoding between elderly healthy subjects and patients with MCI. Therefore, we used a two sample t test to compare activity during the study for those items which were subsequently remembered correctly. We found no significantly stronger activations in healthy controls compared with patients with MCI. Looking at the opposite contrast, stronger encoding activation was found for patients with MCI than for healthy controls for subsequently remembered items, with the most significant activation cluster in the left anterior hippocampus, extending into the surrounding entorhinal and perirhinal cortex (fig 1, table 3). Mean response amplitude for healthy controls and patients with MCI in this cluster is depicted in fig 2.

Further activations were located in the left parietal and frontal lobes: one cluster comprised parts of the precentral gyrus, the inferior parietal lobule and the supramarginal gyrus (Brodmann area (BA) 2, 3, 40), one cluster was located in the precentral and the medial frontal gyrus (BA 3, 4), while another one comprised the medial frontal gyrus and anterior cingulate (BA 6, 24).

To further clarify the relationship between MTL activity and memory performance in patients with MCI compared with healthy controls, we looked at the correlation between memory performance on the independent memory task conducted before scanning (VLMT) and the amount of MLT activation during encoding. This was calculated as the effect size of the BOLD response averaged across trials. Figure 3 shows the

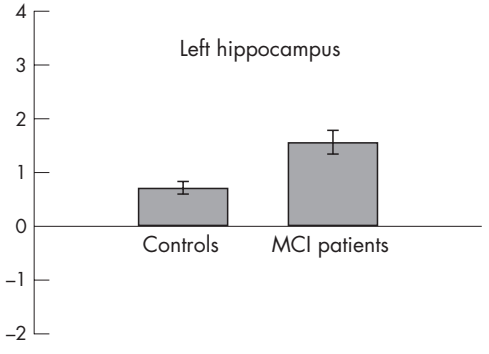

Figure 2 Parameter estimates for hits in the medial temporal lobe (MTL) activation cluster. Plots of the parameter estimates, indexing response amplitude in the MTL activation cluster, are shown for healthy controls and patients with mild cognitive impairment (MCI). The graph shows the mean parameter estimate and the standard error for the healthy controls and the patient group, respectively. Labelling of the y axis is in arbitrary units.

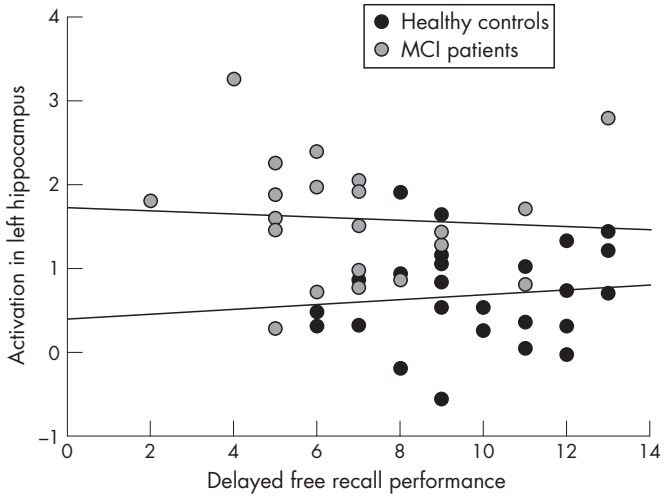

Figure 3 Correlation of memory performance on the independent memory task and hippocampal activation during encoding. Plot of the correlation between memory performance on the independent memory task conducted before scanning (Verbal Learning and Memory Test (VLMT)) and the amount of medial temporal lobe activation during the encoding task. Memory performance during the delayed recall task of the VLMT is plotted against the amplitude of activation of the most significant cluster of the intergroup contrast, which is located in the left hippocampus. Data from healthy controls and patients with mild cognitive impairment (MCI).

