Declarative memory impairments in Alzheimer’s disease and semantic dementia

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Received 2 June 2005; revised 26 August 2005; accepted 5 October 2005

Semantic dementia (SD) and Alzheimer’s disease (AD) are both disorders in which early pathology affects the temporal lobe yet they produce distinct syndromes of declarative memory impairment—loss of established semantic knowledge with relatively preserved episodic memory in the former and the converse in the latter. Groups with mild SD and mild AD who showed a double dissociation in these two aspects of declarative memory were studied—the SD group’s episodic memory and the AD group’s semantic knowledge each being comparable to controls. Positron emission tomography and volumetric magnetic resonance imaging were used to map deficits in regional cerebral metabolic rate and mesial temporal lobe (MTL) atrophy, respectively. Episodic memory impairment in AD was associated with dysfunction of an integrated network (mesial temporal lobe, mamillary bodies, dorso-mesial thalamus and posterior cingulate). Semantic memory impairment in SD was associated with bilateral rostral temporal lobe hypometabolism. The SD group had comparable MTL atrophy and hypometabolism to that found in AD but the remainder of their limbic–diencephalic network was preserved suggesting that the latter explains their ability to acquire new episodic memories. The results challenge the view that amnesia in early AD can be explained by the degree of MTL damage alone while showing that semantic impairment can occur with damage restricted to the rostral temporal lobes.

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Keywords: Alzheimer’s disease; Semantic dementia; Episodic memory; Semantic memory; PET

Introduction

Episodic memory impairment is the first and most severe deficit in Alzheimer’s disease (AD). It is often assumed that this deficit is a consequence of mesial temporal lobe (MTL) damage; focal lesions to the MTL are known to cause amnesia (Seoville and Milner, 1957) and this is the site of most severe neurofibrillary tangle deposition in AD (Braak and Braak, 1995; Delacourte et al., 1999). The syndrome of semantic dementia (SD), a variant of fronto-temporal lobar degeneration (Neary et al., 1998), is also associated with neurodegenerative changes in the temporal lobes but gives rise to a different early cognitive profile to that seen in AD. SD cases have progressive loss of previously established semantic knowledge (non-context specific fact, word and object knowledge), yet they are still able to learn new episodic information (Hodges et al., 1992). Thus, in the early stages of disease, a double dissociation in these two aspects of declarative memory can be shown between AD and SD. Preserved episodic memory acquisition in SD was initially interpreted as being due to a relative preservation of MTL structures in this syndrome. This hypothesis was challenged, however, when manual magnetic resonance imaging (MRI) studies found that hippocampal and parahippocampal – including entorhinal cortex – structures were at least as atrophic in SD, when compared to AD (Chan et al., 2001; Davies et al., 2004; Galton et al., 2001). An important caveat is that it was unclear whether the subjects included in these studies exhibited this double dissociation at the time of scanning.

A critical factor in attempting to identify neural explanations for the cognitive deficits seen in these disorders relates to the stage at which cases are studied. Although AD is characterized by episodic memory deficits, semantic memory impairment typically develops with disease progression (Hodges and Patterson, 1995). Likewise in advancing SD, episodic memory impairments are likely to occur although this can be difficult to assess as their semantic deficit may render them untestable on standard neuropsychological measures. However, pathological examinations in either disease are usually carried out in late, or end-stage cases.

Here, we studied cases that displayed the episodic/semantic dissociation at the time of scanning. Functional imaging with SPECT and PET has identified abnormalities in a variety of limbic areas in early AD (Callen et al., 2002; De Santi et al., 2001; Minoshima et al., 1997). In an attempt to understand the neural basis of episodic memory impairment in AD, we had previously...
found that cases with incipient AD (amnesic mild cognitive impairment, MCI), whose only significant neuropsychological deficit was in episodic memory, had hypometabolism restricted to a limbic–diencephalic network comprising the MTL (including hippocampus, dentate gyrus, subiculum and parahippocampal gyrus), mammillary bodies, dorso-mesial thalamus and posterior cingulate cortex (Nestor et al., 2003a). However, we had been unable to assess whether amnesia was a consequence of damage to any one, or to a combination, of these areas. Similarly, Desgranges et al. (2002) showed that episodic memory performance in mild AD (MMSE 23.8 ± 1.9) correlated with entorhinal, perirhinal and retrosplenial areas. However, these correlations cannot clarify whether the memory problem is caused by a lesion to any single region (with the remaining areas degenerating in concert), combined damage to all correlated areas or albeit less plausibly, damage to a wider and more complex network which happens to generate behavioral data that mimic the variance found in the above structures.

The present study had a two-fold aim. The first was to contrast the profile of brain damage in SD and AD cases that, at the time of scanning, exhibited the dissociation in declarative memory performance described above. The questions being whether (i) the SD group would have preserved MTL function compared to AD and (ii) if not, whether there would be a different profile of MTL-connected limbic network dysfunction in SD to that seen in AD. If there was MTL dysfunction in the present SD group, then the degree to which this was associated with damage to the remaining limbic network could inform understanding of the clinical relevance of lesions at these latter sites. The second aim was to map the extent of brain hypometabolism in an early SD group with FDG-PET. Previous MRI studies have highlighted rostral temporal lobe atrophy in SD (Chan et al., 2001; Davies et al., 2004; Galton et al., 2001); however, functional activation studies examining the neural basis of semantic knowledge in healthy subjects usually activate a more distributed network, notably including prefrontal and caudo-lateral temporal areas (Cabeza and Nyberg, 2000). In contrast, rostral temporal lobe activations in such studies are unusual. As FDG-PET is a highly sensitive marker of dysfunction in degenerative brain diseases, the question addressed here was whether hypometabolism beyond the rostral temporal lobes, would be evident or whether semantic knowledge breakdown in SD was due to rostral temporal lobe pathology in isolation.

