Impaired verbal associative learning after resection of left perirhinal cortex

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Some patients considered for left temporal lobectomy for epilepsy present with normal verbal learning and no MRI evidence of hippocampal pathology. In order to preserve learning function, the surgical approach in these cases often aims at sparing the hippocampus. Parahippocampal structures, including the left perirhinal region, however, also appear to contribute to some forms of verbal learning. We studied aspects of verbal learning in four patients with left temporal lobe resections that preserved the hippocampus, but which included perirhinal/entorhinal cortices in two cases. Pre- and postoperative T1-weighted MRI scans were spatially normalized and residual mesial temporal structures identified. The two patients whose resection included perirhinal and entorhinal cortices exhibited a marked decrement in the ability to acquire arbitrarily related word pairs that persisted at 12-month follow-up. Word list learning showed an early postoperative impairment, but recovered to normal levels within 12 months. In two patients, resection encompassed anterolateral and inferior temporal neocortex but spared the perirhinal and entorhinal cortices, amygdala and hippocampus. No postoperative change in verbal learning was evident. We concluded that hippocampal-sparing left temporal lobe resections result in task-specific verbal learning deficits when perirhinal/entorhinal tissue is included in the resection.

Keywords: verbal memory; perirhinal cortex; hippocampus; epilepsy

Abbreviations: MTS = mesial temporal sclerosis; TLE = temporal lobe epilepsy

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Introduction

The ability to encode new associations between stimuli (relational learning) is a core feature of the declarative memory system. This form of learning underpins memory for elementary item–item relationships (e.g. face–name; object–place; word–object; word–word), but also supports acquisition of more complex associations in which activity, time, place and emotional status are conjoined to form the richly textured autobiographical content of declarative memory (Cohen and Eichenbaum, 1993; Cohen et al., 1999). Formation of new item–item associations is critically dependent on mesial temporal structures (Squire, 1992, 1993), but the precise contribution of different components of the mesial temporal region to associative encoding is uncertain.

In its most fundamental form, relational learning is exemplified by the ability to memorize associations between paired words with little or no inherent connection (for example, ‘obey’ – ‘inch’) (Eichenbaum et al., 1992; McClelland et al., 1995; Rolls, 1996). In the absence of a meaningful relationship between members of the pair, learning cannot benefit to any significant degree from pre-existing semantic knowledge, but must rely instead on the formation of a novel and essentially arbitrary association between the items.

As measured by arbitrary verbal paired associates, item–item relational learning is typically impaired in patients with left temporal lobe epilepsy (TLE) and mesial temporal sclerosis (MTS). In contrast, the ability to learn semantically related word pairs and other verbal information with high semantic structure is often intact or only mildly depressed in the same patients (McMillan et al., 1987; Saling et al., 1993; Wood et al., 2000; Akanuma et al., 2003). Since hippocampal disease tends to be the most obvious pathological finding in patients with left MTS and TLE, selective disruption of the ability to learn arbitrary word pairs is often attributed to hippocampal dysfunction. In a recent whole-brain FDG-PET study, however, we demonstrated that uptake of the glucose tracer...
[18F]fluorodeoxyglucose (FDG) in the left perirhinal cortex, but not the left hippocampus, predicts acquisition of arbitrarily related word pairs in patients with left TLE and MTS (Weintrob et al., 2002). This finding raised the possibility that the rhinal cortices contribute directly to basic forms of arbitrary item–item relational learning in patients with left TLE and MTS. Importantly, pathology in patients with TLE and MTS is not confined to the hippocampus, but frequently encompasses parahippocampal structures ipsilateral to the seizure focus (Du et al., 1995; Salmenperä et al., 2000), including the perirhinal cortex (Jutila et al., 2001; Bernasconi et al., 2003). In healthy controls, functional imaging studies show consistent activation of parahippocampal structures during performance of basic relational learning tasks (Kapur et al., 1996; Bernard et al., 2001; Davachi et al., 2003; Kirwan and Stark, 2004).

