Herpes simplex encephalitis: long term magnetic resonance imaging and neuropsychological profile

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Abstract
The first comprehensive in vivo documentation of the long term profile of pathological and spared tissue is described in a group of 10 patients with a diagnosis of herpes simplex encephalitis, who were left with memory difficulties as a major residual sequela of their condition. With a dedicated MRI protocol, which included high resolution images of temporal lobe and limbic system areas, data are provided on structures that have recently gained importance as anatomical substrates for amnesia. The major features of the lesion profile were: (1) unilateral or bilateral hippocampal damage never occurred in isolation, and was often accompanied by damage to the parahippocampus, the amygdala, specific temporal lobe gyri, and the temporal poles; (2) the insula was always abnormal; (3) neocortical temporal lobe damage was usually unilateral or asymmetric. It never occurred in isolation, and was invariably associated with more medial pathological changes; (4) anterior and inferior temporal lobe gyri were damaged more often and more severely than posterior and superior temporal lobe gyri; (5) pronounced abnormality was often present in the substantia innominata (region of the basal forebrain/anterior perforated substance); (6) there was evidence of significant abnormality in the fornix; (7) there was evidence of damage to the mammillary bodies; (8) thalamic nuclei were affected in around 50% of cases, with damage usually unilateral; (9) frontal lobe damage was present in a few patients, and affected medial areas more than dorsolateral areas; (10) there was some involvement of the striatum, although this was usually unilateral and mild; (11) there was usually limited involvement of the cingulate gyrus and of the parietal and occipital lobes; (12) the cerebellum and brain stem were never damaged. Lesion covariance analysis indicated a close relation between the presence of abnormalities in temporal lobe and limbic-diencephalic regions. Unlike severe head injury, lesions in the temporal pole were not associated with the presence of lesions in the orbitofrontal cortex. Long term neuropsychological impairments were characterised by a dense amnesia in 60% of cases, and a less severe but noticeable anterograde memory impairment in the others. Naming and problem solving deficits were found in a small number of cases. Only two patients were able to return to open employment. Severity of amnesia showed a significant relation with severity of damage to medial limbic system structures such as the hippocampus, with bilateral damage being particularly important. By contrast, there was a minimal relation between memory loss and severity of damage to the thalamus, to lateral temporal lobe areas, or to the frontal lobes.

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examine closely limbic system structures, and the limited anatomical description of those structures that were damaged or spared by the infection.

The aims of the present long term study of patients with herpes simplex encephalitis were threefold: Firstly, we aimed to provide a neu- ronatomical profile of abnormal and spared tissue, as indicated by a dedicated MRI protocol. We paid particular attention to the integrity of candidate anatomical structures that in recent years have come to assume critical importance in animal and human lesion studies of memory disorder. We also examined lesion covariance between selected anatomical regions, in view of the finding that in certain types of cerebral pathology, such as severe head injury, particular associations and dissociations may emerge between MRI based lesion distribution.11

Secondly, we wished to ascertain the extent of recovery of cognitive functioning by providing an outline of the profile of patients in a series of neuropsychological tests. In this study, we concentrated on anterograde memory and general cognitive functioning. Other areas, such as semantic memory and the related area of retrograde amnesia, require detailed investigations in their own right, and are only briefly covered in this report. Thirdly, we aimed to ascertain which, if any, correlations might be found between anterograde memory loss and lesions in specific anatomical regions such as the limbic system. Some investigators12,13 have shown that meaningful correlations can be derived between MRI lesion measures and memory test performance. In these papers, and in similar MRI studies,14 tissue abnormality was simply presumed from reduced tissue volume. Whereas patients with herpes simplex encephalitis are similar to other groups such as those with Alzheimer's disease or alcoholic Korsakoff patients in having several coexistent sites of pathology, the particular advantage in studying patients with herpes simplex encephalitis is that the nature of the inflammatory changes in brain water content result in their lesion profile being clearly shown as well demarcated bright signals on T2 image sequences, and as dark signals on T1 sequences. Identification of the extent and severity of lesion profiles can thus be made with more confidence than in many other groups of patients. Because patients with herpes simplex encephalitis generally comprise a younger age group, they also tend not to have ischaemic or other changes that are associated with an older population of subjects.