Methods

Overview

In this study, we selected cases with AD and SD, who at the time of imaging exhibited the double dissociation between episodic and semantic memory. Cases underwent (18F)fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) and volumetric MRI. PET data were analyzed with the voxel-based technique Statistical Parametric Mapping (SPM, Wellcome Department of Imaging Neuroscience) and region of interest methods. The latter method was specifically employed to study changes in small brain regions that are below the resolution of SPM (Mosconi et al., 2005) and for which we had a priori hypotheses. Regions of interest were traced onto individual subjects’ MRI scans, their PET scans were co-registered to their MRI and the metabolic rate for glucose calculated from within each region.

Subjects

A total of 37 subjects participated: n = 14 AD, n = 9 SD and n = 14 healthy controls. The AD group contained cases who, at the time of scanning, had either episodic memory deficits without evidence of non-mnestic cognitive decline – NINCDS-ADRDA criteria for possible AD – or cases with NINCDS-ADRDA probable AD (McKhann et al., 1984). Those with possible AD fulfilled published criteria for MCI (Petersen et al., 2001). Importantly, after scanning, these MCI cases were followed longitudinally (minimum 3 years), and all steadily deteriorated in a manner typical of that seen with Alzheimer type pathology. The cases who displayed additional deficits (n = 4), at the time of scanning, and hence met diagnostic criteria for probable AD (McKhann et al., 1984) also had episodic memory impairment as their most prominent deficit. In view of the aim of this study, AD cases were not selected who exhibited prominent semantic deficits. SD subjects fulfilled published criteria for this diagnosis (Neary et al., 1998) and all showed relative preservation of episodic memory learning (see below). MRI scanning of the SD group revealed characteristic asymmetric focal temporal lobe atrophy that was more severe on the left in seven, and the right in two, cases. Controls were screened to exclude neurological or major psychiatric illness and performed normally on a cognitive screening battery (Mathuranath et al., 2000). Written informed consent was obtained from participants. The study was approved by the Local Regional Ethics Committee and the Administration of Radioactive Substances Advisory Committee, UK (ARSAC).

The three groups were matched for age, sex distribution and education level while the two neurodegenerative groups were further matched for symptom duration, mini-mental state examination score (Folstein et al., 1975), attention – as measured by forward and reverse digit span – (Table 1). Semantic performance was assessed by (i) four category fluency (animals, fruits, dog breeds, birds); (ii) the word and picture versions of the Pyramids and Palm-trees test (Howard and Patterson, 1992), in which for each exemplar presented, the subject has to select the semantically related target in a two item forced-choice paradigm; (iii) a 64-item picture naming test; (iv) a 64-item word–picture matching test. Episodic memory was assessed by 30 min delayed recall of the Rey complex figure (Osterreith, 1944) and immediate and 30 min delayed recall of the non-verbal component of the Doors and People test (Baddeley et al., 1994). Importantly, there was no significant

| Table 1
<p>| Demographic summary of groups |</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>Controls</th>
<th>AD</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M:F)</td>
<td>7:7</td>
<td>8:6</td>
<td>5:4</td>
</tr>
<tr>
<td>Age</td>
<td>61.4 ± 6.9</td>
<td>62.5 ± 5.5</td>
<td>63.4 ± 7.0</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.6 ± 1.5</td>
<td>13.4 ± 3.7</td>
<td>12.8 ± 4.3</td>
</tr>
<tr>
<td>MMSE (/30)</td>
<td>29.8 ± 0.4</td>
<td>26.8 ± 3.0</td>
<td>25.8 ± 3.3</td>
</tr>
<tr>
<td>Symptom duration (years)</td>
<td>–</td>
<td>3.1 ± 1.4</td>
<td>3.6 ± 2.1</td>
</tr>
<tr>
<td>Digit span (forwards)</td>
<td>–</td>
<td>6.6 ± 1.2</td>
<td>7.1 ± 0.9</td>
</tr>
<tr>
<td>Digit span (backwards)</td>
<td>–</td>
<td>4.5 ± 1.5</td>
<td>5.1 ± 1.2</td>
</tr>
</tbody>
</table>
difference in the two groups’ ability to copy the Rey figure (Fig. 1).