Some patients with left TLE who are considered for surgery have no identifiable structural abnormality and exhibit normal patterns of verbal learning. In these cases the surgical approach often aims at preserving the hippocampus in order to avoid or minimize postoperative verbal learning decline (Spencer and Ojemann, 1993; Elger, 2002). In this study we explored the common assumption that hippocampal-sparing left temporal lobe resections preserve verbal associative learning. Specifically, we examined the impact of hippocampal-sparing resections on arbitrary paired associate learning, contrasting this with semantically based (non-arbitrary) associative learning and verbal list learning, a task which is also facilitated by pre-established semantic knowledge. We hypothesized that hippocampal-sparing resections would produce a selective impairment of arbitrary associative learning, but not semantically based forms of learning, when perirhinal cortex is included in the resection.

Material and methods

Subjects

We studied patients who had undergone hippocampal-sparing resections of epileptogenic lesions in the left temporal lobe. Subjects were identified from a series of patients who had undergone left temporal lobectomy in the Comprehensive Epilepsy Program at Austin Health, Melbourne, Australia between December 1993 and June 2002 and were rendered seizure free. Preoperatively, all had well-characterized left TLE that was refractory to antiepileptic medication. The diagnosis of left TLE was based on clinical history and ictal semiology on video-EEG monitoring, magnetic resonance imaging (MRI), interictal positron emission tomography (PET) with [18F]fluorodeoxyglucose and ictal and interictal blood flow single photon emission computerized tomography studies. Exclusion criteria were: ongoing seizures after operation; hippocampal resection; preoperative MRI evidence of hippocampal or extratemporal abnormalities; MRI unavailable for analysis; postoperative seizures; a Full Scale IQ <80; a history of alcohol and/or illicit substance abuse; a history of psychiatric disturbance other than postictal psychosis; a history of cerebral infection or head trauma; schooling in the English medium >5 years.

Memory measures

The verbal learning measures reported here are routinely administered as part of the pre- and postoperative neuropsychological evaluation of patients in the Comprehensive Epilepsy Program and include the Paired Associate Learning (PAL) subtest of the Wechsler Memory Scale (Form I) (Wechsler, 1945) and the Rey Auditory–Verbal Learning Test (RAVLT). Pre-operative memory testing was conducted when the patient had been seizure free for at least 24 h. Here, performance on the PAL subtest is expressed as the total number of semantically related (‘easy’) word pairs (maximum = 18) and semantically unrelated (‘hard’) word pairs (maximum = 12) recalled across three learning trials. Comparison is made with age-based Australian norms published by desRosiers and Ivison (desRosiers and Ivison, 1986). Performance on the RAVLT is expressed as the number of words recalled per learning trial (maximum = 15) and is contrasted with norms reported by Crossen and Wiens (1994). Full Scale IQ was determined by means of Reynold’s short form (Reynolds et al., 1983) of the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981).

MRI acquisition and analysis

Pre- and postoperative MRI scans were acquired using a Siemens 1.5T SOMATOM 4000. A T1-weighted volumetric acquisition (MPRAGE) was obtained (TR = 13 ms, TE = 5 ms, T1 350 ms, flip angle 10°, FOV 23 cm, matrix 224 × 256, NEX 1) in a tilted coronal plane perpendicular to the long axis of the hippocampus. Preoperative MRIs in the case of two patients (Case 2 and Case 4) were not amenable to digital processing (see later). In remaining cases, image registration was performed with the software package AIR 3.08 (Woods et al., 1993). A linear 12 parameter model was used to align native pre- and postoperative images to a normal template MRI previously registered into the standardized stereotaxic coordinate space of Talairach and Tournoux (1998). Residual mesial temporal structures were then identified using previously described anatomical landmarks (Watson et al., 1992; Insauti et al., 1998).

Results

Of the entire series of patients undergoing left temporal lobectomy between December 1993 and June 2002, four met criteria for inclusion in this study.

Case one

Clinical details

This 35-year-old, left-handed man presented with a 2-year history of complex partial seizures. These commenced with an aura during which he would hear echoing voices, followed by diminished awareness, blank staring and oral automatisms. Ictal EEG was unhelpful. MRI showed a left anteromesial temporal lesion involving the amygdala and parahippocampal gyrus. The left hippocampus had a normal appearance. An ictal 99mTc-hexamethyl propylene amine oxime SPECT scan showed hyperperfusion in the left
anterior mesial temporal region and temporal pole. An interictal FDG-PET study revealed left anteromesial temporal hypometabolism. Histopathological analysis of resected tissue disclosed features of a dysembryoplastic neuroepithelial tumour (DNET) and mild cortical dysplasia.