Table 4 Activation peaks of the intragroup contrasts with their localisation

Anatomical region	BA	Coordinates			T value	No of voxels
		x	y	z		
Healthy subjects: study hit > miss						
Right precuneus	19	33	−77	40	4.29	24
Right middle frontal gyrus	10	36	47	17	4.80	35
Right middle temporal gyrus	39	36	−66	23	4.01	25
Left inferior parietal lobule	40	−42	−53	41	4.34	42
MCI patients: study hit > miss						
Left middle occipital gyrus	19	−36	−83	21	4.18	40
Right fusiform gyrus	20	33	−36	−18	5.00	47
Left precuneus	23	0	−60	20	4.88	27
Left cerebellum		−3	−51	−38	4.87	22
Left middle frontal gyrus	9	−45	13	30	4.49	20

BA, Brodmann area nearest to the coordinate and should be considered approximate; MCI, mild cognitive impairment.
Coordinates are listed in Talairach and Tournoux[30] atlas space.
Significance level and the size of the respective activation cluster (number of voxels) at $p<0.05$, corrected.

correlation between memory performance during delayed recall after distraction (pre-scanning) and the amplitude of MTL activation in the most significant cluster in the left hippocampus. As the data show, memory performance in patients with MCI was lower compared with healthy controls. At the same level of memory performance, however, patients with MCI showed an elevated level of hippocampal activation.

We also looked at the subsequent memory effect (ie, the difference in activation during study between those items that were successfully encoded and those that were not). This contrast was examined separately for each of the two groups.

As shown in table 4, in patients with MCI, the subsequent memory effect was found in the right fusiform gyrus (BA 20). Furthermore, there was activation in the left frontal lobe, located in the lateral prefrontal cortex and in the middle frontal cortex (BA 9). There was also activation in the left parietal and occipital lobes, comprising the middle occipital gyrus, extending into the left middle temporal gyrus (BA 19), and in the left precuneus and posterior cingulate (BA 23, 31). An area of the left cerebellum was also activated.

The opposite effect, stronger activation for subsequently forgotten items, showed no significant activation.

In contrast, in healthy subjects, the difference between subsequently remembered and subsequently forgotten items was less pronounced, as shown in table 4. Apart from activation in the right anterior prefrontal cortex, comprising the middle and superior frontal gyri (BA 10), activation was only found in the bilateral occipital and posterior parietal and temporal areas—namely, in the right superior occipital and middle temporal gyrus and right precuneus (BA 19) and left inferior and superior parietal lobule (BA 40).

The opposite effect, a decrease in activation for successful encoding, could not be identified in healthy control subjects. There was also no group by condition (''hits'' over ''misses'') interaction.

DISCUSSION

The aim of our study was to define differences in brain activation measured with fMRI during successful episodic memory encoding in healthy elderly subjects compared with patients with MCI. Participants were examined while they intentionally learned words. Later in the same session, subjects had to recognise learned words among distractor words. In the analysis, we concentrated on brain activation during learning which led to successful memory encoding (ie, activation for words which were remembered correctly in the recognition phase). Patients with MCI showed increased activation in the anterior MTL compared with healthy subjects during successful encoding. In contrast, healthy subjects did not show any increased activation compared with patients with MCI.

In healthy control subjects, episodic memory encoding is related to the degree of MTL activation.[2 3 8 9] Furthermore, it has been shown that greater cognitive effort or a more demanding cognitive task results in an increase in neural activity.[21–23] In light of these findings, a greater increase in signal intensity in brain regions necessary for successful memory encoding among patients with MCI suggests that additional cognitive effort was necessary to accomplish the task successfully. We hypothesise that such increased brain activity may be the result of a compensation mechanism in persons with memory decline using additional cognitive resources to bring encoding to a normal level.

As the data depicted in figure 3 show, memory performance in patients with MCI was lower compared with healthy controls although this difference did not reach statistical significance. At the same level of memory performance, however, patients with MCI show an elevated level of hippocampal activation. It is interesting to note that in healthy controls, an increase in memory performance is accompanied by an increase in hippocampal activation, while patients with MCI show a negative correlation. This further points to the assumption that in patients with MCI, the increase in activation in the left hippocampus is related to the recruitment of additional cognitive resources.

The same assumption might hold true for the differential activation found in the medial frontal areas. It has been shown that persons at genetic risk for developing AD show increased activation of the anterior cingulate gyrus during a memory task.[19] This finding was interpreted as greater cognitive effort employed by these subjects to achieve the same level of performance as subjects who are not at genetic risk.

