Relation between medial temporal atrophy and functional brain activity during memory processing in Alzheimer’s disease: a combined MRI and SPECT study

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Objective: To investigate the relation between atrophy of the hippocampal region and brain functional patterns during episodic memory processing in Alzheimer’s disease.

Patients and methods: Whole brain structural magnetic resonance imaging (MRI) data and single photon emission computed tomography (SPECT) measures of regional cerebral blood flow (rCBF) were obtained during a verbal recognition memory task in nine subjects with mild Alzheimer’s disease and 10 elderly healthy controls. Using the statistical parametric mapping approach, voxel based comparisons were made on the MRI data to identify clusters of significantly reduced grey matter concentrations in the hippocampal region in the Alzheimer patients relative to the controls. The mean grey matter density in the voxel cluster of greatest hippocampal atrophy was extracted for each Alzheimer subject. This measure was used to investigate, on a voxel by voxel basis, the presence of significant correlations between the degree of hippocampal atrophy and the rCBF SPECT measures obtained during the memory task.

Results: Direct correlations were detected between the hippocampal grey matter density and rCBF values in voxel clusters located bilaterally in the temporal neocortex, in the left medial temporal region, and in the left posterior cingulate cortex during the memory task in the Alzheimer’s disease group (p < 0.001). Conversely, measures of hippocampal atrophy were negatively correlated with rCBF values in voxel clusters located in the frontal lobes, involving the right and left inferior frontal gyri and the insula (p < 0.001).

Conclusions: Hippocampal atrophic changes in Alzheimer’s disease are associated with reduced functional activity in limbic and associative temporal regions during episodic memory processing, but with increased activity in frontal areas, possibly on a compensatory basis.

The cardinal clinical feature of Alzheimer’s disease is a pronounced loss of episodic memory. The disease involves an uneventful and progressive loss of neurones, associated with the development of amyloid containing neuritic plaques and neurofibrillary tangles. These pathological changes occur first and with greatest severity in medial temporal structures, including the hippocampus and parahippocampal gyri — regions that are thought to be critical for episodic memory processes. The prominence of medial temporal abnormalities in early Alzheimer’s disease has been confirmed by many in vivo magnetic resonance imaging (MRI) studies, which have reported significant grey matter atrophy in the hippocampal region in Alzheimer subjects relative to healthy controls, often in direct proportion to the degree of memory impairment.

Functional imaging techniques have also been used to compare groups of patients with Alzheimer’s disease with healthy controls, most often measuring resting regional cerebral blood flow (rCBF) or regional glucose metabolism with positron emission tomography (PET) or single photon emission computed tomography (SPECT). A pattern of hypoactivity in the temporal and parietal association cortices in Alzheimer patients is the most characteristic finding in those studies, detected either by visual inspection or by conventional quantitative analyses using regions of interest (ROI). More recent studies, involving equipment of higher spatial resolution and voxel based statistical parametric mapping (SPM) methods for image analysis, have also been able to document resting activity decrements in the medial temporal region in Alzheimer’s disease, as well as in the posterior cingulate gyrus and precuneus in very early stages of the disorder.

Several functional imaging studies have also examined brain activity patterns in Alzheimer patients and healthy controls during the performance of memory activation paradigms, using PET, SPECT, or functional MRI. These studies have often employed tasks involving episodic memory retrieval processes, which in healthy subjects engage a distributed network of regions including the medial temporal, prefrontal, and lateral parietal cortices, as well as the precuneus, cingulate gyrus, and cerebellum. In Alzheimer patients, activation of the medial temporal region during memory tasks is infrequent. On the other hand, patients with mild Alzheimer’s disease often show memory related activity increases in the prefrontal cortex, with a broader spatial extent relative to healthy controls. These frontal activity increases have often been interpreted as a functional compensatory response, related to the increased effort needed by patients with Alzheimer’s disease to perform the tasks.

The relation between findings from the structural and functional imaging fields in Alzheimer’s disease has been little...
methods
subjects and clinical assessment
Nine patients with Alzheimer's disease meeting NINDS/ADRDA criteria for probable Alzheimer's disease20 took part in the study. They were interviewed with the Cambridge mental disorder section for assessment of cognitive function (CAMDEX), and examined with cranial CT, urinalysis, and blood tests including full blood count, liver, renal, and thyroid function tests, vitamin B12 and folate levels, and syphilis serology. Patients with a Hachinski ischaemic score of ≥ 4 or a history of significant hearing deficits were excluded. All patients had scores on the mini-mental state examination (MMSE)21 of ≥ 18.