**Resection parameters**

Pre- and postoperative images are shown in Fig. 1. Prior to analysis, all images were registered into the same anatomical space. The preoperative images (top row) and their corresponding postoperative image (bottom row) therefore represent slices at comparable brain levels. The overall nature of surgery may be appreciated by comparing the preoperative image (Fig. 1A) with the corresponding postoperative image (Fig. 1E). Resection encompassed mesial and lateral temporal structures anteriorly, but preserved the hippocampus. Figure 1B represents the first slice in which rostral perirhinal and entorhinal cortices are clearly visualized. The corresponding postoperative slice (Fig. 1F) demonstrates extensive resection of the entorhinal and perirhinal cortices and anterolateral temporal neocortex. In Fig. 1C, the hippocampal head is visualized ventral to the amygdala. The corresponding postoperative image (Fig. 1G) shows preservation of the hippocampal head. The sagittal views in Fig. 1D and 1H confirm that resection spared most, if not all, of the hippocampus proper.

**Neuropsychological findings**

Case 1 had successfully completed a tertiary degree and was employed as a land surveying assistant. Overall intellectual abilities fell within the Average – Low Average range (estimated Full Scale IQ = 91). Preoperative assessment was carried out 21 months prior to surgery, and revealed normal performances on the PAL subtest and the RAVLT (Table 1). At 1-month postoperative review, however, he showed a marked decline in his ability to learn the set of unrelated word pairs and the word list. In the case of unrelated word pairs, this impairment persisted at 12-month postoperative review. In contrast, word list acquisition recovered substantially and performance on this measure 12 months after surgery mirrored the normal performances seen preoperatively. Acquisition of related word pairs showed a very mild decline at 1-month review, but matched preoperative levels at 12-month follow-up.

Discussion with informants at 12-month postoperative review suggested that surgery had caused a functionally significant decline in memory in everyday life. His wife noted that while his memory had been somewhat inefficient since seizure onset, his forgetfulness in daily life after surgery was notably more pervasive and intrusive. By way of illustration, he was more prone to forget the details of conversations and instructions, and he often needed to be reminded of tasks his wife had asked him to undertake. In light of his poor memory at home, she expressed misgivings about his ability to cope at work. Indeed, the patient noted that he followed a modified and largely routine schedule at work that, relative to his preoperative responsibilities, minimized demands on his memory.

**Case two**

**Clinical details**

This 44-year-old, right-handed woman had a 16-year history of complex partial seizures. These typically commenced with an unusual taste or smell or, less commonly, with déjà vu. Decreased awareness, staring and manual automatisms followed. Ictal EEG localized to the left anterior temporal region. MRI revealed a left anteromesial temporal lesion that was identified as a ganglioglioma at postoperative histopathological examination. The MRI...
appearance of the left hippocampus was reported as normal.

Resection parameters

The preoperative MRI study in this case was saved to hardware rendered obsolete after the hospital introduced new imaging systems. While we were able to visualize the images and could thereby confirm the radiologist’s report, the images were not amenable to digital processing and could not be reproduced here. Relevant sections from the postoperative MRI are shown in Fig. 2. In overview, postoperative MRI revealed a circumscribed resection of left anteromesial structures that included extensive resection of entorhinal and perirhinal cortices but spared most, if not all, of the hippocampus proper. Hippocampal preservation is well illustrated in Fig. 2A and D (in particular, the hippocampal head is clearly visible ventral to the amygdala in Fig. 2D, suggesting that resection spared most of the hippocampus proper). Figure 2B shows complete resection of the left temporal pole. In Fig. 2C, the right entorhinal and perirhinal cortices are clearly visualized: both structures have been extensively resected on the left.

