The neural substrates of episodic memory impairment in Alzheimer’s disease as revealed by FDG–PET: relationship to degree of deterioration

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Summary
In a previous investigation, we raised the hypothesis that in Alzheimer’s disease the cerebral structures implicated in episodic memory deficits may differ according to the severity of cognitive impairment. To test this hypothesis, Story Recall test scores and PET measurements of resting cerebral glucose utilization, a measure of synaptic integrity, were obtained in 40 patients. Using SPM96 (statistical parametric mapping 1996), positive correlations between the two sets of data were calculated on a voxel basis, first in the whole patient sample and then separately in the two subgroups of 20 patients differing in Mini-Mental State Examination score, i.e. those with least impaired and those with most impaired performance (‘less severe’ and ‘more severe’ subgroups, respectively). In the whole sample, significant correlations (P < 0.05, corrected for multiple tests) involved bilaterally not only several limbic structures (the hippocampal/rhinal cortex regions, posterior cingulate gyrus and retrosplenial cortex) but also, and less expectedly, some temporoparietal association areas. However, the subgroup analysis disclosed that, in the less severe subgroup, all significant correlations (P < 0.005, uncorrected) were restricted to the parahippocampal gyrus and retrosplenial cortex, in accordance with both the distribution of changes in tau in early Alzheimer’s disease and the known involvement of this network in normal and impaired memory function, while in the more severe subgroup they mainly involved the left temporal neocortex, which is known to be implicated in semantic memory. These findings suggest that, when episodic memory is mildly impaired, limbic functions are still sufficient to subserve the remaining performance, whereas with more severe memory deficit resulting from accumulated pathology the neocortical areas that are normally involved in semantic memory are recruited, perhaps as a form of (inadequate) compensatory mechanism.

Keywords: positron emission tomography; SPM; CMRGlc

Abbreviations: CMRGlc= cerebral metabolic rate for glucose; FOV = field of view; nCMRGlc = normalized cerebral metabolic rate for glucose; 18FDG = [18]fluoro-2-deoxy-D-glucose

Introduction
The earliest and most severe cognitive deficit in Alzheimer’s disease concerns episodic memory (Gainotti et al., 1998). Pathologically, neurofibrillary tangles first appear in the rhinal cortex, then in the hippocampus, and finally spread into the neocortex (Braak and Braak, 1991; Delacourte et al., 1999). However, the precise relationships between lesions and memory impairment remain elusive because the post-mortem data that are available were obtained on patients with extensive impairment in several different cognitive domains. Functional imaging is one way to assess these relationships in vivo at an early stage. However, activation studies in Alzheimer’s disease have proved difficult to interpret, probably because cognitive strategies are hard to control when making comparisons with normal subjects (Becker et al., 1996; Herbster et al., 1996; Bäckman et al., 1999; Rombouts et al., 2000). We have previously used voxel-based mapping of the correlations between memory performance and resting regional metabolic rates of glucose, and have shown the sensitivity of this approach in unravelling the neural substrates of cognitive impairment in Alzheimer’s
disease (Penniello et al., 1995; Desgranges et al., 1998a; Eustache et al., 2001). Being closely related to synaptic activity, the resting cerebral metabolic rate for glucose (CMRGlc) is sensitive to neurodegenerative processes, and it can show focal metabolic declines even in the presymptomatic stages of familial Alzheimer’s disease (Kennedy et al., 1995; Reiman et al., 1996). Although we (Desgranges et al., 1998a) and others (Perani et al., 1993), using this approach, showed that deficits in particular memory systems (episodic, semantic and working memory) were subserved by distinct structures, in our study the loci of some correlations did not fit hypotheses based on available knowledge. To explain these unexpected findings, we proposed that new mechanisms come into play to compensate for the processes normally employed when these processes become inadequate. In other words, the pattern of metabolic correlations with a given neuropsychological test performance may depend on the degree of cognitive impairment.

