SPECIAL ISSUE

LONG-TERM AMNESIA: A REVIEW AND DETAILED ILLUSTRATIVE CASE STUDY

Andrew R. Mayes[1], Claire L. Isaac[2], Juliet S. Holdstock[1], Pietro Cariga[2], Amanda Gummer[2] and Neil Roberts[3]

([1]Department of Psychology, University of Liverpool, UK; [2]Department of Clinical Neurology, University of Sheffield, UK; [3]Magnetic Resonance and Image Analysis Research Centre, University of Liverpool, UK)

ABSTRACT

Long-term amnesia is a slowly developing form of anterograde amnesia accompanied by retrograde amnesia of variable severity (Kapur, 1996; 1997) often associated with damage to the anterior temporal neocortex and epileptic seizures. The precise neural and functional deficits that underlie this condition are unknown. A patient, JL, who has this condition following a closed-head injury, is described in detail. Her injury caused bilateral anterior temporal neocortex damage that was more extensive on the left and right-sided damage to the perirhinal and orbitofrontal cortices. The hippocampus appeared to be intact bilaterally. Epilepsy developed within two years of JL's injury. Apart from her memory impairments, JL's cognitive functions, including high-level visual perception, attention, semantic memory and executive functions were well preserved. Her memory also seemed well preserved for at least 30 minutes following encoding. The one exception was the patient's relatively greater impairment at difficult visual recognition tests for which verbalization may not have been an effective strategy. This problem may have been caused by JL's right-sided perirhinal and orbitofrontal cortex damage. Her recall and recognition was clearly impaired after a three-week delay. She also showed a retrograde amnesia, which appeared to be milder than her remote post-morbid memory deficit. JL's remote memory was preserved for information first encountered in either the pre- or post-morbid period provided the information had received sufficient rehearsal over long periods of time. Her long-term amnesia may have been caused by anterior temporal neocortex damage, possibly in association with her epileptic seizures. Whether the condition is heterogeneous, involves a deficit in slow consolidation, disruption of unconsolidated memories, or blockage of maintenance or disruption of insufficiently rehearsed memories whether or not these have been slowly consolidated is discussed.

Key words: long-term amnesia, slow consolidation, epilepsy

INTRODUCTION

Several patients who show relatively normal acquisition and initial retention of new memories, but abnormally fast forgetting of these memories over delays of several days or weeks have been described in detailed case studies (De Renzi and Lucchelli, 1993; Ahern et al., 1994; O'Connor et al., 1997; Kapur et al., 1996, 1997; Lucchelli and Spinnler, 1998). This pattern of forgetting has been termed long-term amnesia (LTA) by Kapur, (1996, 1997). The pattern contrasts with the one that is typically seen in the global organic amnesia syndrome. In

this syndrome, patients show impaired recognition and recall within seconds of experiencing new episodic and semantic information provided they are distracted so as to prevent maintenance of the information through rehearsal. Most evidence indicates that the recognition impairment does not increase in size as the delay increases, and that the recall deficit only becomes larger during the first few minutes of retention (Isaac and Mayes, 1999a, 1999b). The different pattern of forgetting seen in patients with LTA has important theoretical implications for studies of the neural bases of memory because it suggests that memories remain labile even when initial consolidation seems to have been achieved relatively normally. In this paper, we review what is currently known about the neural and functional deficits that may underlie LTA and describe a detailed case study of one such patient, which illustrates the distinctive nature of this disorder.

It is unresolved whether different cases of LTA are all caused by a single functional deficit or whether they can be caused by different kinds of functional deficit. In different patients, the disorder has been associated with brain damage arising from several distinct aetiologies. In five single case studies, one patient had anoxia (De Renzi and Lucchelli, 1993), one had encephalitis associated with paraneoplastic disease (Ahern et al., 1994; O'Connor et al., 1997), another had head injury (Kapur et al., 1996), and two had unknown pathologies associated with epilepsy (Kapur et al., 1997; Lucchelli and Spinnler, 1998). The association with epilepsy is strong and LTA has also been reported in groups of patients who have epilepsy with a focus in the temporal lobes (Blake et al., 2000; Martin et al., 1991). Although LTA may originate from several aetiologies, however, there may be only a single underlying kind of neural dysfunction that causes the functional deficit responsible for the condition. The evidence that most, but not all, LTA patients that have been studied in detail have an extensive retrograde amnesia (see Kapur et al., 1997 for an exception) is similarly inconclusive. This is because the extensive retrograde amnesia may be caused by additional damage that underlies a functional deficit unrelated to the LTA.