Neuropsychological findings

While formal examination of intellectual capacities was not undertaken, on clinical grounds Case 2 impressed as being of normal intellect. Prior to surgery, her performances on the PAL subtest and the RAVLT (Table 1) were normal. Surgery was carried out 1 month after the preoperative assessment. A marked decrement in her ability to learn the set of unrelated word pairs was observed at 1-month review, and her performance on that measure remained impaired 12 months after operation. In contrast, word list learning showed a mild decline at 1-month postoperative review, but was normal 12 months after surgery. Her ability to learn the set of semantically related word pairs was not affected by surgery. This patient was lost to neuropsychological follow-up after 12-month review, and the question of whether her psychometrically defined decline in verbal learning was of functional and subjective significance could not be determined.

Case three

Clinical details

This 33-year-old, right-handed woman had a 12-year history of intractable complex partial seizures associated with prominent language arrest. Ictal EEG and ictal SPECT localized to the left temporal lobe. Preoperative MRI studies showed a subtle gyral anomaly involving the left temporal pole. Mesial temporal structures appeared normal, however. FDG-PET prior to surgery revealed mild reductions in FDG uptake in the left frontal, left lateral temporal and right anterior temporal regions. Histopathological analysis of the resected tissue found features of cortical dysplasia.
Resection parameters

Resection parameters are shown in Fig. 3. As all images were registered into the same anatomical space, the preoperative images (top row) and their corresponding postoperative image (bottom row) represent slices at equivalent levels. The axial sections shown in Fig. 3A and D orient the reader to the overall nature of the resection: Surgery in this case encompassed the left temporal pole (also compare Fig. 3B with E), with sparing of the amygdala and subjacent parahippocampal structures and the hippocampus. Resection also encompassed inferolateral regions of the temporal lobe anteriorly, including rostral portions of the inferior and middle temporal gyri (compare Fig. 3E with F). Figure 3C represents the first MRI slice at which perirhinal and entorhinal cortices are clearly visible. The corresponding postoperative image (Fig. 3F) shows good preservation of both those structures, but resection of adjacent anterolateral temporal structures.

Neuropsychological findings

Overall intellectual abilities fell within the average range (estimated Full Scale IQ = 102). Her ability to learn related and unrelated word pairs and the word list was normal preoperatively and was unaffected by surgery, which was carried out 1 month after the initial neuropsychological assessment (Table 1). She continued to regard her memory as normal after surgery and as unchanged relative to preoperative levels.

Case four

Clinical details

This 56-year-old, left-handed woman had a long history of frequent complex partial seizures beginning at the age of 11 years. Seizures were characterized by diminished awareness at onset followed by oral automatisms, head and eye deviation to the right and dystonic posturing of her
right arm. Secondary generalization occurred in some events. Preoperative MRI revealed a solitary, well-defined lesion centred in the fusiform gyrus of the left temporal lobe. This abnormality extended from the level of the hippocampal head anteriorly to the trigone posteriorly. Abnormally high T2 signal was present in the body of the left hippocampus adjacent to the lesion. This was felt to reflect the effect of the adjacent mass rather than hippocampal sclerosis: the hippocampus was of normal size, demonstrated normal internal architecture and showed normal T2 signal in regions anterior and posterior to the neighbouring lesion. Ictal EEG and ictal SPECT localized to the left temporal lobe. The patient was globally aphasic during a left-sided Wada examination, suggesting left hemisphere language dominance. Seizures persisted after initial surgery and she underwent further resection of residual abnormal tissue 2 years after the first procedure. She was seizure free when seen for neuropsychological review 12 months after the second resection. Histopathological examination of resected tissue after both operations showed features of a DNET.

Resection parameters
The digital record of this patient’s preoperative MRI study could not be located and preoperative images were therefore unavailable for further processing. The radiologist’s report was confirmed against the MRI films, however. Final resection parameters (that is, resection margins after the patient’s second operation) are shown in Fig. 4. In overview, resection encompassed the left fusiform and inferior temporal gyri from the level of the hippocampal head anteriorly (Fig. 4B) to the trigone posteriorly (Fig. 4D). Figure 4A represents the level at which the left perirhinal and entorhinal cortices are first clearly visualized: Both structures are intact. The anterior margin of the resection is shown in Fig. 4B: resection at this level encompassed the inferior temporal gyrus, but the hippocampal head and adjacent entorhinal and perirhinal cortices are well preserved. At the level of the hippocampal body (Fig. 4C), the fusiform and inferior temporal gyri have been extensively resected. Cortex along the mesial and lateral banks of the collateral sulcus at this level is intact, however, suggesting preservation of perirhinal/entorhinal cortices. The hippocampal body is also clearly visualized in that image. Parahippocampal cortex posterior to the perirhinal cortex was also extensively resected (Fig. 4D).