To test this hypothesis, we performed a follow-up investigation in an enlarged sample of 40 patients with mild to moderate probable Alzheimer’s disease, expanding upon our previous work on the correlations between resting CMRGlc and episodic memory performance, assessed with the Story Recall test. We predicted that performance in this memory test would correlate with hippocampal–limbic structures in the least impaired patients and with brain areas not normally devoted to episodic memory in the most impaired patients.

Methods

Patients

The subjects of this study comprised the 19 patients of our previous study (Desgranges et al., 1998a) [age 70.5 ± 6.6 years, Mini-Mental State Examination (MMSE) score 20.2 ± 3.5] and 21 new patients (age 73.1 ± 5.6 years, MMSE 22.3 ± 2.5). The whole sample (age 72 ± 6.1 years, MMSE 21.3 ± 3.2) was made up of 22 women and 18 men, all right-handed and with at least 8 years of education. All were selected prospectively on the basis of a neurological examination, and a neuropsychological assessment, using the NINCDS–ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and The Alzheimer’s Disease and Related Disorders Association) criteria for probable Alzheimer’s disease (McKhann et al., 1984). Standard laboratory examinations were normal for all patients and structural imaging (MRI or CT) showed no focal abnormality. At the time of the study, none of the patients was being or had been treated with specific medication, such as anti-acetylcholinesterase agents. The patients gave their consent to the study after detailed information had been provided to them, and the PET procedure was approved by the Ethics Committee of the University of Caen. The study was done according to the Declaration of Helsinki.

General procedure

Within an interval of a few days at most, each patient underwent a neuropsychological examination and a PET measurement of resting CMRGlc.

Neuropsychological protocol

Verbal episodic memory was assessed with a classical 12-item Story Recall task taken from the BEM (Batterie d’Efficience Mnésique) 144 memory battery (Signoret, 1991). This task involves a story about a man whose car is in order and who wants to buy another.

PET study

The CMRGlc was measured at rest, using [18F]fluoro-2-deoxy-D-glucose (18FDG). For the first series of 19 patients, we used a seven-slice LETI-TTV 03 camera [field of view (FOV) = 81 mm], according to the stringent head-positioning procedure described previously (Desgranges et al., 1998a). For the second series of 21 patients, because of equipment upgrading, we used the Emission CAT Exact HR+ device (FOV = 158 mm), with the patient positioned parallel to the canthomeatal line; we used exactly the same scanning protocol as for the first group (for details see Desgranges et al., 1998a). All studies were done in the resting state with the eyes closed in a quiet, dark environment. Following 68Ga transmission scans, 3–5 mCi of 18FDG was injected as a bolus and blood samples were obtained from a radial artery catheter to determine the time-course of 18FDG in plasma and the average plasma glucose concentration. Fifty minutes after injection, a 10 min PET data acquisition period started with the HR+ device, and 63 planes were acquired with septa out (volume acquisition). The lateral resolution used was 2.2 × 2.2 mm and the slice thickness was 2.43 mm. During PET data acquisition, head motion was continuously monitored with, and whenever necessary corrected according to, laser beams projected onto ink marks drawn over the forehead skin. The 18FDG images were transformed into parametric maps of CMRGlc according to the operational equation of Phelps et al. (1979). To take into account the different spatial resolution of the two PET devices, the HR+ data were degraded at reconstruction and smoothed axially to match the effective TTV03 resolution (i.e. x, y, z 5.5, 5.5, 12 mm), according to the procedure described by Small et al. (2000).

As done previously (Desgranges et al., 1998a) and in order to control for the variance in global CMRGlc, the CMRGlc images were divided, pixel by pixel, by the individual value for the cerebellar vermis, resulting in normalized CMRGlc values (nCMRGlc).