Three Alzheimer patients were not on any psychotropic drugs; the remaining six were receiving acetylcholinesterase inhibitor drugs (five patients), antidepressants (two patients), and antipsychotic drugs (one patient).

A control group of 10 healthy elderly subjects was also studied. They were free of symptoms suggestive of physical or mental disorder, based on the CAMDEX interview, general medical questioning, and physical and neurological examination. All healthy controls had an MMSE score of ≥ 28, and a Hachinski ischaemic score lower than 4. No subject in this group was taking any class of psychotropic drug.

A summary of the demographic and clinical characteristics of the two groups is given in table 1. The Alzheimer's disease and healthy control groups did not differ significantly in terms of age, sex, or handedness. There were trends toward a greater number of years of education and a higher socioeconomic status as assessed by standardised criteria23 in the Alzheimer group (table 1).

Subjects from both groups also underwent a neuropsychological test battery including subitems for language comprehension, praxis, remote memory, and recent memory from the CAMDEX section for assessment of cognitive function (CAMCOG); a category verbal fluency task35; and the Fuld object-memory evaluation (FOME).36 Mean scores on these neuropsychological variables for Alzheimer's disease patients and controls are also given in table 1.

Mri acquisition and analysis
Mri images were obtained using a 1.5 Tesla Philips Gyroscan S15-ACS scanner (Philips Medical Systems, Eindhoven, Netherlands). A series of contiguous 1.2 mm thick coronal images across the entire brain was acquired, using a T1 weighted fast field echo sequence (time of echo (TE) = 9 ms, time of repetition (TR) = 30 ms, flip angle = 30°, field of view = 240 mm, 205 × 256 matrix).

Images were analysed with statistical parametric mapping software (SPM99), using the voxel based morphometric (VBM) approach as described by Ashburner and Friston.37 Images were spatially normalised with linear and non-linear transformations into a stereotaxic space that approximates the space defined in the atlas of Talairach and Tournoux,32 with a final voxel size of [2 mm]. The normalised images were then segmented into grey matter, white matter, and cerebrospinal fluid by using a modified mixture model cluster analysis technique.38 This method uses prior probability maps which are overlaid onto the images in order to classify each voxel in terms of its probability of belonging to a particular tissue class.

Table 1 Clinical and neuropsychological characteristics of subjects with Alzheimer's disease (n = 9) and healthy controls (n = 10)

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Alzheimer's disease</th>
<th>Healthy controls</th>
<th>Statistical test</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex [M-F]</td>
<td>7:2</td>
<td>6:4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age [years] (mean (SD), range)</td>
<td>70 (7.75), 62 to 82</td>
<td>70.10 (5.65), 64 to 79</td>
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<td>p = 0.405</td>
</tr>
<tr>
<td>Handedness (right:non-right)</td>
<td>9:0</td>
<td>9:1</td>
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<td></td>
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<tr>
<td>Years of education (mean (SD))</td>
<td>10.67 (3.08)</td>
<td>6.90 (4.63)</td>
<td></td>
<td>p = 0.033</td>
</tr>
<tr>
<td>Social class A/B/C/D/E</td>
<td>0/6/3/0/0</td>
<td>0/2/5/3/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE (mean (SD), range)</td>
<td>21.78 (1.86), 18 to 25</td>
<td>29.10 (0.57), 28 to 30</td>
<td></td>
<td>p = 0.001</td>
</tr>
<tr>
<td>MADRS (mean (SD), range)</td>
<td>13.11 (5.67), 4 to 22</td>
<td>2.60 (2.99), 0 to 8</td>
<td></td>
<td>p = 0.001</td>
</tr>
</tbody>
</table>