Patients and methods

PATIENTS

Ten patients who had a diagnosis of herpes simplex encephalitis, who were at least six months post-recovery, and who were left with significant memory difficulties, formed the group for the present study (table 1). We included cases where there was clear evidence for the presence of a herpes simplex viral infection. The diagnosis of herpes simplex encephalitis is often problematical, even in seropositive cases, and we therefore also took into account clinical and neuropathological features, as well as virological data, for each case. For most of the cases, we were able to trace the relevant pathological records that indicated viral confirmation of a diagnosis of herpes simplex encephalitis, although we also included two patients (cases 2 and 5 in

Table 1 Clinical and neuropsychological profiles of cases of herpes simplex encephalitis

<table>
<thead>
<tr>
<th>Case</th>
<th>Age and sex</th>
<th>Duration of memory disorder (y)</th>
<th>Amnesia severity* (24)</th>
<th>NART estimated IQ score</th>
<th>Verbal IQ subtest scores</th>
<th>Performance IQ subtest scores</th>
<th>Picture naming</th>
<th>Card sorting</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53 Male</td>
<td>7</td>
<td>0</td>
<td>106</td>
<td>Infor = 8</td>
<td>Pict ar = 8</td>
<td>Impaired</td>
<td>2/30</td>
</tr>
<tr>
<td>2</td>
<td>39 Female</td>
<td>15</td>
<td>1</td>
<td>117</td>
<td>Simil = 6ψ</td>
<td>B des = 15</td>
<td>Normal</td>
<td>Pronounced impairment</td>
</tr>
<tr>
<td>3</td>
<td>42 Female</td>
<td>10</td>
<td>2</td>
<td>113</td>
<td>Simil = 7</td>
<td>D sy = 11</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>45 Female</td>
<td>3</td>
<td>3</td>
<td>110</td>
<td>Infor = 5ψ</td>
<td>D sy = 14</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>59 Male</td>
<td>7</td>
<td>4</td>
<td>122</td>
<td>Infor = 10</td>
<td>D sy = 14</td>
<td>Normal</td>
<td>21/30</td>
</tr>
<tr>
<td>6</td>
<td>39 Male</td>
<td>4</td>
<td>7</td>
<td>(Long-standing dysnesia)</td>
<td>Simil = 7</td>
<td>D sy = 14</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>70 Male</td>
<td>3</td>
<td>9</td>
<td>98</td>
<td>Infor = 12</td>
<td>D sy = 14</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>57 Male</td>
<td>2</td>
<td>12</td>
<td>(Dysphasia affected test score) 89</td>
<td>Infor = 5ψ</td>
<td>D sy = 14</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td>65 Male</td>
<td>7</td>
<td>13</td>
<td>89</td>
<td>Infor = 5ψ</td>
<td>D sy = 14</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>10</td>
<td>24 Female</td>
<td>1</td>
<td>23</td>
<td>107</td>
<td>Infor = 9ψ</td>
<td>D sy = 7</td>
<td>Normal</td>
<td>22/30</td>
</tr>
</tbody>
</table>

* Severity of amnesia was based on a composite score reflecting performance on the Wechsler memory scale-revised, the recognition memory test, and the concurrent test. Infor = Information; Arith = Arithmetic; Simil = Similarities; Pict ar = Picture arrangement; B des = Block design; D sy = Digit symbol.