Imaging

The imaging methods and analysis for both ROI and whole brain voxel-based techniques have been described in detail previously (Nestor et al., 2003a). Briefly, subjects underwent 3T-volumetric magnetic resonance imaging (MRI) and fasting (18F)fluor-2-deoxy-d-glucose positron emission tomography (FDG-PET) with glucose maps calculated according to the autoradiographic method (Phelps et al., 1979). MRI scans were oriented into stereotaxic space (aligned to the ac–pe line) and then regions of interest traced, blinded to group, onto the individual scans for the MTL (hippocampus, subiculum and adjacent parahippocampal gyrus), mamillary bodies, anteromedial thalamus (designed to include anterior, medio-dorsal and lateral dorsal nuclei), posterior cingulate and temporal pole. In the second analysis, the MTL was split into three ROIs along its long axis: posterior (10 × 1 mm coronal slices caudal to the posterior commissure), middle (10 × 1 mm coronal slices rostral to the posterior commissure) and anterior (the area remaining rostral to the middle ROI—also approximately 10 mm). Full details of the tracing method and landmarks used can be found at http://fs0.wbic.cam.ac.uk/papers/. For the manual volumetric MRI study in analysis 2, a measurement of intracranial skull volume was extracted from each subject and this was applied as a scaling factor to his or her MTL measurements to correct for normal interindividual variability in premorbid brain volume. All of the above procedures related to MRI processing were performed using Analyze version 6 software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN, USA). FDG-PET was co-registered to MRI and cerebral metabolic rate (CMRglc) calculated in the ROIs. CMRglc was normalized to the cerebellar vermis (nCMRglc) to minimize normal interindividual variability in brain metabolism. In the ROI studies, to adjust for artefactual decrease in metabolic rate through atrophy, a three-compartment (gray matter, white matter, cerebrospinal fluid) partial volume correction was applied (Meltzer et al., 1999). The voxel-based analysis was done with Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK), the precise details of which were described previously (Nestor et al., 2003a) with the only exception that for the statistical analysis of the SD group the voxel threshold mask had to be reduced to >10% of the mean so as not to erroneously discard severely hypometabolic temporal polar voxels. In all PET ROI results figures, the y-axis represents nCMRglc. In all figures, y-error bars indicate 95% confidence interval.

Results

Neuropsychology

The memory assessment of each group identified the double dissociation between performance on neuropsychological tests of episodic and semantic memory (Fig. 1). The SD group was significantly impaired on semantic tasks relative to AD with the converse profile being found on the episodic tasks. Compared to healthy, aged controls, the mean z score for the semantic battery was \( z = -12.17 \pm 13.0 \) for the SD cases and \( z = -0.18 \pm 0.6 \) for the AD cases (\( P = 0.02 \)) while for the episodic battery the means were \( z = -0.25 \pm 1.4 \) and \( z = -2.48 \pm 0.9 \) (\( P = 0.001 \)), respectively. All individual SD subjects had a lower mean z score for the semantic compared to the episodic battery and all individual AD subjects had the converse profile.

Imaging

Analysis 1

Analysis of variance (ANOVA) at each node in the network yielded significant group effects (degrees of freedom, \( df, 2, 34 \)) in all regions, except the right thalamus, as follows: MTL, right \( F = 3.5, P = 0.04 \); left \( F = 16.7, P < 0.0001 \); mamillary bodies \( F = 3.9, P = 0.03 \); thalamus, right \( F = 1.3, P = 0.3 \); left \( F = 4.6, P = 0.02 \); posterior cingulate, right \( F = 19.0, P < 0.0001 \); left \( F = 20.0, P < 0.0001 \). Post hoc unequal t tests found significant reductions in nCMRglc in the AD group at each of these loci compared to controls (Table 2). The nCMRglc reductions in the AD group were also significantly greater than those of the SD group in the left thalamus and bilateral posterior cingulate while the mamillary bodies showed a trend in the same direction (\( P = 0.08 \)). Post hoc analysis of the nCMRglc for the MTL revealed a different pattern. While the AD group displayed significant reductions from controls, the SD group had asymmetric changes: on the right, nCMRglc was not significantly different from AD and showed a trend toward significant reduction compared to controls (\( P = 0.06 \)). On left, however, the SD group had a significantly lower nCMRglc compared to both controls and the AD group (\( P = 0.001 \) and \( P = 0.01 \), respectively).

To survey the extent of cortical hypometabolism, statistical parametric maps (SPM) were created for each group compared to controls (Fig. 2 and Table 3). At \( P_{\text{corrected}} \leq 0.05 \), the SPM analysis of the AD group had significant reductions in nCMRglc maximal in posterior cingulate region but also in right and left lateral

Fig. 1. Behavioral data. Performance of the AD and SD groups on semantic (top) and episodic memory tests. *Mann–Whitney U tests, \( P < 0.05 \). Abbreviations: CF: category fluency; PPTp and PPTw: Pyramids and Palmtrees picture and word versions; WPM: word-picture matching; RC: Rey complex figure copy; RR: Rey complex figure 30 min delayed recall; DPvIR and DPvDR: visual version of the Doors and People test—immediate and delayed recall, respectively.
controls in the right temporal pole; however, on left side, there was a mild reduction in nCMRglc that just reached statistical significance ($P = 0.04$). The finding of relative preservation of the mammillo–thalamo–
cingulate network in SD is consistent with our a priori hypothesis. Bilateral MTL hypometabolism in SD is, however, paradoxical since this deficit ought to be associated with episodic memory impairment. A second analysis was conducted to explore three potential explanations. (i) The profile of MTL damage may differ along the long axis in SD and AD. This hypothesis was based on a priori knowledge that SD cases have graded hippocampal atrophy (worse rostrally) whereas atrophy is homogeneous in AD (Chan et al., 2001; Davies et al., 2004) and an observation derived from PET imaging that suggested functional changes in AD may be graded in the opposite direction. The retrosplenial cortex displays very early and severe metabolic changes in AD (Nestor et al., 2003b) and an observation derived from PET imaging that suggested functional changes in AD may be graded in the opposite direction. Analysis 2

To explore these hypotheses, the right and left MTLs were divided into anterior, middle and posterior sub-regions for PET calculation of glucose metabolism and structural volumetric MRI measurements. Significant group effects for PET (ANOVA, $df = 2, 34$) were found for left middle and left anterior regions only: $F = 6.6, P = 0.004$ and $F = 7.1, P = 0.003$, respectively. At these points, post hoc tests found that each group’s nCMRglc was significantly reduced compared to controls, but not significantly separated from each other, although there was a trend to greater left anterior hypometabolism in the SD group ($P = 0.07$). As there were no other significant regional group effects, further post hoc comparisons were not undertaken. It was noted, however, that the long axis metabolic profile in AD paralleled that of controls. By contrast, the SD group showed a sloping contour worsening in the posterior to anterior direction. Of particular note, the SD group’s right posterior region nCMRglc was the same as that of controls (Fig. 3).