Scores on neuropsychological tests

| CAMCOG (mean (SD)) | Language comprehension | 8.11 (0.93) | 8.80 (0.63) |                 | p = 0.073 |
|--------------------|-----------------------|-------------|-------------|                 |             |
| Praxis             | 9.89 (1.17)           | 11.00 (1.25) |             |                 | p = 0.062 |
| Remote memory      | 3.22 (1.64)           | 5.00 (0.94) |             |                 | p = 0.009 |
| Recent memory      | 1.44 (1.24)           | 3.50 (0.71) |             |                 | p = 0.001 |
| Category fluency   | 10.33 (3.00)          | 13.90 (3.7) |             |                 | p = 0.035 |
| FOME delayed recall (mean (SD)) | 4.89 (3.89) | 9.75 (0.46) |             | p = 0.003 |

CAMCOG: Cambridge cognitive examination for the elderly; FOME: Fuld object-memory evaluation; MADRS: Montgomery-Asberg depression rating scale; MMSE: mini-mental state examination.
The final values for the belonging probabilities are in the range of 0 to 1, with most voxels classified close to one of the two extremes. Finally, in order to reduce variation caused by individual differences in sulcal and gyral anatomy, the grey matter segments were smoothed using an isotropic Gaussian kernel of 8 mm full width at half maximum.

The mean grey matter concentration in Alzheimer patients and healthy controls was compared at all brain voxels which had values above an absolute grey matter threshold of 0.05 (resulting in a search volume of approximately 250 000 voxels). The statistics for each voxel were transformed to Z scores and displayed as a statistical parametric map (SPM) into standard space, at a threshold probability of $Z = 2.33$ ($p < 0.01$). The resulting SPM was inspected for the presence of any clusters of reduced medial temporal grey matter concentration in Alzheimer patients relative to controls, in which the voxel of peak statistical difference attained a probability (p) value of $< 0.001 (Z > 3.09)$.

After the cluster of greatest medial temporal grey matter atrophy in Alzheimer patients was identified, a Matlab program was used to obtain the coordinates of all voxels included in this cluster that surpassed the initial cut off of $Z > 2.33$. The mean intensity values for this cluster were then calculated for all Alzheimer subjects using the smoothed MR images, providing a measure of the mean grey matter concentration within that region.

The use of the liberal cut off of $Z = 2.33$ was intended to serve the inclusion of a greater number of voxels in the selected medial temporal cluster, in order to provide a measure that would be representative of the degree of grey matter atrophy over a large extension of hippocampal tissue. The mean intensity values for each Alzheimer subject in this cluster were stored for subsequent use in the correlational analysis with the rCBF SPECT data.

**SPECT image acquisition**

The SPECT acquisition was conducted in all subjects within two weeks of the MRI session. A split dose $^{99m}$Tc-HMPAO technique was used, allowing the acquisition of two rCBF SPECT scans within the same session, each after the performance of a different cognitive task. Initially, subjects were kept in a quiet testing room, where a venous cannula was inserted in the right arm. They were positioned supine with eyes closed, wearing earphones through which they received the instructions for the first (control) task. During this task, subjects heard the words “yes” (24 times) and “no” (36 times) randomly alternated, at a rate of one word every five seconds. Subjects were instructed to press a button with their right hand every time they heard the word “yes”. After one minute into this task, a first $15 \text{ mCi}^{99m}$Tc-HMPAO injection was given. The task was continued for an additional period of four minutes, after which the subjects were taken to the scanning room for the first rCBF SPECT acquisition.

After the first SPECT scan, subjects returned to the testing room for the performance of the verbal memory task. During an initial learning stage of the memory experiment, subjects were presented, through their earphones, with a list of 12 common Portuguese words (at a rate of one word every two seconds), and they attempted to memorise these words over five trials. After an interval of 90 seconds, the recognition phase of the experiment was started. Subjects were presented with a list of 60 words (at a rate of one word every five seconds), including the 12 words previously learned (presented two times each), randomly mixed with 36 new words. Subjects were instructed to press the button each time they heard a word that had been presented during the learning phase of the experiment. The second $15 \text{ mCi}^{99m}$Tc-HMPAO injection was given during the recognition memory task. The task was continued for another four minutes, after which the second SPECT scan was acquired.

For both the baseline and recognition memory tasks, visual analogue scales (0–10) were used to document self reported anxiety; measures were taken five minutes after tracer injection, when subjects were asked to rate how they felt during the performance of the task they had just completed.