Our data suggest that functional alterations within the MTL regions during the evolution of AD pathology may precede the development of significant atrophy. This hypothesis must be tested in future longitudinal studies in patients with MCI, where functional and structural data can be compared. Findings from other studies point in the same direction. In healthy persons carrying the APOE e4 allele with greater risk for AD, enhanced activation of the hippocampus and prefrontal cortex during explicit memory tasks has been found in comparison with healthy carriers of the APOE e3 allele,[19] suggesting that otherwise healthy APOE e4 carriers are beginning to employ added cortical processing (ie, cognitive work) to maintain memory performance as covert pathology develops. Another study[18] re-examined this question, focusing specifically on the hippocampus and adjacent structures. Strikingly, these authors showed that those subjects who went on to develop memory decline over the next 2.5 years had the highest levels of brain activation in the right parahippocampal

gyrus during memory encoding. When AD pathology proceeds further, and by the time AD is diagnosed clinically, memory related MTL activation is decreased.[14–17] Presumably, MTL degeneration has at that time proceeded so far as to avert a compensatory hyperactivation. Our data presented here support the hypothesis that there is a phase of increased MTL activation early in the course of AD development, prior to clinical dementia.

The reason for the increased MTL activation during memory encoding in MCI has not yet been completely elucidated. Individuals with MCI might encode information using a different cognitive processing strategy.[31] Given that the MTL is highly interconnected with neocortical brain regions, changes in its activation may reflect differences in the recruitment of neural networks outside the MTL, as has been observed in patients with AD.[32–34] Additional neural resources may be recruited in order to compensate for the beginning stages of AD pathology, a mechanism which has been suggested by animal studies.[35]

The absence of MTL activation in the hits>misses contrast may be explained in two ways. Firstly, the behavioural results (hits, misses) during our recognition phase rests on at least two separate processes, successful encoding and successful retrieval. If one of these fails, we get a ''miss''. If there are overly unsuccessful retrieval trials, the successful encoding trials may thus be ''diluted''. Secondly, in MCI as well as in healthy subjects, the number of hits was about twice as large as for the misses. So the variance of the data differs between event types which might preclude significance of weaker signal changes.

Apart from MTL activation, we also found increased activation of the left inferior parietal area, including the supramarginal gyrus. This region is often activated by tasks requiring verbal working memory and is believed to be part of a phonological loop that supports rehearsal and short term-maintenance of phonological material.[36 37] Possibly, increased involvement of phonological working memory and silent rehearsal of the to-be-learned words is necessary for successful memory encoding in patients with MCI.

In conclusion, it may be possible to detect alterations in the MTL early in the prodromal phase of the disease, at a time when disease modifying or neuroprotective strategies may have great clinical impact.[38] Further fMRI studies investigating the relationship between MTL activation, memory performance and clinical status across the continuum of MCI should clarify whether fMRI measures can be translated into markers for early disease detection or a tool for monitoring the effects of disease modifying therapies.[39] Early detection of alterations in brain function that underlie focal memory impairment has the potential to identify candidates for treatment that may halt or delay progression of cognitive deficits.

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NEUROLOGICAL PICTURE

Herpes zoster duplex bilateralis

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Herpes zoster (HZ), caused by reactivation of varicella zoster virus (VZV) from latency in a sensory ganglion, is almost always a condition involving a single dermatome.[1 2] Usually it occurs because of an age related decline in cellular immunity or immune compromised conditions. When spreading, it might involve one or two adjacent dermatomes or disseminate systemically (disseminated HZ).[3] The simultaneous reactivation of VZV from more than one ganglion is an extremely rare condition.[4]

Case report

A 64-year-old Arab woman was hospitalised with generalised weakness, urinary tract infection and a vesicular eruption on her back and thigh.

Four months previously she had been diagnosed with polymyositis associated antisynthetase syndrome, treated with 60 mg/day prednisone which was gradually tapered down to 20 mg/day by the time of presentation. She had type II diabetes and sustained a left basal ganglia stroke 2 years prior to her presentation.