Analysis of the volumetric MRI data (Fig. 3) established significant group effects for all regions, except the right posterior MTL, $F = 2.1, P = 0.13$, as follows: right middle, $F = 6.3, P = 0.005$; right anterior, $F = 4.1, P = 0.03$; left posterior, $F = 7.9, P = 0.002$; left middle, $F = 9.7, P < 0.001$ and left anterior, $F = 4.6, P = 0.02$, MTL regions. Post hoc pair-wise comparisons showed that the SD group’s volumes were significantly reduced compared to controls in all five regions in which the ANOVA was significant: right middle ($P = 0.0002$), right anterior ($P = 0.004$), left posterior ($P = 0.001$), left middle ($P < 0.0001$) and left anterior ($P = 0.01$) MTL regions. Compared to controls, the AD group had significant volume loss in the left middle MTL ($P = 0.02$) but in no other sub-region. Compared to AD, the degree of volume loss in SD was significantly greater in right middle ($P = 0.006$), left posterior ($P = 0.02$), left middle ($P = 0.05$) and left anterior ($P = 0.04$) MTL regions. Importantly, compared to SD, volume loss in AD was not worse in

Table 2

<table>
<thead>
<tr>
<th>Region of interest summary</th>
<th>Region</th>
<th>Control</th>
<th>AD</th>
<th>SD</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Temporal pole</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>0.69 ± 0.07</td>
<td>0.73 ± 0.09</td>
<td>0.42 ± 0.13</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.85 ± 0.07</td>
<td>0.74 ± 0.08</td>
<td>0.41 ± 0.13</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>MTL: long axis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. posterior</td>
<td>0.82 ± 0.05</td>
<td>0.78 ± 0.05</td>
<td>0.82 ± 0.09</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>L. posterior</td>
<td>0.86 ± 0.05</td>
<td>0.80 ± 0.05</td>
<td>0.79 ± 0.10</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>R. middle</td>
<td>0.81 ± 0.04</td>
<td>0.74 ± 0.05</td>
<td>0.76 ± 0.11</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>L. middle</td>
<td>0.87 ± 0.06</td>
<td>0.76 ± 0.04</td>
<td>0.71 ± 0.10</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>R. anterior</td>
<td>0.84 ± 0.04</td>
<td>0.78 ± 0.05</td>
<td>0.75 ± 0.12</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>L. anterior</td>
<td>0.86 ± 0.04</td>
<td>0.78 ± 0.05</td>
<td>0.66 ± 0.15</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td><strong>Papez connections of MTL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grand mean (R + L)</td>
<td>1.22 ± 0.04</td>
<td>1.03 ± 0.04</td>
<td>1.20 ± 0.11</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>R. network mean</td>
<td>1.14 ± 0.05</td>
<td>0.97 ± 0.04</td>
<td>1.12 ± 0.13</td>
<td>0.0007</td>
<td></td>
</tr>
<tr>
<td>L. network mean</td>
<td>1.16 ± 0.04</td>
<td>0.97 ± 0.04</td>
<td>1.16 ± 0.12</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Normalized cerebral metabolic rate for glucose (mean ± 95% confidence interval) for each region studied (post hoc tests—$a: P < 0.05$, $b: P < 0.01$, $c$: $P < 0.001$ compared to controls; $d: P < 0.05$, $e$: $P < 0.01$, $f$: $P < 0.001$ compared to the other degenerative group).

temporo-parietal association cortex and left dorso-lateral prefrontal cortex. In contrast, the only significant regions of hypometabolism in the SD group were in bilateral temporal lobes, more extensive on the left side and maximal in the poles and ventro-rostral surface. On both sides, there was complete involvement of the temporal pole (BA 38). Moving caudally from the pole on the left, there was involvement of all regions excluding the superior temporal gyrus (to Talairach co-ordinate $y \approx -20$); caudal to this, the lesion involved fusiform and inferior temporal gyri (to $y \approx -24$) and thereafter involved fusiform alone up to, but not including BA37 ($y \approx -38$). Moving caudally from the pole on the right, the hypometabolic lesion involved fusiform and inferior temporal gyrus (to $y \approx 0$) and thereafter fusiform alone (BA 20/36 to $y \approx -16$). The area that has been designated perirhinal cortex in humans (Insauti et al., 1998) was entirely subsumed within the hypometabolic field on each side. At the reduced statistical threshold of $P_{corrected} \leq 0.1$, the temporal lobe abnormalities were slightly larger but no other hypometabolic areas emerged. The polar abnormality was quantified with a region of interest study (Table 2)—the ANOVA found significant group effects on each side (right $F = 10.9, P = 0.0002$ and left $F = 23.3, P < 0.0001$). As expected from the SPM analysis, post hoc comparisons confirmed highly significant reductions in nCMRglc in SD compared to both controls and AD subjects. The AD group had similar nCMRglc to...
any sub-region. Regarding the relationship of atrophy to functional loss (Fig. 4), there was a significant positive correlation between loss of regional volume and reductions in rCMRglc in SD ($r = 0.37, P = 0.005$) but not in AD where there was an unexpected trend for a negative correlation ($r = -0.20, P = 0.07$). It should be noted that these two measures were completely independent in the control population ($r = 0.01, P = 0.9$) as would be expected in healthy brains (N.B. CMRglc is expressed per unit weight of tissue).