SPECT images were acquired with a double detector GE-OPTIMA system (General Electric Medical Systems, Milwaukee, Wisconsin, USA). For both the baseline and memory scans, high resolution collimators were used, with 128 views acquired on a $64 	imes 64$ matrix (10 seconds per view). Images were reconstructed as cubic voxels ($14.5 \text{ mm}^3$) by filtered back projection (ramp filter), with Butterworth postfiltering (cut off = 0.59, order number = 10). Attenuation correction was performed using the algorithm of Chang (uniform linear attenuation coefficient = 0.12 cm$^{-1}$).

**SPECT image analysis**

The rCBF SPECT images were also analysed using SPM99. Initially, the pair of baseline and memory scans of each subject were realigned (sinc interpolation) with each other, and spatially normalised to standard anatomical space with a final voxel size of [2 mm]$^3$. Given the stability of the $^{99m}$Tc-HMPAO distribution in the brain for several hours after injection, the regional count density measured during the memory SPECT scan represented a superimposition of the tracer uptake patterns obtained during the second injection over the uptake patterns corresponding to the first, baseline injection. Therefore, in order to obtain a net measure of the $^{99m}$Tc-HMPAO uptake originating from the second injection, the decay corrected, normalised baseline scan was subtracted from the normalised memory scan on a voxel by voxel basis. The normalised baseline and subtracted memory rCBF SPECT scans of each subject were then both smoothed with an isotropic 12 mm (FWHM) Gaussian kernel.

First, the mean regional $^{99m}$Tc-HMPAO uptake patterns obtained during the memory task were statistically compared between Alzheimer patients and controls for each voxel of the smoothed brain volume using unpaired $t$ tests. Only voxels with signal intensities above a threshold of 0.5 relative to the mean global were entered in each analysis (resulting in a search volume of approximately 272 900 voxels). In order to account for interindividual differences in global cerebral blood flow, the regional $^{99m}$Tc-HMPAO uptake was standardised to the mean global uptake using proportional scaling. To account for the influence of memory task performance on the rCBF patterns elicited in Alzheimer subjects and controls, the between-group comparisons were repeated with covariance for scores on the word recognition test.

Second, a $2 	imes 2$ factorial analysis was undertaken in order to compare the patterns of rCBF activation during the memory task relative to the control condition between Alzheimer patients and controls. The condition and subject effects were estimated according to the general linear model at each voxel, and linear contrasts were used to identify significant differences between conditions and subjects.

Finally, voxel based correlational analyses were performed between rCBF values in the Alzheimer’s disease group and the mean values of grey matter concentration in the medial temporal region extracted from the VBM analysis described above. In order to account for the confounding effect of intersubject differences in global grey matter atrophy, this correlational analysis included a measure of the total amount of grey matter in each subject (given by the sum of the intensity values of all voxels from the smoothed grey matter MR images) as a confounding covariate.

In all analyses above, resulting statistics were transformed to $Z$ scores, thresholded at $Z = 2.33$, and displayed as SPMs. The SPMs generated from the correlational analyses between medial temporal atrophy and rCBF values were first inspected for the presence of significant findings ($p < 0.001, Z > 3.09$) in
the regions where hypofunctional patterns could be predicted a priori in Alzheimer patients relative to controls—namely the temporal and parietal association cortices, the medial temporal region, the cingulate cortex, and the precuneus. Second, the SPMs were inspected for significant correlations (p < 0.001) involving the frontal lobes, where rCBF increases could be predicted to occur during the memory task. Finally, the SPMs were inspected for the presence of significant correlations between medial temporal atrophy and rCBF values in unpredicted regions; the latter correlations were reported as significant only if resisting correction for multiple comparisons based on Gaussian random field theory (p < 0.05).