Neuropsychological findings
Findings described are those documented before the patient’s first operation and 1 month and 12 months after her second resection. Formal estimates of overall intellectual abilities prior to surgery fell within the average – low average range (Full Scale IQ = 90). Acquisition of related and unrelated verbal paired associates was normal on initial neuropsychological assessment 2 years prior to surgery (Table 1). Although a mild decline was seen at 1-month postoperative review, her performances on those measures remained within normal parameters. Importantly, by the 12-month mark, acquisition of arbitrary word pairs was very similar to that documented preoperatively. Prior to surgery, acquisition of the word list fell within normal parameters (Table 1). Performance on that measure was mildly depressed at 4-week postoperative review, but showed good recovery by the end of the first postoperative year. She believed her memory was unchanged relative to preoperative levels.

Discussion
Our findings suggest that one of the most fundamental aspects of verbal learning is impaired by anterior parahippocampal resection even when there is a surgical intention to preserve the hippocampus. In our series, preoperative verbal learning was normal in all cases. In two patients, surgery encompassed the amygdala, most of the perirhinal and entorhinal cortices and temporal pole, including 2–3 cm of anterolateral temporal neocortex. Both cases exhibited a marked postoperative decrement in the ability to learn unrelated word pairs that showed no improvement at 12-month postoperative review.
In contrast, word list learning and semantically based associative learning showed no enduring postoperative effect. Learning was not affected by resection of the temporal pole and anterolateral temporal neocortex (Case 3) or by extensive removal of the fusiform and inferior temporal gyri (Case 4). In Cases 3 and 4 the perirhinal and entorhinal cortices were spared.

**Functional neuroanatomy**

Each of the four cases had normal memory function preoperatively. Neuronal dysplasias can be physiologically active (Kirschstein et al., 2003), and there is evidence they participate in cognition (Janszky et al., 2003). Resection of these lesions, therefore, poses a risk to cognitive function (Janszky et al., 2003). This study has shown that the location of the developmental lesion plays a role in the nature of the postoperative memory impairment. The critical neuroanatomical difference between the two cases with postoperative learning impairment and those with preserved verbal learning is excision of anteromesial temporal structures, namely the amygdala and subjacent perirhinal and entorhinal cortices. The rhinal cortices are nodal points in the convergence of neocortical and subcortical projections to the hippocampus proper (Gloor, 1997). It is possible, therefore, that hippocampal deafferentation underlies the verbal learning decrement observed in Case 1 and Case 2, the parahippocampal structures acting as passive conduits to the hippocampus. That perspective, however, is challenged by mounting human and animal evidence of a direct role for parahippocampal regions in learning (Zola-Morgan et al., 1993; Buffalo et al., 1999; Verfaellie et al., 2000), including basic forms of associative learning (Higuchi and Miyashita, 1996; Bernard et al., 2001; Weniger et al., 2004).

Alongside perirhinal and entorhinal cortices, the amygdala was also extensively resected in Case 1 and Case 2. The amygdala may contribute to emotional components of learning (Cahill et al., 1996; Maren and Fanselow, 1996), but is not usually associated with declarative forms of learning (Bechara et al., 1995). In non-human primates, circumscribed bilateral lesions of the amygdala do not affect performance on measures sensitive to hippocampal and parahippocampal pathology (Zola-Morgan et al., 1989; Murray and Gaffan, 1994). Conversely, bilateral hippocampal and parahippocampal damage that spares the amygdala causes significant memory dysfunction in monkeys (Mahut et al., 1981; Zola-Morgan and Squire, 1986) and humans (Bechara et al., 1995; Kitchener et al., 1998). In functional imaging studies, perirhinal, but not amygdalar, activity at encoding correlates with basic forms of verbal learning (Alkire et al., 1998). There is, therefore, little precedent for the view that the learning decrement present in Case 1 and Case 2 is specifically attributable to amygdalar resection.