Thus, to address the first hypothesis, no sub-regions were significantly more affected in the AD group suggesting that although there was a different long axis profile, there was nothing in this group’s MTL metabolic profile that could explain the greater episodic memory deficit of AD compared to SD. Turning to the second hypothesis, there was asymmetry in the degree of MTL hypometabolism in the SD, but not in the AD, group (Fig. 3). This raised the possibility that there may be a material-specific episodic deficit in SD. To this end, it should be noted that the episodic tasks employed in this study comprised non-verbal tests only (see Discussion). There was, however, little to support the hypothesis that relative preservation of the right MTL explained their superior performance on the episodic battery. For instance, there was no significant correlation between the SD group’s

Table 3
Summary of statistical peaks from the SPM analysis

<table>
<thead>
<tr>
<th>Cluster size</th>
<th>Region</th>
<th>Brodmann area</th>
<th>Talairach co-ordinates</th>
<th>$P_{\text{corrected}}$</th>
<th>$T$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$x$</td>
<td>$y$</td>
<td>$z$</td>
</tr>
<tr>
<td>8070</td>
<td>L. ventro-rostral temporal lobe</td>
<td>BA 20/38</td>
<td>-40</td>
<td>6</td>
<td>-36</td>
</tr>
<tr>
<td></td>
<td>L. ventral temporal lobe</td>
<td>BA 20</td>
<td>-40</td>
<td>-8</td>
<td>-34</td>
</tr>
<tr>
<td>2397</td>
<td>R. ventro-rostral temporal lobe</td>
<td>BA 20/38</td>
<td>42</td>
<td>2</td>
<td>-36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4603</td>
<td>L. posterior cingulate/precuneus</td>
<td>BA 31/7</td>
<td>-12</td>
<td>-58</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>R. posterior cingulate</td>
<td>BA 31</td>
<td>8</td>
<td>-58</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>R. posterior cingulate</td>
<td>BA 23</td>
<td>2</td>
<td>-28</td>
<td>30</td>
</tr>
<tr>
<td>778</td>
<td>L. supramarginal gyrus</td>
<td>BA 40</td>
<td>-44</td>
<td>-56</td>
<td>30</td>
</tr>
<tr>
<td>1569</td>
<td>R. inferior occipital lobe</td>
<td>BA 18</td>
<td>44</td>
<td>-84</td>
<td>-6</td>
</tr>
<tr>
<td></td>
<td>R. middle temporal gyrus</td>
<td>BA 37</td>
<td>60</td>
<td>-58</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>R. inferior occipital lobe</td>
<td>BA 18</td>
<td>32</td>
<td>-92</td>
<td>-14</td>
</tr>
<tr>
<td>431</td>
<td>Quadrigeminal cistern</td>
<td></td>
<td>-2</td>
<td>-28</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>L. posterior parahippocampal gyrus</td>
<td>BA 27</td>
<td>-10</td>
<td>-32</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>L. parahippocampal gyrus/retrosplenial cortex</td>
<td>BA 35/30</td>
<td>-18</td>
<td>-38</td>
<td>-2</td>
</tr>
<tr>
<td>1297</td>
<td>L. inferior frontal gyrus</td>
<td>BA 46</td>
<td>-44</td>
<td>42</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>L. middle frontal gyrus</td>
<td>BA 10</td>
<td>-30</td>
<td>60</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>L. middle frontal gyrus</td>
<td>BA 9</td>
<td>-42</td>
<td>38</td>
<td>28</td>
</tr>
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Fig. 2. Statistical parametric maps projected onto MRI (top) and glass-brain format at $P_{\text{corrected}} = 0.05$. 
performance on delayed recall of the Rey figure and, either, right posterior MTL nCMRglc ($r = 0.42, P > 0.2$) or averaged overall right MTL nCMRglc ($r = 0.33, P > 0.2$). Furthermore, in contrast to the group mean, some individual SD cases had worse right, compared to left sided, hypometabolism, yet these cases still had relatively preserved performance on the episodic memory tasks: the SD subject with the lowest right MTL nCMRglc ($z = -3.1$) performed above the control mean ($z = +0.9$) for Rey figure delayed recall; this contrasts with one AD subject whose nCMRglc for the same region was above control ($z = +1.2$) yet was significantly impaired on delayed recall of the Rey figure ($z = -3.1$). And finally, the volumetric data found similar – or worse – atrophy in the right MTL regions in SD compared to AD. It is also worth noting that the SD group did not exhibit a material-specific deficit in semantic memory: they were impaired on the picture version of the pyramids and palm-trees test, a test of non-verbal associative knowledge.

The third hypothesis – that the critical difference between the two groups episodic memory performance relates to the cumulative insult to the limbic–diencephalic network – was tested by examining mean metabolic rate of the circuit. The nodes of the limbic–diencephalic circuit (mamillary bodies, right and left thalami, right and left posterior cingulate) minus the MTL were collapsed together to calculate a grand mean—thus gauging the contribution of the network connections exclusive of the MTL (Fig. 5). Using this measure of limbic metabolic rate, a significant group effect was identified (ANOVA, $df, 2, 34$, $F = 12.3, P < 0.0001$); this finding was maintained when either the right or left half of the network was considered in isolation $F = 9.0, P = 0.0007$ and $F = 12.7, P < 0.0001$, respectively. Post hoc testing found a significant reduction in network nCMRglc for the AD group compared to either controls or the SD group, while the latter two groups were similar to each other. Adding the MTL into this limbic–diencephalic network diluted the magnitude of the effect but not the overall findings (ANOVA total network: $F = 9.7, P = 0.0005$; right side $F = 7.2, P = 0.002$; left side $F = 10.4, P = 0.0003$; post hoc comparisons of AD and SD $P < 0.05$, $P < 0.05$, respectively).