RESULTS
Between-group structural MRI comparisons
The VBM analysis showed widespread clusters of significantly reduced grey matter concentration in Alzheimer patients relative to the controls at the p < 0.001 level, located mainly in the temporal and parietal lobes. As predicted, one of these clusters was located in the medial temporal region, encompassing the hippocampus/parahippocampal gyrus on both hemispheres (fig 1). This cluster contained 1162 voxels that surpassed the initial threshold of Z = 2.33, and had its two peaks of statistical difference located, respectively, in the medial border of the left posterior parahippocampal gyrus (Zmax = 3.35; p < 0.0005; x,y,z = −6, −38, 6), and in the right posterior parahippocampal gyrus (Zmax = 3.21; p < 0.001; x,y,z = 26, −40, −6). The cluster, which included a total of 1162 voxels, is shown in the figure extending anteriorly on both hemispheres, to reach the entorhinal cortex and the amygdala on the right side and the mid portion of the hippocampus and parahippocampal gyrus on the left side. The mean grey matter concentration in this hippocampal cluster was extracted for all Alzheimer patients and used for the subsequent correlational analysis with the rCBF measures obtained during cognitive activation. L, left hemisphere; R, right hemisphere.

Figure 1 Clusters of reduced grey matter concentration in the medial temporal region in patients with Alzheimer’s disease (n = 9) relative to healthy controls (n = 10) are shown in red and yellow, at the statistical threshold of Z = 2.33 (p < 0.01), overlaid on coronal sections (left column) and sagittal sections (right column) from a reference brain spatially normalised according to the Talairach and Tournoux stereotactic atlas. The numbers at the right bottom corner provide the y and x axis coordinate values of each coronal and sagittal view, respectively. The areas with the MT label correspond to the bilateral cluster of greatest grey matter reduction in Alzheimer patients, which had its two voxels of peak statistical significance located, respectively, in the medial border of the left posterior parahippocampal gyrus (Zmax = 3.35; p < 0.0005; x,y,z = −6, −38, 6), and in the right posterior parahippocampal gyrus (Zmax = 3.21; p < 0.001; x,y,z = 26, −40, −6). This cluster, which included a total of 1162 voxels, is shown in the figure extending anteriorly on both hemispheres, to reach the entorhinal cortex and the amygdala on the right side and the mid portion of the hippocampus and parahippocampal gyrus on the left side. The mean grey matter concentration in this hippocampal cluster was extracted for all Alzheimer patients and used for the subsequent correlational analysis with the rCBF measures obtained during cognitive activation. L, left hemisphere; R, right hemisphere.
grey matter concentration in Alzheimer patients did not retain statistical significance at the p < 0.001 level; this suggested that the degree of grey matter decrement in this region did not surpass the level of overall brain atrophy in the Alzheimer group. The detailed VBM results for the other brain regions have been described in a separate report, including an extended sample of Alzheimer patients.21

**Behavioural results during the rCBF measurements**

All subjects in both groups presented a 100% rate of correct responses during the “yes–no” control condition with the exception of two Alzheimer patients and one healthy control, who missed one “yes” hit each. All subjects in the Alzheimer group were also able to comply with the memory activation paradigm, but presented a trend towards a lower mean (SD) number of correct word recognition scores when compared with healthy controls (19.2 (2.9) v 21.1 (3.1), t = 1.60, p = 0.122), as well as a significantly greater mean number of false positive hits (4.8 (5.7) v 0.8 (0.9), t = 2.58, p = 0.016). Also, the mean number of words recalled during the learning phase of the experiment before the SPECT procedure was lower in the Alzheimer patients relative to the controls (5.4 (1.6) v 6.9 (0.9), t = 3.09, p = 0.005).

**Comparisons of rCBF patterns between Alzheimer patients and healthy controls**

The between-group SPM comparisons of SPECT data showed no significant rCBF increases in the Alzheimer group relative to the controls during the memory task. On the other hand, clusters of reduced rCBF in Alzheimer patients relative to controls (p < 0.001, uncorrected for multiple comparisons) were detected in temporal and parietal regions, as shown in fig 2. These clusters were located in: the right anterior superior temporal gyrus Brodmann area (BA 22) (Zmax = 4.06; x,y,z = 64,−2,−4); the right and left precuneus (BA7) (Zmax = 3.46; x,y,z = 6,−76,44), extending anteriorly towards the posterior cingulate gyrus (BA31); the left hippocampus (Zmax = 3.09; x,y,z = −30,−20,−10); and the right postcentral gyrus (Zmax = 3.57; x,y,z = 54,−24,38). Additional foci of reduced rCBF in the Alzheimer group (p < 0.001, uncorrected) were detected in the upper portion of the left superior frontal gyrus (BA6) (Zmax = 3.25; x,y,z = −16,−4,76), and in the anterior portion of the right medial frontal gyrus (BA10) (Zmax = 3.77; x,y,z = 6,68,−14) (fig 2). None of those regions showed significantly decreased rCBF values in Alzheimer patients compared with controls when the SPECT scans obtained during the control condition were compared between the two groups.