The LTA patients studied so far performed normally when memory was tested at delays of 30 minutes (e.g. Martin et al., 1991). However, precisely when patients begin to lose memory abnormally fast, and whether this process continues indefinitely or only lasts for a limited time is unknown. It may be that the onset of abnormally fast forgetting varies across patients and may even be determined by the severity of the underlying functional deficit(s). However, there has been no attempt to explore the precise extent of the period of normal memory although all studies have shown that memory is relatively normal when tested after short delays (e.g. 30 minutes). Memory has also usually only been tested at a single long delay. Thus, Martin et al. (1999) found a memory deficit at a delay as short as 24 hours, whereas others have only looked for and found memory deficits at much longer delays of up to eight weeks (Blake et al., 2000).

Abnormal forgetting has usually been explained in terms of a deficit in consolidation processes (Isaac and Mayes, 1999a and b). Recent theories have postulated that episodic and perhaps semantic information is stored in long-term memory through an initial process of rapid consolidation followed by a more

drawn out process of slow consolidation. Although it is widely agreed that the medial temporal lobes, and particularly the hippocampus, are crucial for the rapid consolidation and initial storage of information that binds together the components of episodic and semantic memory, there is disagreement about the neural mechanisms underlying the slow consolidation processes. On the one hand, Alvarez and Squire (1994) have postulated that, over time, probably through a process that involves both repetition and rehearsal, the information that binds episodic and semantic memories together is gradually stored in neocortical sites whilst the hippocampal store gradually fades. They argued that this slow consolidation of neocortical storage involves some kind of interaction between the hippocampus and neocortex. In contrast, Nadel and Moscovitch (1997) have argued that, although long-term storage of semantic information gradually comes to depend entirely on the neocortex, some aspects of episodic memory can only be stored in the medial temporal lobes, and particularly the hippocampus. With repetition and rehearsal, these aspects of episodic memory are stored with more and more redundancy within a slowly increasing proportion of medial temporal lobe, and particularly hippocampal, neurons. Therefore, as long as episodic memories last, they remain dependent on the integrity of structures in the medial temporal lobes.

Consistent with the account of Alvarez and Squire (1994), all the single cases of LTA described above have had damage or disruption to temporal neocortex. Thus, two had bilateral structural damage to anterior temporal cortex (O'Connor et al., 1997; Kapur et al., 1996) and in the case of Kapur et al. (1996) also to lateral temporal cortex. A third showed evidence of a bilateral functional deficit in posterior superior temporal regions (De Renzi and Lucchelli, 1993). One of the final two patients had electroencephalographic (EEG) abnormalities in the left anterior temporal cortex (Lucchelli and Spinnler (1998) and the other had abnormalities in the right temporal lobe and left lateral temporal lobe (Kapur et al. (1997). In contrast to cases of organic amnesia that have been caused by medial temporal lobe pathology, only the patient reported by Kapur et al. (1997) showed any evidence of hippocampal damage and this was a subtle abnormality of uncertain significance. Although the groups of patients, studied by Blake et al. (2000) and Martin et al. (1991), would have had temporal lobe EEG abnormalities associated with their epilepsy, the extent and frequency of medial temporal lobe scleroses in these patients was not determined. Apart from the patient reported by De Renzi and Lucchelli (1993), all the single case study patients also suffered from epilepsy.