SPM method

The nCMRGlc images were transferred to a Sun workstation. Manipulation of the image matrix (stereotaxic normalization)
and statistical calculations were carried out with MATLAB (Mathworks, Sherborn, Mass., USA). With the SPM96 (statistical parametric mapping 1996) software (Wellcome Department of Cognitive Neurology, London, UK), individual images from both PET data sets were transformed into Talairach’s stereotaxic space (Talairach and Tournoux, 1988) and smoothed in three dimensions using the same three-dimensional Gaussian filter of 16 mm. Resliced voxel size was 2 × 2 × 2 mm. In order to minimize ‘edge effects’ without excluding hypometabolic tissue, only those voxels with values >40% of the mean for the whole brain were selected for the statistical analysis (Desgranges et al., 1998a). The SPM analysis was restricted to the common FOV segment (i.e. that of the TTV03 device; Fig. 2). The results were obtained in two forms: (i) projection of the significant voxels onto a standard MRI template; (ii) peaks with their Talairach coordinates, using M. Brett’s set of linear transformations (www.mrc-cbu.cam.ac.uk/imaging/mnispace.html).

### Statistical analysis

In order to characterize the patients in terms of episodic memory performance, their Story Recall scores were compared with those obtained for a group of 30 healthy controls (Desgranges et al., 1996) (age 70.7 ± 9.9 years). The patient sample was then subdivided with respect to the median MMSE score for the whole group (i.e. 21) into two equal subgroups of 20 patients each: a ‘less severe’ subgroup and a ‘more severe’ subgroup. There was no significant difference between the two subgroups regarding either age or number of years of education (Table 1).

Correlations between Story Recall scores and PET data were searched first in the whole sample and then separately in the two subgroups, using the general linear model (Friston et al., 1995). Although resting glucose utilization by the brain reflects local baseline integrated synaptic activity and is thus sensitive to neuronal lesions as well as synaptic dysfunction, both of which are altered in Alzheimer’s disease (McCulloch, 1982), all studies that have performed voxel-based atrophy correction of resting glucose utilization by the brain have concluded that the reduction in cerebral metabolism represents a true loss of functional activity and not simply an artefact caused by brain atrophy (e.g. Ibanez et al., 1998; Baron et al., 2001; Bokde et al., 2001). Moreover, some correlational studies (not voxel-based) took cerebral atrophy into account in their analysis and the results were nearly the same as those obtained without correction for atrophy (e.g. Slansky et al., 1995). We looked for all voxels where nCMRGlc was significantly and positively correlated with Story Recall score. The statistical threshold chosen was adjusted for sample size. Thus, for the whole group (n = 40), SPM maps thresholded at Z > 3.09, P < 0.001 were obtained, but only those correlations significant at P < 0.05, cluster-level corrected for multiple tests, were retained. With respect to the two subgroups, a statistical threshold of P < 0.005 (uncorrected) was chosen. This is less liberal than the threshold used in many previous SPM correlative studies (e.g. O’Brien et al., 1992; Grasby et al., 1993; Nyberg et al., 1996; Desgranges et al., 1998a; see also Discussion). As described previously (Desgranges et al., 1998a), the influence of age was controlled by setting age as a confounding variable in all these linear regressions.

### Results

#### Story Recall

#### Whole group

The mean Story Recall scores ± standard deviation were 2.44 ± 1.34 and 6.2 ± 2.1 for the Alzheimer’s disease and control groups, respectively (P < 0.001). In the Alzheimer’s disease group, there was marked interindividual variability (range 0.5–6.5).

#### Less severe subgroup

The mean MMSE score ± standard deviation was 23.8 ± 1.9 and the mean Story Recall score was 3.2 ± 1.3 (Table 1), which were significantly different from corresponding scores for controls (P < 0.001). Eight out of 20 patients obtained a Story Recall score below the lower confidence limit of controls (i.e. 2.7, P < 0.05, one-tailed).

#### More severe subgroup

The mean MMSE score was 18.8 ± 2 and the mean Story Recall score was 1.7 ± 0.8, which were significantly different from control scores (P < 0.001).