When the between-group comparisons of rCBF patterns during the word recognition task were repeated with covariance for memory performance, significant rCBF reductions in Alzheimer patients relative to controls were detected in similar regions as reported above (p < 0.001, uncorrected). These included: the right anterior superior temporal gyrus (BA22) (Zmax = 3.60; x,y,z = 64,−2,4); the right and left precuneus (BA7) (Zmax = 3.22; x,y,z = 8,−76,46); the right postcentral gyrus (Zmax = 3.28; x,y,z = 52,−24,58); the upper portion of the left superior frontal gyrus (BA6) (Zmax = 3.26; x,y,z = −12,22,60); and the anterior portion of the right medial frontal gyrus (BA10) (Zmax = 3.37; x,y,z = 66,66,−16). In addition, a focus of reduced rCBF in Alzheimer patients emerged in the left lateral parietal cortex (inferior parietal lobule; BA40) (Zmax = 3.77; x,y,z = −48,−42,58). On the other hand, the above focus of reduced left hippocampal rCBF that had been detected in the Alzheimer patients failed to reach statistical significance after covariance for recognition memory scores (Zmax = 2.67).

Factorial analysis investigating between-group differences in the activation patterns elicited by the memory task revealed greater rCBF increases in the control group relative to the Alzheimer patients (p < 0.001, uncorrected) in two foci in the prefrontal cortex, involving, respectively: the upper portion of the right superior and middle frontal gyri (591 voxels; Zmax = 3.42; x,y,z = 44,18,50; BA9/8), and the left lateral inferior frontal gyrus (96 voxels; Zmax = 3.44; x,y,z = −54,38,4; BA45/46). In addition, memory related rCBF increases were greater in the controls than in the Alzheimer patients in several temporal and parietal regions, including the left inferior parietal lobule and post-central gyrus (Zmax = 4.25; x,y,z = −52,−32,54; BA40/2); the posterior portions of the left middle (Zmax = 3.97; x,y,z = −42,−66,14; BA19) and inferior temporal gyri (Zmax = 3.21; x,y,z = −56,−42,−18; BA37/20); the right anterior superior temporal gyrus (Zmax = 3.47; x,y,z = 62,−2,0; BA22); and the right precuneus (Zmax = 3.39; x,y,z = 14,−48,48; BA7). Conversely, memory related rCBF increases were greater in the Alzheimer patients than in the
controls in a large bilateral inferior frontal cluster (with 3333 surpassing the initial threshold of Z = 2.33) (p < 0.001, corrected for multiple comparisons). This cluster had its voxel of peak statistical significance located in the inferolateral portion of the right middle frontal gyrus (Z_{max} = 4.08; x, y, z = 30,50,2), and also included the right and left orbital and rectal gyri (BA11 and BA47); the right and left subcallosal medial frontal cortex (BA25); and additional inferolateral portions of the right inferior, middle, and superior frontal gyri (BA10/11/47, up to the z coordinate level of +12). Memory related rCBF increases were also greater in Alzheimer patients than in the controls in a smaller cluster (158 voxels) located in the left dorsal medial prefrontal and anterior cingulate cortices (Z_{max} = 3.47; x,y,z = -14,34,28; BA9/32).

**Correlations between medial temporal atrophy and rCBF patterns in the Alzheimer group**

Table 2 summarises the results of the voxel based correlational analysis calculated in the Alzheimer group between the rCBF measures obtained during the memory task and the measure of grey matter concentration in the hippocampal region, including the total amount of grey matter in the brain as a confounding covariate. Significant direct correlations (p < 0.001, uncorrected) were seen between the hippocampal grey matter concentration and rCBF values in two of the regions where regional hypoxic activity had been detected in the Alzheimer patients relative to the controls—namely, the right anterior superior temporal gyrus (BA22/38) and the left hippocampus/parahippocampal gyrus (table 2). These results indicated that the rCBF values in those areas were lower in Alzheimer patients relative to controls in the expected sites, including the lateral left hemisphere (Z_{max} = 5.22; x,y,z = 34,10,−4; p < 0.001 corrected for multiple comparisons) and the left hemisphere (Z_{max} = 5.14; x,y,z = −40,12,0; p < 0.001 corrected). Finally, one unpredicted inverse correlation in the Alzheimer group was seen between the measure of hippocampal grey matter concentration and rCBF values during the memory task in a voxel cluster encompassing both cerebellar hemispheres, which retained statistical significance after correction for multiple comparisons (p < 0.001) (table 2).