**Task specificity**

Our findings suggest that left temporal lobe pathology may be associated with dissociable patterns of verbal learning impairment as a function of lesion location. While anteromesial temporal resection caused a persisting impairment of the ability to learn unrelated word pairs, acquisition of semantically related word pairs and the word list were intact at 12-month review. Could the dissociation have been caused by selective effects of practice on the semantically structured learning tasks? This does not appear to be a convincing or complete explanation of our findings. A similar dissociation is reliably seen on initial testing in presurgical cases with destructive pathology in the left mesial temporal region (mesial temporal sclerosis): specifically, learning of unrelated verbal associates is impaired (Saling et al., 1993; Wood et al., 2000; Weintrob et al., 2002), with preserved acquisition of related word pairs, prose or word lists (Miller et al., 1993; Hermann et al., 1994; Helmstaedter et al., 1997; Harris et al., 2001; Akanuma et al., 2003). Further, Cases 1 and 2 (perirhinal resection) are differentiated from Cases 3 and 4 (preserved perirhinal cortex) by the non-recovery of arbitrary paired associate learning rather than the recovery of semantic forms of learning.

Outcome did not vary systematically with lesion size. In particular, although Case 4 underwent a large resection of the fusiform and inferior temporal gyri that is comparable in its anterior–posterior extent with the rhinal resections in Case 1 and Case 2, only the latter showed a decline in discrete aspects of learning.

In contrast with unrelated word pairs, semantically related word pairs and word list acquisition present relatively greater opportunities to exploit inherent semantic relationships for the purposes of learning. Interestingly, performance on these tasks was unaffected by the imposition of: (i) anteromesial temporal damage with sparing of inferolateral temporal structures as in Case 1 and Case 2 or; (ii) inferolateral temporal damage with sparing of anteromesial temporal structures as in Case 3, but particularly Case 4. Resection of anterolateral neocortical structures as part of standard left anterior temporal lobectomy in patients with left TLE produces additional decrements in the ability to learn verbal material with a high semantic content (Ojemann and Dodrill, 1985; Perrine et al., 1994), including word list acquisition (Helmstaedter et al., 1996; Sziklas et al., 2000). The absence of a similar effect in our sample may relate to the fact that standard left anterior temporal lobectomy involves relatively greater resection of anterolateral temporal tissue than was excised in Case 3 and Case 4.

The extent of hippocampal resection does not usually correlate with outcome on standard verbal memory tests following left anterior temporal lobectomy (Wolf et al., 1993; Wyler et al., 1995; Jones-Gotman et al., 1997). The extent of perirhinal/entorhinal resection, but not the extent...
of hippocampal resection, has recently been linked with performance on an item–item associative learning task (Weniger et al., 2004). Unlike previous studies, our focus here was not the extent of resection, but whether excision of discrete parahippocampal structures impacted on learning when a normal hippocampus is spared.

**Clinical considerations**

Central to present findings is the possibility that left parahippocampal structures play a critical role in basic aspects of verbal item–item associative learning. One of the principle concerns associated with standard left anterior temporal lobectomy for relief of intractable TLE is the risk of postoperative verbal learning impairment (Chelune et al., 1993). Factors associated with increased risk of a surgically induced decline in verbal learning include: (1) good preservation of preoperative verbal learning (Hermann et al., 1995; Jokeit et al., 1997) and (2) the relative absence of sclerotic changes in the dominant hippocampus (Baxendale et al., 1998; Seidenberg et al., 1998). In the presence of these factors, common neuropsychological practice is to recommend a surgical approach that spares the hippocampus: The assumption is that hippocampal preservation will obviate, or at least minimize, postoperative verbal learning decline (Spencer and Ojemann, 1993; Elger, 2002; Akanuma et al., 2003). Our findings suggest, however, that left temporal lobe resections that spare the hippocampus do not preclude an enduring decrement in fundamental aspects of verbal learning when perirhinal/entorhinal cortices are excised.

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