#### Correlations between Story Recall scores and nCMRGlc

#### Whole group

Significant (P < 0.05, corrected for cluster level) correlations were extensive and concerned principally the hippocampal region (Fig. 1A), the posterior cingulate cortex and the precuneus, in a bilateral and strikingly symmetrical manner, but also the temporal and occipital association cortical areas with strong right-sided predominance, as well as the cerebellum (Fig. 2, top row). Data from the peak printout produced by the SPM software are shown in Table 2.
Less severe subgroup
Significant correlations were located exclusively in the right perirhinal/parahippocampal, entorhinal and retrosplenial cortices (Table 3, Fig. 1B and Fig. 2, middle row).

More severe subgroup
Significant correlations were more widely distributed and concerned only left-sided neocortical regions [fusiform gyrus (Fig. 1C), superior, middle and inferior temporal gyri, cuneus and inferior parietal lobule] (Table 4 and Fig. 2, bottom row).

Discussion
This is the first study to show that the sites of significant correlations between memory scores and resting metabolism vary according to the severity of cognitive impairment, suggesting that in Alzheimer’s disease the brain areas that subserve residual episodic memory shift from the limbic to the neocortical association structures with increasing impairment. In other words, with respect to Story Recall, patients in the less severe subgroup rely on brain areas that normally subserve episodic memory processes, whereas patients in the more severe subgroup would bring into play other structures, such as those normally involved in semantic memory, yet still produce a lower performance in this test.

This study was carried out in a group of Alzheimer’s disease patients whose clinical and metabolic features were quite typical. Thus, as expected (Butters et al., 1995; Hodges et al., 1995; Desgranges et al., 1996), there was a significant decline in Story Recall in the group of Alzheimer’s disease patients, with marked intersubject variability. The correlations observed in the whole group involved principally the limbic structures, namely the hippocampal regions (including the rhinal cortices) and the bilateral posterior cingulate and retrosplenial cortices, consistent with our previous study (Desgranges et al., 1998a), though here with bilateral extension. Our finding of correlations that were more strongly significant and more extensively distributed than those in our previous study is presumably due to the 2-fold larger sample used here. Previously, significant correlations between Story Recall and hippocampal integrity, as assessed by structural MRI, have been observed in Alzheimer’s disease patients (e.g. Deweer et al., 1995; de Toledo-Morrell et al., 2000), as well as in patients with temporal lobe epilepsy (Abrahams et al., 1997; Martin et al., 1999) and combat veterans (Bremner, 1999).

Other, less expected, correlations concerned the cerebellum and the association cortical areas, with right-sided predominance (note that, at the $P < 0.01$ threshold, the latter correlations were bilateral; data not shown). The correlations with the cerebellum and the right superior and middle temporal cortex are similar to our previous findings with the Word Learning test, which also evaluates verbal episodic memory (for detailed discussion of these foci, see Desgranges et al., 1998a). To explain these findings, we proposed in that article that they might represent compensatory mechanisms.

Although we cannot exclude the possibility of false positives, the same hypothesis will explain the similarly unexpected correlations found here with Story Recall, especially the correlations with the right fusiform gyrus, the left lingual gyrus and the right inferior temporal gyrus.
In the present study, to test this hypothesis, we assessed whether the sites of the significant correlations varied with disease severity. For the two subgroups, we used an uncorrected threshold of $P < 0.005$, which may not protect fully against results due to chance but would seem to be more suitable for clinical research with relatively small samples of patients. Furthermore, all the observed correlations were in the positive direction, which might be expected neurobiologically (i.e. any decline in cognitive performance was predicted to relate to a fall rather than an increase in CMRGlc), and this strengthens their statistical validity. Furthermore, in both subgroups, the peak with the most significant correlation, located in the right parahippocampal and left fusiform gyri, respectively, survived the more stringent level of $P < 0.001$ (Fig. 1B and C), supporting the overall robustness of our findings.