The pattern of forgetting characteristic of LTA can, therefore, be interpreted as showing that the links which bind together the components of episodic and semantic information are initially consolidated and stored normally by relatively intact medial temporal lobe and particularly hippocampal sites. However, this information is not slowly transferred into neocortical storage sites either because structural damage to these sites prevents memories from becoming established in them or because transfer to them is disrupted by epileptic activity (e.g. Kapur, 1997). This interpretation assumes that the slow consolidation processes that lead to neocortical storage take place primarily over a period of weeks rather than many years. The interpretation, therefore, suggests that the very long

gradients of retrograde amnesia that have been reported in organic amnesics are unrelated to the transfer of long-term storage to neocortical sites, and may require a different explanation (Mayes and Roberts, 2001).

If structural damage to temporal cortex sites can cause the pattern of forgetting seen in LTA, then patients with other syndromes in which this damage is often found should show a similar pattern of forgetting. Patients with focal retrograde amnesia in whom extensive retrograde amnesia is observed in the presence of normal or nearly normal acquisition of new memories (Kapur, 1993) often show damage in similar cortical sites to those affected in patients with LTA. It has not been formally assessed, but there is some evidence that forgetting in at least some patients with focal retrograde amnesia is not normal. Thus, it has been reported (e.g., Kapur et al., 1992, 1996) that, although memory is initially surprisingly normal, there is impaired memory for knowledge that has been slowly acquired through multiple exposures in the post-morbid period. This implies that, at least some patients with focal retrograde amnesia, show relatively normal rapid consolidation of facts and perhaps episodes, but impairment of the slow consolidation process that may transfer such memories to neocortical storage.

Patients with semantic dementia, who suffer a progressive loss of semantic memory for verbal and non-verbal kinds of knowledge (Snowden et al., 1989; Hodges, 1992), also have atrophy mainly to anterior temporal neocortex sites that overlap with the sites disrupted in patients with LTA. Epilepsy is unusual in patients with semantic dementia so they would only be expected to show accelerated forgetting over a period of weeks if structural damage to the anterior temporal neocortex is sufficient to cause LTA. It is hard to check whether this expectation is met because of the impoverished ability of semantic dementia patients to interpret newly encountered information semantically. However, relatively normal memory at short delays has been shown for more perceptual kinds of information (e.g. Simons et al., 2001). To our knowledge, no attempt has been made to determine whether these kinds of memories are forgotten abnormally fast over a period of weeks in semantic dementia patients. However, one patient who was re-taught at least some aspects of the meanings of words that he had forgotten, subsequently forgot over a period of several weeks what he had successfully relearned (Simons et al., 1999). Therefore, although the evidence is weak and unsystematic, this condition provides some support for the view that structural damage to the temporal cortex can cause the pattern of forgetting seen in LTA.

The precise nature and location within the temporal cortex of the damage that causes LTA, focal retrograde amnesia, and semantic dementia is controversial. Indeed, several researchers have proposed that damage to the perirhinal cortex in the anterior medial temporal lobes may be a contributory cause of semantic dementia (Murray and Bussey, 1999; Buckley and Gaffan, 2000). These researchers have shown that monkeys with bilateral perirhinal cortex lesions are impaired at discriminating which object is the odd one out when shown several different views all but one of which is of a single object, and also at learning knowledge about objects in associative learning tasks (see Buckley and Gaffan, 2000). Perirhinal cortex lesions may disrupt object

discrimination because this cortex is critical for representing and storing the complex conjunctions of visual features from which objects and other items are composed. It may play this role because some representations of items' constituent visual features converge only upon it because of its position late in the ventral visual processing stream. It is not responsible for representing simpler features, which may be represented and stored earlier in the processing stream.

If the perirhinal cortex stores as well as represents highly integrated visual (and possibly also other sensory modality) information about objects, as these researchers argue, then it may be involved in storing semantic memories about object features as well as in the perception of objects. The impairment in learning knowledge about objects suggests that the perirhinal cortex may also play a role in semantic memory for other kinds of knowledge about objects as well. This implies that the perirhinal cortex forms part of a more extended semantic memory network. This view predicts that perirhinal cortex damage should not only impair recognition memory for recently encountered objects, but also that it should cause a subtle impairment of object perception as well as disrupt the acquisition and retention of some kinds of semantic memory. As semantic dementia may be accompanied by the symptoms of LTA, it is also possible that perirhinal cortex damage causes or contributes to LTA.