Discussion

In this study, cases with SD and AD who, at the time of scanning, exhibited a double dissociation between impairments of new episodic memory learning and established semantic memory were shown to have comparable MTL atrophy and hypometabolism. The groups were, however, differentiated by the distribution of lesions beyond this region. In AD, there were metabolic deficits in limbic–diencephalic connections of the MTL – most
significantly in the posterior cingulate region – while in SD, there was focal damage to the rostral temporal lobes.

Episodic memory

In AD, MTL damage has been regarded as the prime candidate to explain episodic memory impairment given that this is the first region affected by neurofibrillary tangle pathology (Delacourte et al., 1999) and numerous studies of patients with focal lesions implicate damage to this area in the genesis of amnesia. Our findings suggest that the neural basis of amnesia in AD is more complex. In contrast to SD, the group with AD showed impairment of anterograde episodic memory for non-verbal material but did not display significantly greater MTL damage (atrophy or hypometabolism). Based upon the metabolic data alone, it could be argued, nevertheless, that MTL damage is the explanation for the amnesia in AD. That is, one could hypothesize that MTL hypometabolism is a consequence of local damage in AD whereas, in SD, it reflects loss of synaptic inputs from neurons arising in the temporal isocortex that are not involved in learning. The volumetric data argue strongly against this interpretation. SD cases had equivalent or even greater MTL atrophy than the AD cases and, moreover, the degree of atrophy correlated with metabolism in the former group only. This suggests that reductions in MTL metabolism were more a consequence of local tissue loss in the SD rather than the AD group. Taken together, these findings offer evidence that MTL damage – in isolation – does not explain the marked episodic memory impairment characteristic of early AD. Rather, the data suggest that episodic memory impairment occurs when damage at multiple sites in a functionally integrated network comprising MTL and related limbic–diencephalic circuitry reaches a critical threshold. This may help reconcile a problem in interpretation of volumetric MRI studies in AD. Such studies can identify significant volume differences in MTL structures, such as hippocampus and entorhinal cortex, at a group level (Galton et al., 2001; Xu et al., 2000); however, there is typically a huge overlap between individual cases and controls even though such individuals, by definition, do not overlap in episodic memory performance. Finally, although the SPM analysis also identified lateral temporo-parietal and frontal association cortex hypometabolism in the AD group, we have shown previously that amnesia in MCI can exist without such changes (Nestor et al., 2003a). These findings are unlikely to be a major contributing factor in explaining the episodic memory impairment.

The trend for a negative correlation between MTL metabolism and volume in AD, particularly when contrasted to the significant positive correlation in SD, was an unexpected result. A possible explanation is that this reflects pathological heterogeneity in the AD group. Those cases with greater MTL volumes – but who are, nonetheless, matched for degree of episodic learning impairment – may require greater damage to the network to generate the same cognitive profile. This, in turn, would be reflected in uncoupling of metabolism and volume due to greater loss of remote synaptic inputs in cases with the most preserved MTL volumes. However, to avoid over-interpretation, it is crucial to note that the AD finding was only a statistical trend in a cognitively homogeneous population. It does not follow that if one studied an AD cohort that included all clinical severity stages (amnestic MCI through to terminal dementia) that the same negative trend would be evident. Intuitively, one would still predict that across the whole spectrum of clinical severity, a positive correlation between structure and function would emerge given that disease progression is associated with both worsening atrophy and worsening metabolic rate. Nevertheless, the contrasting MTL structure/function relationships in AD and SD have important implications for the interpretation of brain/behavior relationships in these degenerative disorders. The findings suggest that there is a reasonably tight coupling between structure and function in SD, the implication of which being that measurements of either (provided the method is sufficiently accurate) can be used to infer relationships between lesion topography and cognitive deficits. In other words, extrapolating from these data one would expect that if a given brain region was structurally intact, it would also be functionally preserved whereas if it were atrophic the prediction would be for associated loss of metabolic rate (unfortunately, the dilemma of deciding ‘how much’ atrophy or hypometabolism is clinically significant remains problematic). However, the situation with AD is much more difficult. Although there is very strong evidence that within
subjects there is progressive volume loss in AD (Fox et al., 1999), cross-sectional studies investigating the neural basis for specific cognitive impairments may be confounded by the lack of correlation of structure and function. This conclusion was anticipated by clinical experience in that patients with the clinical syndrome of SD characteristically exhibit focal temporal lobe atrophy whereas AD patients, in spite of unequivocal clinical deficits, often have remarkably unimpressive structural imaging changes. The negative trend found in AD for the correlation of structure and function suggests that resolution of this latter problem is not simply a question of developing more sophisticated measures of regional brain atrophy as it predicts that for a given cognitive stage uncoupling of structure and function may occur. Consequently, the present observation suggests that studies aiming to correlate MRI-derived volume loss with a given neuropsychological profile are at greater risk of producing false-positive and false-negative results than previously thought. In this light, a small but striking observation in a study by Harasty et al. (2001) is particularly noteworthy—they found that severe cortical neuron loss could be seen within areas of preserved cortical volume in AD.