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table 1) for whom we were unable to locate the relevant virological data at the time of admission, but where herpes simplex encephalitis was the firm diagnosis reached after their hospital admission, and where there were strong clinical and neuropathological grounds for supporting such a diagnosis. All of our patient sample could therefore be classified as definite or probable herpes simplex encephalitis. There was no difference in clinical or anatomical profile between the eight definite cases and the two probable cases of herpes simplex encephalitis.

NEUROPSYCHOLOGICAL TEST PROCEDURES

Patients were given the national adult reading test,13 a short form of the Wechsler adult intelligence scale-revised, the Wechsler memory scale-revised, the recognition memory test,16 the graded naming test,17 and the modified card sorting test.18 As the orientation subtest of the Wechsler memory scale-revised is partly cultural-specific to the United States, a short orientation test was drawn up and given to patients—it assessed orientation for place (town), year, month, day of the week, and current prime minister of Great Britain. A score of 1 or 0 was given, resulting in a maximum score of 5.

Table 1 gives our patients’ general neuropsychological test scores. As some patients with herpes simplex encephalitis may show surface dyslexia,1 and as the national adult reading test assesses reading of irregular words, its scores may not meaningfully relate to levels of premorbid cognitive functioning. Although other estimates of premorbid cognitive functioning may also have their own limitations, we decided to base our interpretations of intellectual impairment on performance on individual subtests of the Wechsler adult intelligence scale-revised. A dagger marks those age related subtest scores from the scale where patients performed more than one SD below the mean score of 10 that was derived from the distribution of scores in the original normative study (less than 7). In the case of verbal IQ subtests, the most common test to show an impairment was the information subtest, with 40% of patients having a score of 5 or 6. This test mainly assesses general knowledge that would normally have been acquired before the patient’s illness, and to this extent it will pick up retrograde and semantic memory deficits that are present. In the case of performance subtests, only one patient obtained an age scaled score below 7, this being for the digit symbol subtest. Forty per cent of patients showed a naming deficit on the picture naming task—guidelines provided in the manual were followed for deciding if a score represented a deficit. Impaired performance primarily consisted of a naming score lower than would have been expected on the basis of the patient’s reading score and educational background, and which resulted from paraphasic errors. It is worth noting that most of the patients with naming deficits did not have clinically obvious dysphasia during their conversational speech. A similar number of patients were impaired to some degree on the modified card sorting test. An impairment was considered to be present when patients sorted into less than four categories or had more than 50% perseverative errors.

Table 2 shows the detailed memory test results for the Wechsler memory scale-revised and the recognition memory test. Sixty per cent of cases displayed a dense amnesia, defined as a delayed memory quotient of 50 or less (the delayed memory quotient does not yield scores lower than 50). A composite amnesia severity score was derived that took into account performance on the Wechsler memory scale, the recognition memory test, and the current awareness test. This score was derived by examining each patient’s test score across the 24 memory tests and subtests in question, rating the score as 0 or 1 according to whether it was impaired or normal, and then summing scores across the various subtests.

### Table 2  Memory test scores of patients with HSE

<table>
<thead>
<tr>
<th>Case</th>
<th>WMS-R verbal memory quotient</th>
<th>WMS-R visual memory quotient</th>
<th>WMS-R general memory quotient</th>
<th>WMS-R attention/concentration quotient</th>
<th>WMS-R delayed recall quotient</th>
<th>RMT (age-scaled score)</th>
<th>Current awareness test (max = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;50</td>
<td>50</td>
<td>50</td>
<td>105</td>
<td>&lt;50</td>
<td>Faces &lt;4</td>
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<td>2</td>
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<td>&lt;50</td>
<td>50</td>
<td>79</td>
<td>&lt;50</td>
<td>Words &lt;4</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>100</td>
<td>&lt;50</td>
<td>Faces &lt;4</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>Words &lt;4</td>
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<td>75</td>
<td>50</td>
<td>108</td>
<td>&lt;50</td>
<td>Faces &lt;4</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>77</td>
<td>56</td>
<td>81</td>
<td>76</td>
<td>Words &lt;4</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>78</td>
<td>82</td>
<td>72</td>
<td>113</td>
<td>&lt;50</td>
<td>Faces &lt;4</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>&lt;50</td>
<td>98</td>
<td>52</td>
<td>95</td>
<td>59</td>
<td>Words &lt;4</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>103</td>
<td>110</td>
<td>103</td>
<td>72</td>
<td>100</td>
<td>Faces &lt;4</td>
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<tr>
<td>10</td>
<td>79</td>
<td>80</td>
<td>77</td>
<td>98</td>
<td>75</td>
<td>Faces &lt;4</td>
<td>5</td>
</tr>
</tbody>
</table>