Whether perirhinal cortex damage causes any of these deficits in humans is currently disputed. First, nearly total damage of the perirhinal cortex has been reported to disrupt recognition of complex visual patterns severely, but to leave perceptual discrimination of these patterns unaffected (Buffalo et al., 2000, Stark and Squire, 2000). Squire and his colleagues argued that if perception seems to be disrupted by perirhinal cortex damage, the disruption is probably caused by incidental damage to area TE the perceptual functions of which are well documented. However, object perception may only be impaired by perirhinal cortex damage when patients have to make difficult judgements using integrated object representations. This remains to be done in humans. Second, the view that perirhinal cortex lesions disrupt certain kinds of previously well established semantic memory has not been systematically tested in humans; however, there is currently no evidence for it. Third, the possibility that perirhinal cortex damage contributes to LTA has not been examined at all because large lesions of this structure cause a severe rapid onset anterograde amnesia. Indeed, the available evidence indicates that even the slow acquisition of semantic memories through multiple repetitions over long periods of time is grossly impaired following large perirhinal cortex lesions as might be expected if such memories are stored for as long as they last in the perirhinal cortex (Verfaellie et al., 2000). Nevertheless, when perirhinal cortex lesions are relatively small, new semantic memories (and episodic memories that depend on object information) may be able to form fairly normally through rapid consolidation even though slow consolidation is grossly impaired. If information that is relevant to both semantic and episodic memory remains stored in the perirhinal cortex for as long as it lasts, even a modest level of perirhinal cortex damage may impair slow consolidation by severely disrupting any increase in the number of neurons involved in storage. If such semantic memories are gradually transferred to more

lateral temporal neocortex structures, slow consolidation may also be disrupted because interactions with perirhinal cortex are severely disrupted.

As already indicated, however, all reported patients with LTA (with the exception of the patient of De Renzi and Lucchelli, 1993) also suffer from epilepsy so their pattern of forgetting may not be caused by structural damage either to the temporal neocortex or to the perirhinal cortex. In these patients, epileptic activity within the medial temporal lobes may be disrupting the slow consolidation or even the long-term maintenance of episodic and semantic memories. Epileptic activity could be causing or contributing to the causation of LTA in two main ways. First, it could be repeatedly disrupting orderly interactions between the medial temporal lobes and the temporal neocortex so as to grossly impede the transfer of memory storage from the medial temporal lobes to the temporal neocortex (e.g. Kapur, 1997). If episodic as well as semantic memories are disrupted, then this mechanism supports Alvarez and Squire's (1994) position. Second, epileptic activity could be degrading storage by directly and repeatedly disrupting normal activity in the medial temporal lobes. If this mechanism disrupts episodic memories regardless of their age prior to the onset of the disorder, then it supports the Nadel and Moscovitch (1997) position. If it only disrupts episodic memories that were acquired within weeks or a few months prior to the onset of the disorder, then its existence is consistent with Alvarez and Squire's (1994) position.

A finding by Riedel et al. (1999) indicates that it is not implausible that repetitive epileptic activity in the medial temporal lobes should disrupt memories even following initial consolidation. These workers showed that inactivating the dorsal hippocampus with a water soluble AMPA/kainite antagonist for seven days, beginning either one or five days after the end of training on the Morris water maze, disrupted memory even though this was tested when the hippocampus seemed to be working normally. They concluded that prolonged hippocampal inactivation was either disrupting a slow consolidation process that was stabilizing the spatial memory or it was degrading the already present synaptic changes underlying long-term spatial memory. Repetitive epileptic activity in the hippocampus and connected structures may have similar effects. Such activity during the delay between acquiring new memories and test could be a contributory cause of LTA or its sole cause. If this is the case, then there should be a correlation in temporal lobe epileptics between severity of the impairment for memories that are several weeks old and frequency of seizures with foci in the medial temporal lobes. The evidence about such a correlation in patients with LTA is equivocal. Whereas Blake et al. (2000) noted that reported seizure frequency in epileptic patients was not related to the amount of forgetting they showed, O'Connor et al. (1997) attributed the forgetting seen in their patient to frequency of seizures.