The findings of this study strongly support our working hypothesis. Thus, in the less severe subgroup, the significant correlations were located exclusively in the parahippocampal gyrus (entorhinal, perirhinal and parahippocampal cortices) and retrosplenial cortex. The former is the first to be affected by changes in tau in Alzheimer’s disease (Delacourte et al., 1999) and is known to be involved both in normal memory function (Gabrieli et al., 1997; Tulving and Markowitsch, 1997; Lepage et al., 1998) and in amnesia (Buffalo et al., 1998), whereas the latter—also a paralimbic region—is now known to be strongly implicated in episodic memory (Valenstein et al., 1987; Wiggs et al., 1999). Although, at the statistical cut-off value chosen, all these correlations were right-sided, which may appear surprising for a verbal test, at the $P < 0.05$ level there were also significant correlations in the left hippocampal region (data not shown).

By contrast, the correlations obtained in the more severe subgroup were clearly shifted away from the limbic/paralimbic network and involved exclusively the left (essentially temporal) association neocortices. One could argue that the lack of correlation with the medial temporal lobe might be due to the fact that there was not enough tissue to allow meaningful glucose uptake. However, we have evidence that this is not the case. In fact, in all SPM analyses in this study, only those voxels with values >40% of the mean for the whole brain were retained, and the medial temporal lobe was not excluded by this procedure (Fig. 2). Accordingly, the plot of the actual values for the hippocampal region for the whole sample clearly shows substantial glucose uptake in this region for each patient (Fig. 1A).

In this study, we were interested in studying the relationships between disease severity and memory–CMRGlc correlations. However, the MMSE score reflects the degree of global cognitive deterioration but is heavily weighted by episodic memory. We therefore wondered what would be the result if our Alzheimer’s disease sample were split according

![Image](image.png)
### Table 2
Significant ($P < 0.05$, corrected for cluster level, from SPM maps thresholded at $Z > 3.09$) correlations between scores in the Story Recall test and nCMRGlc for the whole group ($n = 40$)

<table>
<thead>
<tr>
<th>Cluster size (no. of voxels)</th>
<th>Region</th>
<th>BA</th>
<th>Talairach coordinates of peaks</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 796</td>
<td>R hippocampal region</td>
<td>20</td>
<td>$-39$</td>
<td>$-3$</td>
</tr>
<tr>
<td></td>
<td>L posterior cingulate gyrus</td>
<td>31</td>
<td>$-46$</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>L precuneus*</td>
<td>-17</td>
<td>$-42$</td>
<td>$-13$</td>
</tr>
<tr>
<td></td>
<td>R posterior cingulate/precuneus*</td>
<td>27</td>
<td>$-11$</td>
<td>$-25$</td>
</tr>
<tr>
<td></td>
<td>L lateral cerebellum</td>
<td>41</td>
<td>$-46$</td>
<td>$-26$</td>
</tr>
<tr>
<td></td>
<td>R lateral cerebellum</td>
<td>20</td>
<td>$-21$</td>
<td>$-26$</td>
</tr>
<tr>
<td></td>
<td>R cerebellum (vermis)</td>
<td>1</td>
<td>$-50$</td>
<td>$-17$</td>
</tr>
<tr>
<td></td>
<td>L lateral cerebellum</td>
<td>57</td>
<td>$-58$</td>
<td>$-23$</td>
</tr>
<tr>
<td></td>
<td>R lateral cerebellum</td>
<td>27</td>
<td>$-36$</td>
<td>$-23$</td>
</tr>
<tr>
<td></td>
<td>R lateral cerebellum</td>
<td>57</td>
<td>$-48$</td>
<td>$-20$</td>
</tr>
<tr>
<td></td>
<td>R fusiform gyrus</td>
<td>57</td>
<td>$-38$</td>
<td>$-22$</td>
</tr>
<tr>
<td></td>
<td>L lingual gyrus</td>
<td>19</td>
<td>$-12$</td>
<td>$-54$</td>
</tr>
<tr>
<td></td>
<td>R superior temporal gyrus</td>
<td>41</td>
<td>$-54$</td>
<td>$-20$</td>
</tr>
<tr>
<td></td>
<td>R inferior temporal gyrus</td>
<td>57</td>
<td>$-27$</td>
<td>$-21$</td>
</tr>
<tr>
<td></td>
<td>L lateral cerebellum</td>
<td>29</td>
<td>$-60$</td>
<td>$-23$</td>
</tr>
<tr>
<td></td>
<td>R middle temporal gyrus</td>
<td>52</td>
<td>$-65$</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>R middle temporal gyrus</td>
<td>48</td>
<td>$-65$</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>L perirhinal cortex</td>
<td>33</td>
<td>$-19$</td>
<td>$-26$</td>
</tr>
<tr>
<td></td>
<td>R middle temporal gyrus</td>
<td>55</td>
<td>$-63$</td>
<td>5</td>
</tr>
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</table>