**DISCUSSION**

In this study, we acquired both structural MRI and rCBF SPECT data in the same sample of subjects with mild Alzheimer’s disease and healthy controls, in order to investigate the relation between hippocampal atrophy and rCBF patterns elicited during the performance of a verbal memory retrieval task.

Before calculating correlations between structural and functional imaging indices in Alzheimer patients, we did between-group comparisons on the data with both modes, and obtained results that are broadly in agreement with previous imaging studies in Alzheimer’s disease. Thus we detected bilateral reductions in grey matter concentration in Alzheimer patients relative to controls in the hippocampal region, consistent both with the results of ROI based morphometric studies and with more recent studies using the VBM approach. Also, the between-group SPECT comparisons showed significant rCBF reductions in Alzheimer patients relative to controls in the expected sites, including the lateral
and medial temporal cortices and the parietal lobe. Such rCBF reductions in Alzheimer patients were seen during the memory task but not during the control condition; this pattern is consistent with the findings of earlier PET and SPECT studies, and supports the view that the performance of complex cognitive tasks may enhance regional brain metabolic differences between Alzheimer patients and healthy controls. Finally, our Alzheimer subjects showed significantly broader rCBF increases in the frontal cortex than the controls during the verbal memory task, although this involved more inferiorly located regions compared with the prefrontal activation foci seen in the healthy control group. These results are consistent with previous PET studies which have included the orbitofrontal cortex among the frontal cortical sites where compensatory rCBF increases may occur in Alzheimer patients during episodic memory activation paradigms.

With regard to the relation between the structural MRI and SPECT data, we detected significant direct correlations between the degree of hippocampal atrophy in Alzheimer patients and rCBF reductions bilaterally in the temporal neocortex, as well as in the left hippocampus and the left posterior cingulate cortex. While the correlations involving the temporal neocortex are in agreement with the results of previous resting functional imaging studies of Alzheimer’s disease, significant correlations between hippocampal atrophy and the functional activity in limbic regions have been absent in those studies. It is possible that our correlations involving the temporo-limbic cortex and the posterior cingulate gyrus were detected because of the greater sensitivity of the voxel based methodology in comparison with the traditional ROI approach for the identification of findings in medially located structures of complex anatomy. However, in the study by

Figure 3 (A–D) Plots of the significant direct linear correlations (p < 0.001) observed in the Alzheimer’s disease group (n = 9) between the mean grey matter concentration in the medial temporal region and regional cerebral blood flow (rCBF) measures obtained during the memory task in: (A) the right anterior superior temporal gyrus; (B) the left hippocampus/parahippocampal gyrus; (C) the left middle temporal gyrus (BA21); (D) the left posterior cingulate cortex (BA31). (E, F) Plots of the significant inverse correlations (p < 0.001) between the measure of hippocampal grey matter and rCBF in (E) the right and (F) left inferior frontal gyrus/insula. In all analyses, the total amount of grey matter in the brain was treated as a confounding covariate. The numbers between brackets in the x axes correspond to the coordinates of the voxel from which the rCBF indices were obtained. Further statistical details are provided in table 2. L, left hemisphere; R, right hemisphere.
Meguro et al., the resting glucose metabolic values in the entire brain were inspected using a similar voxel based approach, and significant correlations with the indices of hippocampal atrophy were restricted to lateral necrotical portions of the temporal and parietal cortices. It could be argued that our medial temporal functional-structural correlations were determined by partial volume effects caused by local atrophy on the rCBF measurements, as these were obtained in our study using a SPECT imaging technique with limited spatial resolution. However, an influence of artefactual partial volume effects on our correlational results is unlikely, as our significant direct relation between hippocampal atrophy and rCBF values in the left hippocampus emerged only during the verbal retrieval task and not during the control condition; the same applied for the correlation between hippocampal atrophy and rCBF values in the left posterior cingulate cortex. This indicates that, rather than being static, the relation between hippocampal atrophy and functional activity in limbic regions in our study was modulated by the cognitive state during which the rCBF tracer \(^{99}\)Tc-HMPAO was given.