Combining the volume/metabolic correlation data with the finding that posterior cingulate hypometabolism in the AD group was significantly worse than that found in the MTL, raises the provocative possibility that damage to the former structure is the greatest single contributor to the genesis of amnesia in this disease. With regard to this hypothesis, it is important to note that, although rare, focal lesions to the retrosplenial part of the posterior cingulate cortex are associated with amnesia in humans (McDonald et al., 2001; Valenstein et al., 1987), and that this brain region activates during episodic memory retrieval in healthy subjects (Cabeza and Nyberg, 2000). It is also notable that episodic memory retrieval performance correlates with posterior cingulate metabolism in MCI (Chételat et al., 2003). This last point may suggest that posterior cingulate hypometabolism could be purely physiological (de-afferentation). We, and others, have previously entertained this hypothesis speculating that posterior cingulate hypometabolism may have been secondary to MTL degeneration (Minoshima et al., 1999; Nestor et al., 2003a). However, the SD results suggest that this is incorrect as MTL hypometabolism was not associated with posterior cingulate hypometabolism in this group. In contrast, there is evidence from MRI volumetry for primary neurodegeneration at this site—as well in the mammillary body and anterior thalamus—in probable AD (Callen et al., 2001). Furthermore, primary posterior cingulate degeneration appears to be a very early feature of AD; it has been shown that patients with familial AD undergo accelerated and specific posterior cingulate and hippocampal volume loss in the years preceding symptom onset (Scahill et al., 2002).

This is not to suggest that severe MTL damage is not sustained with progression of AD pathology and that such damage would further exacerbate the cognitive profile. Furthermore, in contrast to the present results, others have found that hippocampal damage correlates with episodic memory performance in MCI (Chételat et al., 2003) thus suggesting a significant contribution from MTL damage. It should be noted, though, that, in a progressive neurodegenerative syndrome in which both memory performance and MTL damage are ineluctably worsening, there is always a risk that correlation is a function of a non-causal coincidence between these two factors. In a similar vein, some studies have found a positive correlation between hippocampal volume and the magnitude of episodic memory task-induced posterior association cortex activation (Garrido et al., 2002; Remy et al., 2005). Although the authors of these studies did not explicitly propose a biological explanation, it is assumed that their implication was that attenuation of the activation signal was secondary to loss of hippocampal input. The present results would suggest that the relationship between these two observations could be simply that each (attenuation of activation and hippocampal volume loss) is a relatively independent feature of AD but that each is a function of pathological stage. In this light, as the authors of these reports acknowledged, it is notable that the correlations were generated in small groups (n < 10 in each study) over a wide spectrum of severity—extremely so in the case of Remy et al.’s study (MMSE range: 26–11). The alternate hypothesis would be that MTL atrophy in SD would also cause attenuation of episodic memory task-induced activation but this prediction would be even more problematic; as episodic memory performance in SD was comparable to controls, an attenuation of the signal would raise concerns about the relevance of activation magnitude to memory performance.

Reversing the question to examine why the SD group had relative preservation of episodic memory in spite of MTL hypometabolism and atrophy, the second analysis suggested that preservation of integrated limbic–diencephalic circuitry, rather than a left/right or rostral/caudal dissociation, is the most parsimonious explanation. As discussed above, the significant correlation between volume and metabolism in SD suggests that there is local MTL pathology in this syndrome. Given the behavioral data, we propose that this degree of damage is insufficient to cause impairment of episodic learning. An alternate hypothesis is that the profile of damage within the MTL structures—hippocampus versus entorhinal cortex—is different in SD compared to AD. We did not feel that PET had adequate resolution to address this issue (the entorhinal cortex being severely atrophic in many SD subjects). However, previous volumetric MRI work makes this hypothesis very unlikely. It has been shown that significant entorhinal and hippocampal atrophy is present in both pathologies and, moreover, that the relative degree of atrophy (i.e. entorhinal cortex worse than hippocampus) is also common to both (Chan et al., 2001; Davies et al., 2004; Du et al., 2004; Pennanen et al., 2004). Furthermore, a recent pathological study of SD cases found severe neuronal loss in perirhinal, entorhinal and CA1 (hippocampal) areas of the MTL in a distribution similar to that predicted by volumetric MRI (Davies et al., in press).

One important caveat to highlight is that the SD group had more severe left sided MTL damage than AD and the possibility that this could cause a material-specific verbal episodic memory deficit in SD cannot be excluded. The interpretation of SD patients’ performance on verbal episodic memory tests—as such as story, or word–list, recall—is problematic. It is impossible to know whether impairment on such tests—as is typically the case—is a consequence of impairment to the established semantic knowledge base, episodic learning or both systems. There is some evidence that even recognition-based memory for known words is defective (Graham et al., 2002) which contrasts with their typically excellent episodic memory for non-verbal material (Lee et al., 2003).

The conclusion from the SD results that the degree of MTL damage is inadequate to account for the episodic memory deficit of early AD may seem at odds with data from static lesions. For instance, infarction restricted only to bilateral, hippocampal CA1 fields is sufficient to cause anterograde amnesia in humans (Zola-Morgan et al., 1986). However, this paradox may be reconciled through consideration of the pathology of infarction versus that of
neurodegeneration. In the former, even though the lesion may be small, complete loss of neurons would be expected within the infarcted field. In contrast, neurodegeneration is characterized by a progressive loss of neurons such that, in the early stages of disease, there may be a sufficient number of viable neurons remaining to sustain a given cognitive task. In this light, we interpret the modest but comparable reductions in MTL volume and metabolism in AD and SD groups as being insufficiently severe to cause anterograde amnesia.