WMS-R=Wechsler memory scale-revised; RMT=recognition memory test.
Each patient could receive a maximum score of 24.

Amnesia was by far the most disabling deficit found in our patient group. It is of note that two of the three most severely amnesic patients (case 2 and case 3) had normal picture naming scores, and two similarly amnesic patients (case 1 and case 3) had normal performance on the modified card sorting test.

In terms of everyday adjustment, only two patients were able to return to open employment. One patient (case 6) was employed in a closely supervised post with British Rail, and did relatively new to tax his memory. The other patient (case 10), who had the least severe memory impairment in the series, returned to her work as a care assistant, and was able to cope with the help of memory aids.

Magnetic resonance imaging was carried out with a Philips 0.5 Tesla Gyroscan T5 scanner. Our protocol was designed to obtain both an overview of the entire brain and to obtain dedicated views of candidate anatomical regions important for memory, such as structures in the limbic-diencephalic system, the temporal lobes, and the frontal lobes.

An initial set of "survey" sagittal scans was carried out to enable planning of dedicated cuts. This survey had nine cuts.

A whole brain axial scan was then carried out. This comprised proton density and T2 weighted 5 mm images with an 0.5 mm interslice gap (TR = 2129; TE = 90/30; matrix size = 205 by 256; field of view = 220). Twenty slices were obtained, with the centre line being positioned along the axis of the corpus callosum.

A coronal inversion recovery T1 weighted scan was then performed, covering the anterior two thirds of the brain (TR = 1500; TE = 30; TI = 400; matrix size = 205 by 256; field of view = 220). Around 17 slices were obtained, each of 5 mm width and 1.0 mm interslice gap.

Finally, a sagittal scan was carried out with the specific aim of imaging mid-line structures such as the mammillary bodies (TR = 523; TE = 25; matrix size = 205 by 256; field of view = 250). This scan was T1 weighted, and had 3 mm width slices, with a 0.5 mm interslice gap. The centre line for this scan, which encompassed seven slices, was positioned to lie along the middle of the third ventricle.

We used image analysis procedures similar to those of other studies. Scans were independently assessed by three raters (DE, JB, and SB), who were all blind to the neuropsychological test results relating to individual patients. All three raters had many years of experience in neuroanatomy and neuroradiology, and when inspecting the scans they had available a number of anatomical atlases and MRI reference texts to assist in their ratings. Initially, all scans were assessed by DE and JB. There was 80–90% agreement between these two ratings. Where there was disagreement for a particular structure, this area was rated by SB, who was blind to the raw rating score from either of the two sets of earlier ratings.

A standard table of structures was provided to each rater, who indicated whether there was a mild or major abnormality in a particular structure. For initial ratings by one of the raters, we used normal images from MR atlases for reference, but for the final sets of ratings we only used data that were obtained on the basis of comparisons between herpes simple infection and routine tasks that did not tax his memory, that is, age matched control subjects. In all, six control subjects were scanned (four men 18, 45, 55, and 70 years old, and two women 31 and 39 years old), so as to provide appropriate comparative images of the normal appearance of structures. For a specific comparison, the subject for a matched control scan was always aged within five years of a particular patient with herpes simplex encephalitis, except for case 10 where the relevant control subject was six years younger. All control subjects were carefully screened to ensure the absence of any neurological illness or injury, or alcohol abuse. The scan protocol given to control subjects was identical to that received by patients with herpes simplex encephalitis.