The clusters are listed in decreasing order of peak Z score. *This area was identified on the SPM printout only (Fig. 2, top row). BA = Brodmann area; L = left; R = right.

### Table 3
Significant ($P < 0.005$, uncorrected) correlations between scores in the Story Recall test and nCMRGlc for the less severe subgroup ($n = 20$)

<table>
<thead>
<tr>
<th>Cluster size (no. of voxels)</th>
<th>Region</th>
<th>BA</th>
<th>Talairach coordinates of peaks</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>455</td>
<td>R perirhinal/parahippocampal cortex</td>
<td>36</td>
<td>$-37$</td>
<td>$-2$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
<td>$-36$</td>
<td>$-20$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>$-32$</td>
<td>$-27$</td>
</tr>
<tr>
<td>5</td>
<td>R entorhinal/perirhinal cortex</td>
<td>28/35</td>
<td>$-9$</td>
<td>$-23$</td>
</tr>
<tr>
<td></td>
<td>R retrosplenial cortex²</td>
<td>29/30</td>
<td>26</td>
<td>2.67</td>
</tr>
</tbody>
</table>

The clusters are listed in decreasing order of peak Z score. BA = Brodmann area; R = right. *$P < 0.001$; ²this area was identified on the SPM printout only (Fig. 2, middle row).

### Table 4
Significant ($P < 0.005$, uncorrected) correlations between scores in the Story Recall test and nCMRGlc for the more severe subgroup ($n = 20$)

<table>
<thead>
<tr>
<th>Cluster size (no. of voxels)</th>
<th>Region</th>
<th>BA</th>
<th>Talairach coordinates of peaks</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>2865</td>
<td>L fusiform gyrus</td>
<td>20</td>
<td>$-57$</td>
<td>$-15$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20/37</td>
<td>$-45$</td>
<td>$-48$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39/22</td>
<td>$-41$</td>
<td>$-54$</td>
</tr>
<tr>
<td></td>
<td>L superior temporal gyrus</td>
<td>37</td>
<td>$-56$</td>
<td>$-56$</td>
</tr>
<tr>
<td></td>
<td>L inferior temporal gyrus</td>
<td>37</td>
<td>$-54$</td>
<td>$-58$</td>
</tr>
<tr>
<td></td>
<td>L inferior temporal/fusiform gyri</td>
<td>37</td>
<td>$-48$</td>
<td>$-54$</td>
</tr>
<tr>
<td>57</td>
<td>L inferior parietal lobule</td>
<td>40</td>
<td>$-40$</td>
<td>$-22$</td>
</tr>
<tr>
<td>29</td>
<td>L cuneus</td>
<td>18</td>
<td>$-14$</td>
<td>16</td>
</tr>
</tbody>
</table>

The clusters are listed in decreasing order of peak Z score. BA = Brodmann area; L = left. *$P < 0.001$. 