Other studies have failed to find a clear relationship between memory and seizures in patients with temporal lobe epilepsy who did not show the LTA pattern of deficit (Bergin et al., 1995; Delaney et al., 1980; Dodrill et al., 1986). For example, Bergin et al. (1995) administered tests of memory while patients with temporal lobe epilepsy were undergoing video telemetry. Two days later, memory performance of patients who had experienced seizures during the delay

did not differ from that of those who had not. It is possible, however, that memory functioning is related to subclinical seizures. The evidence for this is currently weak. Thus, Bridgman et al. (1989) found subclinical seizure activity in two patients that was detected using depth electrodes. In one patient, such activity was associated with a mild learning impairment and slowing during recall. In the second patient, however, no association was found, although it was argued that the temporal lobe in which activity occurred was not supporting memory function.

The evidence that seizure activity in the medial temporal lobes is partially or totally responsible for most, if not all, cases of LTA is, therefore, still far from convincing. It is also unexplained why many patients with temporal lobe epilepsy are impaired at learning and retention over much shorter delays than is found in LTA (e.g. Martin et al., 1988; Giovagnoli et al., 1996; Hermann et al., 1987). There are several possible explanations. First, LTA cases may simply have a milder form of the same memory deficit shown by patients who show memory impairments at short delays. Second, the location and kind of seizure activity could be critically important. Third, LTA could be produced by a particular kind of interaction between location of structural damage and seizure characteristics.

It is important that new cases of LTA are investigated in order to identify the neural dysfunction(s) and functional deficit(s) that underlie LTA. In this paper, we describe a patient, JL, who developed temporal lobe epilepsy following a head injury. Following this injury, the patient complains that although she could acquire new memories and retain them for several days, she typically forgot them over the following weeks.

The first and main aim of the investigation was to identify her memory and cognitive performance on a wide range of cognitive tests. In particular, we aimed to characterize JL's memory performance at short delays, her forgetting rate over long delays of several weeks, and her remote pre- and post-morbid memory. The second aim was to describe JL's structural damage carefully using magnetic resonance imaging (MRI) so that the location of her brain damage could be compared with previous cases of LTA. Our MRI analysis indicated that JL had a perirhinal cortex lesion, which was markedly worse on the right hand side. The third aim of the investigation was, therefore, to examine whether she showed any impairments of high-level visual perception and of her previously very well established semantic memories as the view of Murray and Bussey (1999) suggests she might.

Case History

Clinical Background

JL is a woman, who was born on 22nd November 1958. In 1975, at the age of 17 years, she suffered a closed-head injury when a car knocked her off her motorcycle. At that time she was studying for "A" levels. She was unconscious for a few minutes and then had post-traumatic amnesia for 11 days. X-rays revealed one basal fracture and two linear fractures to the skull. She made a good recovery, but was diagnosed two years later with temporal lobe epilepsy

and anti-epileptic drugs were prescribed. She is currently taking 800mgs of Epilim and 50mgs of Tiagabin a day. Despite taking anti-epileptic drugs since her diagnosis, she has suffered around 20-30 partial complex seizures each month with a slight reduction in frequency over the few days following menstruation. Prior to this, however, she had complained of strange feelings often brought on by music, so it is likely that her seizures predated this diagnosis. A CT scan carried out at this time revealed a probable low-density artefact in the right anterior temporal area. In June 1978, an EEG showed a right-sided posterior quadrantic emphasis. The patient has no psychiatric history and has made a good adjustment to her memory problems.

Neuropathology

MRI was carried out in May 1998 using a Picker International 1.5 Tesla scanner to acquire a T1 weighted 3D volume scan (RFFAST) and T2 Fluid attenuated inversion recovery scan (FLAIR) (figure 1).