Results

Magnetic resonance imaging findings

Detailed neuroanatomical profiles for individual structures were mapped on to medial (fig 1 (upper) and surface (fig 1 (lower)) views of the brain. These show the number of patients with lesions in specific brain regions. For illustrative purposes, we have collapsed mild and major lesions into one category. Data from the four thalamic areas have been combined, as have data from the anterior and posterior cingulate gyrus. This anatomical profile shows the invariable damage in the hippocampus and adjacent structures such as the amygdala and the insula, the greater involvement of anterior and inferior temporal lobe gyri, and the damage often found in structures such as the mammillary bodies and the anterior perforated substance.

The striatum, which is not displayed in the figure, showed left sided damage in three cases, right sided damage in two cases, and bilateral damage in one case. The third ventricle was enlarged in seven cases. There was bilateral enlargement of the lateral ventricles in six cases, and unilateral (right sided) enlargement in three cases.

Lesion covariance between damage in selected anatomical regions was also assessed. The coincidence of lesions between six hemispheric sites and each of 10 target anatomical structures was computed as a binomial probability (two tailed). The six hemispheric sites were the right and left limbic-diencephalic systems, right and left temporal poles, and right and left temporal lobes (excluding poles). The 10 target anatomical structures included these six areas, and also the right and
left orbitofrontal regions, and the right and left medial and dorsal frontal regions. For the purposes of this analysis, the limbic-diencephalic system included the hippocampus, parahippocampal gyrus, uncus/entorhinal cortex, amygdala, substantia innominata, fornix, thalamus, mammillary bodies, and cingulate gyrus. We examined those hemispheric sites for which there were at least six patients who showed lesions. We then ascertained which structures from the set of target anatomical structures would also show damage. There were significant contingent associations between the presence of lesions in the right and left limbic-diencephalic areas (p < 0.02); left limbic-diencephalic and left temporal pole areas (p < 0.04); left temporal pole and left limbic-diencephalic areas (p < 0.008); right temporal lobe (excluding temporal pole) and right temporal pole areas (p < 0.008); left temporal lobe (excluding temporal pole) and left limbic-diencephalic areas (p < 0.03); and left temporal pole (excluding temporal pole) and left temporal pole areas (p < 0.03).

There was no significant lesion covariance relating temporal lobe to frontal regions. A notable finding relating to lesion dissociation was that we had one patient with bilateral damage in the mammillary bodies but a normal fornix (case 5), and one patient with bilateral damage in the fornix, but normal mammillary bodies (case 6).

MEMORY-ANATOMY CORRELATIONS
We analysed our data both for group correlations between severity of damage in a defined anatomical area and degree of impairment on a memory task, and also for individual cases of dissociations between anatomy profiles and memory profiles. With a sample size of only 10 patients, it is not meaningful to derive memory-anatomy correlations for each
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A score of 0 was ascribed to a structure that showed no evidence of damage, a score of 1 indicated the presence of a mild abnormality, and a score of 2 was allocated if there was pronounced abnormality. It was possible, therefore, to obtain for individual structures indices of right sided, left sided, and total amount of abnormality. We also separately computed an index of bilaterality of pathology by giving a score of 0 if the lesion was unilateral, a score of 1 if there was a mild lesion on one side and a mild lesion on the other side, a score of 2 if there was a mild lesion on one side and a pronounced lesion on the other side, and a score of 3 if there was marked abnormality on both sides.

In the case of memory test measures, we considered the following variables: (a) the four memory quotients from the Wechsler memory scale-revised; (b) the faces recognition memory age corrected percentile score from the recognition memory test; (c) the words recognition memory age-corrected percentile score from the recognition memory test; (d) the composite amnesia severity score described earlier; (e) performance on the information subtest of the Wechsler adult intelligence scale-revised - this provides a simple index of general knowledge and semantic memory that would have been intact in most patients before their illness. It therefore provides a simple index of retrograde memory loss.