On physical examination, she was afebrile, alert and fully oriented. She did not have organomegaly or lymphadenopathy without residual deficit from the stroke. She had a vesicular eruption, confined to dermatomes D8 on the left and L4 on the right (figs 1, 2). Laboratory tests, including complete blood count and basic biochemistry panel, were unremarkable, except for a C reactive protein level of 3.7. Diagnosis of HZ in these two dermatomes was established and treatment with intravenous acyclovir 10 mg/kg three times a day was initiated, followed by gradual improvement with crusting of the lesions. No recurrent zosteriform lesions were noticed during a follow-up period of 2 months.

Discussion

Following chicken pox, VZV establishes latent infection in peripheral sensory ganglia. Although the mechanisms of VZV reactivation from latency are unknown, its association with immunological decline suggests that an effective immune system maintains the viral genome in the latently infected cell and prevents viral replication and spread via retrograde axonal flow to the skin.[5] Although the latent viral genomes are present in many peripheral sensory ganglia,[6] HZ is usually confined not only to a single dermatome but also, and unlike reactivations of herpes simplex virus, to a single episode. Thus it seems that the biological context that supports the phenomenon of reactivation from a single ganglion under systemic immune compromised conditions also requires local factors: these may include the number of viral copies present in the tissue/cell or local trauma such as pressure on the nerve root or ganglion. The context that enables VZV reactivation seems to be so restrictive and dependent on local factors that simultaneous reactivation becomes an extremely rare phenomenon. While in the present case the mechanisms of bilateral VZV reactivation are unknown, it seems that the combined severe immunosuppression provided the required milieu to facilitate such a phenomenon. Whether it occurred independently in two separate ganglia or was caused by viral spread from one ganglion to another remains speculative.

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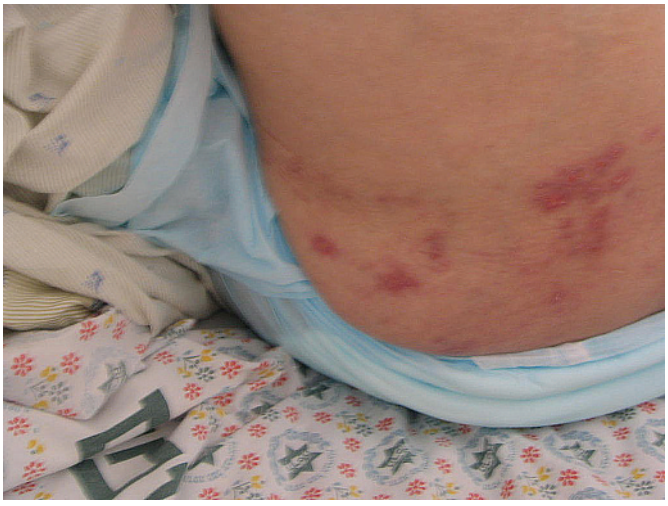

Figure 1 Zostiform vesicular eruption within the D8 dermatome on the left.

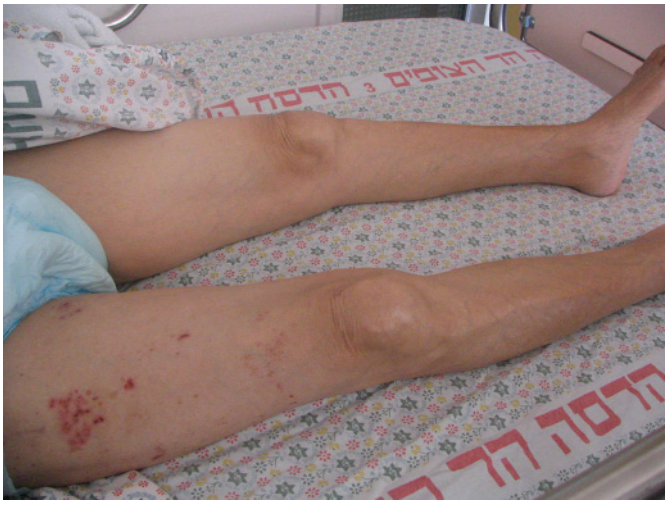

Figure 2 Zostiform vesicular eruption within L4 on the right.

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Informed consent was obtained for publication of figs 1 and 2.

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