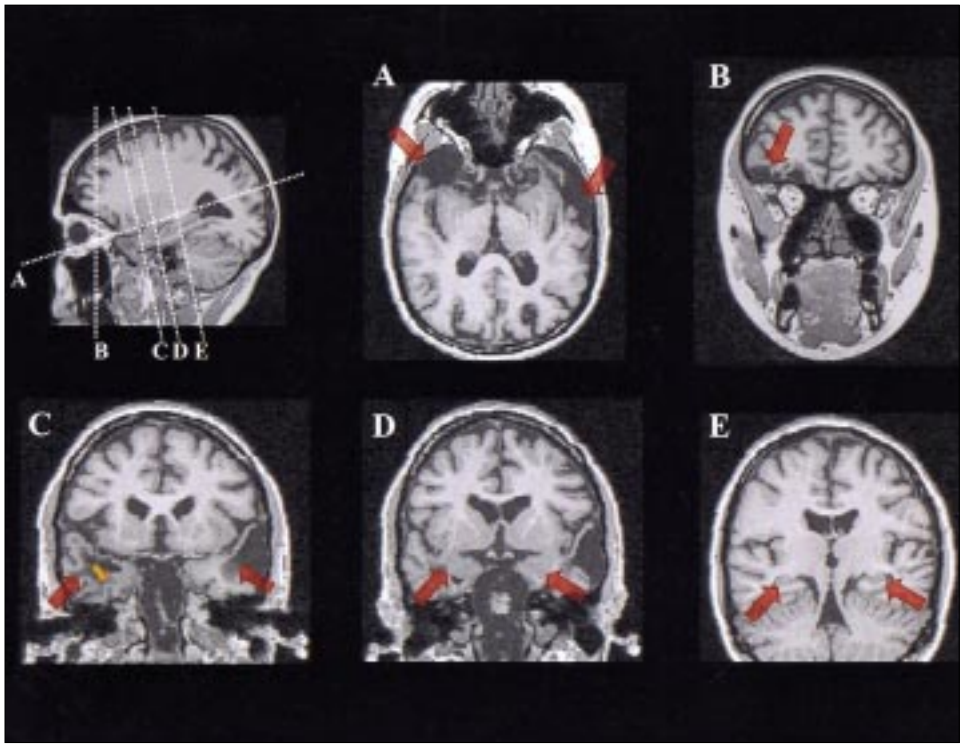

Fig. 1 – *T_1-weighted 3D images of patient JL. All images are left/right reversed. The sagittal image on the top left of the figure shows the location of images A-E. (A) axial image showing damage to the temporal lobes bilaterally (arrows) with the more severe damage on the left; (B) coronal image showing damage to the right orbitofrontal cortex (arrow), which extends into the right gyrus rectus; (C) coronal image showing bilateral damage to the temporal lobes (red arrows) and perirhinal cortex on the right (yellow arrow); (D) coronal image showing that the main body of amygdala was intact (arrows); and (E) coronal image showing the normal hippocampus bilaterally (arrows).*

In the temporal lobes, there was bilateral damage to the superior, middle and inferior temporal gyri. On the left, this damage was estimated to affect the anterior 60 percent of these structures and, on the right, it was estimated to affect the anterior 40 percent. The perirhinal cortex was also damaged. This damage was markedly more extensive on the right than on the left. There was also evidence of partial damage to the amygdala on the right. Finally, there was damage to JL's right medial and lateral orbitofrontal cortex, which was estimated to involve 75 percent of this region. The damage extended into the anterior half of the right gyrus rectus.

In order to obtain a more precise estimate of the extent of damage to the perirhinal cortex, entorhinal cortex and hippocampus, the volumes of these structures were measured. In order to make these measurements, the 3D volume data sets were reoriented perpendicular to the ac-pc line (the line between the anterior and posterior commissures), and resampled into 2mm slices. The stereological point counting technique was then used to estimate volumes using a square grid of size 2.34 mm. Volume measures of entorhinal and perirhinal cortices (figure 2) were obtained using the boundaries defined by Insausti et al. (1998). This revealed a volume for JL's right perirhinal cortex that was 6.3 standard deviations below the mean of a group of three matched control subjects. The volume of JL's left perirhinal cortex was within two standard deviations of the control mean, but was below the range of volumes of the