Spearman rank correlation coefficients were computed between memory test scores and lesion indices. The Spearman test is a conservative statistic that only uses the ordinal properties of data, and so it was particularly appropriate with the type of data gathered in this study.

The most comprehensive index of memory loss, that reflected performance over a wide range of memory tests, is the overall amnesia severity score. This showed the highest correlations with bilateral hippocampal damage \((-0.97, p < 0.01\)\) and bilateral limbic system damage \((-0.89, p < 0.01)\). Amnesia severity also correlated with total limbic-diencephalic damage \((-0.86, p < 0.05)\), total hippocampal formation damage \((-0.84, p < 0.05)\), and total temporal lobe damage \((-0.67, p < 0.05)\).

Although measures of delayed retention are among the most sensitive indices of memory loss, the zero delayed recall scores of some of our patients with herpes simplex encephalitis renders this index less valuable than the overall amnesia severity score. Taking this into account, the most sensitive single index of memory impairment from the Wechsler memory scale-revised, the delayed recall quotient, correlated best \((-0.89, p < 0.01)\) with total amount of damage to the hippocampal formation. It also showed a correlation with bilateral limbic-diencephalic damage \((-0.82, p < 0.05)\), total limbic-diencephalic damage \((-0.77, p < 0.05)\), and bilateral hippocampal damage \((-0.78, p < 0.05)\).
It is of note that there was little evidence to relate material specific memory loss with unilateral damage. Indeed, visual memory quotient showed a number of significant correlations with left sided damage, perhaps reflecting the verbal loading on subtests in this scale and the immediate rather than delayed retention that is measured by this quotient. These included correlations between visual memory quotient and left sided limbic diencephalic damage ($-0.92$, $p < 0.01$), bilateral limbic-diencephalic damage ($-0.70$, $p < 0.05$), left sided hippocampal formation damage ($-0.78$, $p < 0.05$), bilateral hippocampal formation damage ($-0.66$, $p < 0.05$), and left sided temporal lobe damage ($-0.80$, $p < 0.05$). Verbal memory quotients correlated with bilateral limbic-diencephalic damage ($-0.84$, $p < 0.05$), total limbic-diencephalic damage ($-0.79$, $p < 0.05$), bilateral hippocampal damage ($-0.90$, $p < 0.05$), and total hippocampal damage ($-0.77$, $p < 0.05$). Also, faces recognition memory showed a significant correlation with only one index of abnormality—namely, total limbic-diencephalic damage ($-0.70$, $p < 0.05$).

Both left sided thalamic damage and left temporal lobe damage correlated with performance on the information subtest ($-0.80$, $p < 0.05$ and $-0.74$, $p < 0.05$ respectively). We found an absence of any significant correlation between thalamic damage and antero- grade memory test scores. This was further borne out by an examination of individual cases: for the three most severely amnesic patients in our series (cases 1, 2, and 3), both the right and left thalami were found to be normal. Although the number of cases with frontal lobe damage was too small to enable us to carry out meaningful correlational analyses, it is worth noting that case 2 and case 5—who scored at floor on the delayed recall quotient—had normal frontal lobes. Case 1, who was the most severely impaired patient in our series, only had mild damage in the left medial frontal lobe. In the case of the two patients referred to earlier with varying degrees of mammillary body and fornix damage, it was the patient with bilateral mammillary body damage and a normal fornix (case 5) who had a more severe amnesia than the patient (case 6) with bilateral fornix damage and normal mammillary bodies.