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to their Story Recall score itself, which reflects the degree of verbal episodic memory deterioration. However, the results of this post hoc analysis were very similar to those obtained when the sample was split according to their MMSE scores. Thus, in the subgroup of best performers (15 patients in this subgroup also belonged to the less severe subgroup), the only significant cluster at $P < 0.005$ was located in the right perirhinal and retrosplenial cortices, whereas for the worst performers (15 of whom also belonged to the more severe subgroup) the correlations concerned principally the left neocortical areas (data not shown).

Our findings suggest that, in the early stages of Alzheimer’s disease, hippocampal region function is impaired but is still sufficient to subserve the remaining episodic memory performance, whereas later on, as the burden of the lesions progresses, this region might become progressively inadequate, so that the association neocortical areas are recruited, constituting a compensation mechanism. Although these areas are classically considered to be of little importance in episodic memory and damage to them does not usually result in a full-blown amnesic syndrome, our interpretation fits with three pieces of evidence. First, these areas are part of the large neuronal network that is activated in young, healthy subjects during episodic encoding and retrieval (for reviews see Desgranges et al., 1998b; Cabeza and Nyberg, 2000). Secondly, the left parietotemporal cortex is thought to be involved in memory compensation processes in Alzheimer’s disease according to some activation studies (Becker et al., 1996; Stern et al., 2000). Thirdly, the regions whose metabolism was correlated to verbal memory scores in our study, all of which are located in the left cerebral hemisphere, are known to be involved in semantic memory, as indicated by both neuropsychological data (Coughlan and Warrington, 1978; Hodges et al., 1992; Hodges and Patterson, 1996) and activation studies in healthy subjects (Mummery et al., 1999; Cabeza and Nyberg, 2000). Likewise, in Alzheimer’s disease, semantic memory impairments correlate with resting perfusion and metabolism of the left association neocortices (Perani et al., 1993; Penniello et al., 1995; Slansky et al., 1995; Grossman et al., 1997; Desgranges et al., 1998a; Hirono et al., 2001). The idea that brain structures that are normally devoted to semantic memory may be involved at least partially in an episodic memory task is also consistent with reports of patients being able to achieve normal performance in a typical episodic memory test despite impaired autonoetic consciousness, which suggests the contribution of processes that must be semantic in some way (Wheeler et al., 1997; Levine et al., 1998). However, recourse to these regions obviously does not result in episodic performance that is as good as that obtained when the limbic system can still be used.

From a more theoretical standpoint, our findings support Tulving’s hierarchical model (Tulving, 1995), which contends that episodic memory, the most sophisticated of all memory systems, should be particularly vulnerable to neurodegenerative processes, whereas semantic memory should be more resistant, at least at the early stages of the disease. Thus, in the more severe subgroup, productions would be driven by components of semantic knowledge linked to any single element of the story (e.g. the item ‘car’, given by the examiner as a cue whenever the patient fails to respond, may activate other representations, such as ‘engine failure’ or ‘garage’, that are also included in the script). In such cases, the patient’s performance would depend, at least partially, on brain areas involved in the storage of semanticized knowledge.

Overall, our results confirm the prominent part taken by hippocampal and parahippocampal damage in the pathogenesis of memory impairment in mild Alzheimer’s disease. They also suggest further insights into potentially compensatory mechanisms that would come into operation when the most impaired patients are faced with a verbal episodic memory task. Though logistically impractical, longitudinal cohort studies assessing the actual displacement of correlations over time as performance declines would be of considerable interest.

Acknowledgements

We wish to thank S. Schaeffer, F. Le Doze, V. Beaudouin, B. Landeau, G. Chételat, M.-H. Noël, G. Perchey, M.-C. Onfroy and P. Conejeno for help with this project.

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Received September 7, 2001. Revised November 27, 2001. Accepted December 12, 2001