Semantic memory

The semantic memory deficit in SD was associated with hypometabolism restricted to the ventral and temporal lobes including MTL. Previous MRI studies in SD have identified rostral temporal lobe atrophy (Chan et al., 2001; Galton et al., 2001; Mummery et al., 2000; Rosen et al., 2002; Williams et al., 2005) but structural imaging was unable to rule out the possibility that more diffuse physiological abnormalities were associated with the semantic deficit. The lack of metabolic abnormalities beyond the ventro-rostral temporal lobe – found here and in one previous study (Diehl et al., 2004) – produces compelling evidence that marked semantic deficits can occur with lesions restricted to the these regions alone and, most notably, in the absence of damage to classical left hemisphere language areas. This finding accords with both activation studies using ($^{15}$O)H$_2$O-PET in healthy volunteers, and lesion overlap studies in patients, that have implicated areas within the ventro-rostral temporal lobe in performing semantic tasks such as linking conceptual exemplars – for instance faces or objects – to their names (Damasio et al., 1996, 2004; Grabowski et al., 2001; Tranel et al., 2003). It has been suggested that left and right temporal poles have differential roles in object- and person-based knowledge and naming abilities (Grabowski et al., 2001). Studies in SD have sought to draw similar distinctions by examining cases with greater right or left temporal atrophy (Snowden et al., 2004; Thompson et al., 2003). The present PET finding of severe bilateral polar hypometabolism in SD (see Table 2: temporal poles) illustrates that there is some degree of limitation in the extent to which this syndrome can be used to address left versus right differences.

Herpes simplex encephalitis (HSVE) is also associated with focal anterior temporal lobe damage. However, unlike SD, semantic deficits in HSVE are often heterogeneous with not infrequent reports of category-specific effects (living versus nonliving, etc.) (Laiacona et al., 1997; Pietrini et al., 1988; Siri et al., 2003). The current data suggest that, in contrast to HSVE, the rarity of category-specific effects in SD may relate to the latter having a more homogeneous profile of rostral bi-temporal pathology compared to the, often patchy, pathology of the former.

The finding of localized ventro-rostral temporal lobe hypometabolism in cases with semantic memory breakdown also raises important methodological issues for studies of the neural organization of semantic memory. For instance, static lesions – such as stroke – seldom involve bilateral rostral temporal lobes in the absence of more extensive damage; furthermore, functional MRI experiments of semantic memory are at risk of yielding false-negative results in temporal polar regions because of this area’s vulnerability to signal attenuation due to susceptibility artifact (Ojemann et al., 1997). Thus, the contribution of the rostral temporal lobes in sustaining semantic memory may be underestimated with these other methodologies.

Declarative memory systems

Regarding the neural dissociability of different aspects of declarative memory, the present data are consistent with the view that the limbic–diencephalic network supports acquisition of episodic memory while established semantic memory can be sustained independently of this network—provided the ventro-rostro temporal lobes remain intact. The preservation of semantic memory in the AD group indicates that its storage and retrieval are independent of the limbic–diencephalic system but cannot rule out a role for this system in the acquisition of new semantic information. This hypothesis is supported by a recent study in which hippocampal amnesics were found to have acquired less semantic facts in the time since – as well as for a temporally limited period before – the onset of pathology but not for the very remote past (Manns et al., 2003). Several neuropsychological studies in SD also support this view in that patients exhibit relatively better performance with events from the recent – as opposed to remote – past both for semantic facts (Graham et al., 1998; Hodges and Graham, 1998; Snowden et al., 1996) and autobiographical details (Graham and Hodges, 1997; Nestor et al., 2002; Piolino et al., 2003).

The current results are also germane to theories of declarative memory organization in relation to mesial temporal lobe anatomy. In particular, the hierarchical model, in which the hippocampus sits at the apex of a functional system, directly below which lies the entorhinal cortex and at the base of which is the perirhinal cortex (Mishkin et al., 1998), is challenged by the current results. According to this strict hierarchical model, lesions to the whole mesial temporal system will result in profound deficits in the acquisition of both semantic and episodic information whereas lesions to the apex alone may selectively impair episodic memory. Importantly for the present discussion, this hierarchical model predicts that lesions to the base (perirhinal cortex) will also impair both forms of memory because the functions carried out at the apex (hippocampus) are conditional on the former’s integrity. The SD group findings suggest that this is not the case with regard to episodic memory acquisition. This group had severe bilateral perirhinal hypometabolism – consistent with recent findings that SD is associated with very severe perirhinal atrophy using MRI volumetry (Davies et al., 2004) – and semantic memory impairment, yet was comparable to controls in their acquisition of new information on neuropsychological tests of anterograde memory.

Conclusion

In summary, we found that the episodic memory impairment heralding the onset of AD, is likely to be the result of a summation of damage to the limbic–diencephalic network but cannot be explained by focal MTL dysfunction. Within this network, it is possible that posterior cingulate dysfunction may be of greatest importance in generating the cognitive deficit. In the SD group, relative preservation of episodic memory was associated with relative preservation of this network and occurred in spite of (i) degradation of established semantic memory and (ii) MTL damage at least as severe as was found in amnesic AD. In contrast, significant loss of established semantic memory can be associated with damage restricted to the ventro-rostral temporal lobes without significant involvement of other brain regions.
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