**Discussion**

In a series of 10 cases, the profile of neuropsychological recovery after severe herpes simplex encephalitis infection was characterised by pronounced memory impairment, with a variable degree of additional cognitive deficits. A dense amnesia was the most disabling of the handicaps in the sample. Naming and problem solving deficits were also found, but did not seem to be as such a major handicap. All but two patients were unable to resume any form of open employment. The anatomical lesion profile was characterised by damage to hippocampal and adjacent medial temporal lobe structures, by pathology in anterior and inferior temporal lobe gyri, by involvement of the insula, by dissociable damage to the mammillary bodies and fornix, and by lesions in the anterior perforated substance. Lesion covariance analysis showed associations between damage in temporal and limbic structures rather than between temporal and frontal regions. Damage to medial limbic structures correlated with severity of memory impairment, with hippocampal structures rather than thalamic nuclei showing the closest association with severity of amnesia.

Our findings largely confirm those made at postmortem by Hierons et al. Specific procedures are such that their sample of patients probably included more severe cases of herpes simplex encephalitis than the patients seen in our study. Even with this proviso, our lesion profiles were strikingly similar to those found by Hierons et al. and this conclusion holds true even if we restrict our comparison to cases in their study (cases 2, 4, and 9) who seemed to have an amnestic disorder and who were therefore most comparable with our herpes simplex encephalitis population.

Our MRI lesion profiles paralleled those that have been documented in the acute, recovery phase of herpes simplex encephalitis. Specific comparisons with individual studies are difficult to make in view of differing imaging protocols and anatomical descriptions of lesions. It does seem that the major pattern of lesions is similar in the acute and in the chronic phases of herpes simplex encephalitis, but that the size of lesions in particular regions, as well as the degree of involvement of subcortical structures such as basal ganglia, is somewhat attenuated in the chronic phase.

In our study, unilateral or bilateral hippocampal damage never occurred in isolation, and was often accompanied by parahippocampal abnormality, by damage to the amygdala, by variable damage to specific temporal lobe gyri, and by involvement of the temporal poles. To this extent, the MRI profile in herpes simplex encephalitis differs from that found in paraneoplastic encephalitis, where there often seems to be more focal damage that is restricted to the hippocampus and to immediately adjacent structures such as the parahippocampal gyrus and the amygdala.

The insula was always damaged in our study. It is uncertain as to its precise role in human memory disorder, and recent studies have in fact linked it to autonomic functions such as heart rate, to recovery of motor function, and to multimodal sensory integration.

Because of the size of our patient sample, and due to the covariance of damage in adjacent structures in the medial and lateral temporal lobe, anatomy-memory correlations in our study must be regarded as preliminary. It is of note, however, that some of our findings did confirm established relations from other clinical and methodological approaches.
Thus, we found that bilateral damage to the hippocampal formation showed the highest correlation with severity of amnesia. Bilaterality of damage rather than total amount of damage seemed to be critical for the severity of memory loss. By contrast, structures such as the thalamus and the frontal lobes were minimally associated with severity of memory loss. Damage to temporal lobe gyri was also much less closely associated with severe anterograde memory impairment. Our findings confirm the primacy of medial temporal lobe damage, especially bilateral damage, in accounting for amnesia in patients with temporal lobe abnormality, and complement similar sets of data from other neurological conditions.27

Neocortical temporal lobe damage was usually unilateral or significantly asymmetric. In this respect, it seemed to differ from hippocampal pathology, which was bilaterally severe in those cases where it was very abnormal. It remains possible that at the histopathological level, such damage was in fact asymmetric and mimicked what was happening at the neocortical level, but there was no firm evidence for this from the postmortem study of Hierons et al.3 Neocortical temporal lobe damage never occurred in isolation, and was invariably associated with more medial damage. Our profile thus differs from that found in other types of brain insult, such as head injury or cerebral infarction, where damage may sometimes be restricted to neocortical structures. Anterior and inferior temporal lobe gyri suffered damage more often and more severely than posterior and superior temporal lobe gyri, which were completely spared in a few cases. In this respect, the profile of temporal lobe cortical and white matter lesions was similar to that found after some forms of cerebral radionecrosis.28