It is interesting that the posterior cingulate gyrus (BA 31) was the only region beyond the temporal cortex that showed significant direct rCBF correlations with the degree of hippocampal atrophy in our Alzheimer patients during the memory task. The posterior cingulate cortex, affected early in Alzheimer's disease and in subjects at genetic risk for the disorder, has reciprocal anatomical connections with the parahippocampal cortex, and has also been implicated in the functional imaging literature of memory activation in healthy subjects. In a voxel based PET study of resting glucose metabolism in Alzheimer's disease, regional metabolic deficits in the left posterior cingulate cortex and the left hippocampal/parahippocampal region were specifically related to impairments in verbal episodic memory, while the performance in other memory domains correlated significantly with resting metabolic deficits in different brain regions. Together with those findings, our correlational results suggest that the degree of hippocampal atrophy influences the disrupted functioning of a left sided network that is particularly relevant to verbal episodic memory deficits in Alzheimer's disease, involving the medial temporal cortex and the interconnected posterior cingulate gyrus.

In contrast to the above findings, we detected frontal cortical clusters where rCBF values during the memory task were inversely correlated with the hippocampal grey matter concentration in the Alzheimer group. These findings are consistent with the view that frontal rCBF increases in Alzheimer patients studied during episodic retrieval paradigms are compensatory responses, related to the increased effort needed to perform the memory tasks. The correlational patterns reported here suggest that compensatory changes in activity in the frontal cortex may be elicited in Alzheimer patients in direct proportion to the degree of anatomical abnormality in the hippocampal areas primarily affected by the neuropathological disease process. However, caution is needed with this interpretation as there was no spatial overlap between the frontal clusters, where rCBF correlated significantly with the MRI measures, and the orbitofrontal areas, where rCBF increases were seen during the memory task relative to the control condition in the Alzheimer group. On the other hand, this apparent inconsistency could be explained by the fact that the significant correlations between hippocampal grey matter and rCBF values in the inferior frontal gyrus/insula were present not only during the memory task but also during the control condition. This pattern of results indicates that the degree of hippocampal neuronal damage in Alzheimer's disease may influence the emergence of compensatory frontal rCBF increases not only during memory processes but also during other cognitive operations of lesser complexity.

Conclusions and limitations

Our results provide an indication that hippocampal atrophic changes in Alzheimer's disease are associated with reduced functioning of temporal and posterior cortical regions during verbal episodic retrieval, but with increased activity in frontal areas, probably on a compensatory basis. However, there are important limitations to the study which should also be highlighted.

First, the relatively long duration of the SPECT imaging session and the need to perform MRI measurements on a separate occasion complicated our recruitment of a larger study sample. Although the inspection of our data did not indicate the influence of outliers on the correlational patterns detected, replication of the present findings with larger groups is clearly needed.

Second, our Alzheimer sample included subjects who were receiving stable doses of psychotropic drugs that may have influenced our rCBF measurements. In particular, it has been suggested that cognition enhancing cholinergic agents reduce task related rCBF activation in the frontal cortex in healthy subjects, as well as decreasing the rate of resting brain functional decline in Alzheimer patients. It is thus possible that the use of those drugs in a proportion of our Alzheimer subjects might have prevented us from demonstrating larger between-group rCBF differences or greater significant correlations between hippocampal atrophy and hypofunctional patterns in the Alzheimer group.

Finally, the limited temporal resolution of the SPECT methodology and the restriction of performing only two acquisitions in the same session prevented us from separately assessing the rCBF patterns elicited by each of the several cognitive processes involved in the verbal recognition memory task. Such limitations could be overcome in imaging studies using novel paradigms combining structural and functional MRI (fMRI). Using event related designs with memory tasks, the fMRI technique may successfully detect haemodynamic changes associated with single trials of item recognition and rejection, as well as discriminating those transient functional responses from the activity patterns associated with the maintenance of the retrieval mode. Future studies using those paradigms may be ideally suited to extending the preliminary correlational results reported here.

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