A notable finding in our study was the appreciable damage often found in the substantia innominata (region of the basal forebrain/anterior perforated substance). At the anatomical level, this finding is not in itself surprising, in view of the proximity of this region to structures such as the amygdala and the anterior hippocampus. This area has been implicated in conditions such as rupture of aneurysms of the anterior communicating artery,29 and it is also adjacent to the nucleus basalis of Meynert, which itself has been implicated in the pathology of Alzheimer’s Disease.30

Magnetic resonance images of small, deep structures such as the mammillary bodies must be interpreted with caution, as slice thickness and angle of cut may sometimes determine the quality of the outline shape which is obtained. Taking this qualification into account, our study found evidence of damage to the mammillary bodies and also evidence of significant damage to the fornix. A number of postmortem studies have provided evidence that sheds light on the integrity of the mammillary bodies after medial temporal lobe damage. Warrington and Duchen31 reported mammillary body atrophy in their patient with long standing bilateral medial temporal lobe lesions. Some authors, however, have found normal mammillary bodies in amnesic patients with hippocampal pathology.32-35 Woods et al36 found demyelination in the fornix after bilateral hippocampal lesions. They did not specifically comment on the mammillary bodies, both of which appeared normal in their coronal section of the brain. The efferent pathways from the hippocampus via the fornix to the mammillary bodies make damage to the mammillary bodies highly likely, but our data suggest that, instead of a “connectionist” disease model, an “anatomical proximity” model might better explain the distribution of damage in herpes simplex encephalitis. This possibility is reinforced by our finding of cases of “double dissociation” between the presence of mammillary body damage and the presence of fornix damage. The proximity of the mammillary bodies to the anterior hippocampus and amygdala suggests that the inflammatory process itself involved structures adjacent to the main disease focus. It is, however, likely—as Hierons et al37 pointed out—that both pathological mechanisms operate in herpes simplex encephalitis, especially in respect of the longer term sequelae of the disease, where some secondary degeneration might be expected to occur after a number of years. Our own data would seem to point to the disproportionate degree of primary rather than secondary damage in this part of the brain.

Our finding of major mammillary body involvement casts doubt on the often made distinction between temporal lobe amnesia and diencephalic amnesia that has been proposed on the basis of comparisons between patients with herpes simplex encephalitis and alcoholic Korsakoff patients.37 It would now seem that both sets of patients have mammillary body damage, and this fact must therefore be a constraining factor in anatomical interpretations of differences between the memory performance of temporal lobe and diencephalic amnesic patients.

Thalamic nuclei were affected in around 50% of cases, and damage was usually unilateral. The lesser degree of involvement of thalamic nuclei compared with mammillary body nuclei again points to primary rather than secondary mechanisms underlying such damage, in view of the mammillothalamic connections between these structures. Frontal lobe damage was only present in a few patients, and affected medial areas more than dorsolateral areas.

We found a different profile of lesion covariance to that shown by Wilson et al3 for patients with head injury. They reported that lesions in the temporal pole often coexisted with lesions in the orbitofrontal regions. When we analysed our data in precisely this fashion, we did not find such a lesion covariance profile. This finding highlights the distinctive profiles of these two types of damage, even though they often render similar clinical and neuropsychological sequelae.

In conclusion, we have documented the
long term neuropsychological and MRI lesion profiles shown by patients who had had herpes simplex encephalitis and the extent of involvement of temporal lobe, limbic-diencephalic, and frontal lobe structures. This study must perform reflect recovery of function in a subset of patients with herpes simplex encephalitis. Those who die as a result of the infection, or those who make an apparently complete clinical recovery, may show a different lesion profile and a different neuropsychological profile. Studies of those patients should help to complete the overall picture of pathology and recovery of function that follows this type of viral infection.

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