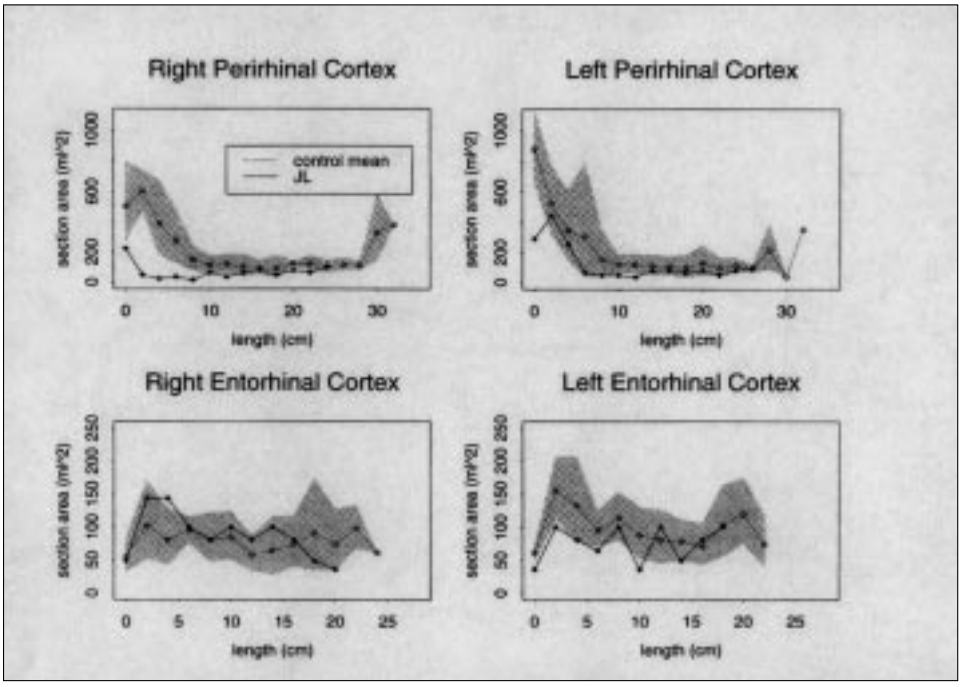

Fig. 2 – *Graphs showing the estimated areas of cortices in consecutive coronal slices through the right perirhinal (top left), left perirhinal (top right), right entorhinal (bottom left), left entorhinal (bottom right) regions for patient JL (solid line) in relation to the control mean (dashed line). The shaded area represents two standard deviations above and below the control mean.*

control subjects. Volume estimates for both left and right entorhinal cortex were above the mean level of JL's control subjects. Volume measures of the hippocampus followed the procedure of MacKay et al. (1998). Use of this procedure revealed that this structure was larger bilaterally than the mean of a group of 17 women of similar age to JL. It was not possible to estimate the volume of her amygdala on either side because the proximity of cortical damage made landmark definition impossible.

Assessment of general cognition and semantic memory

JL's performance was assessed on standardized neuropsychological tests of pre- and post-morbid intelligence, pre- and post-morbid information processing speed, attention, visual perception, semantic memory, and executive functions. JL's performance on these tests is shown in Tables I and II. JL's intelligence was in the

TABLE I

JL's performance on standardised tests of non-memory cognitive function. Intelligence quotients are provided for tests of pre-morbid and post-morbid intelligence; percentile scores are provided for tests of information processing (SCOLP), verbal fluency (COWAT) and attention (TEA); a profile score (maximum score of four) is provided for the Zoo Map from the BADS; raw scores are provided for the CET and WCST

Cognitive function	Test	Measure	JL's performance
Premorbid Intelligence	NART	FIQ	114
Postmorbid Intelligence	WAIS-R	FIQ	122
		VIQ	118
		PIQ	121
Information Processing	SCOLP	Speed of comprehension	99 %ile
		Spot the Word	50-75 %ile
		Discrepancy	50-75 %ile
Executive functions	CET		1 (1.3 sds superior to control mean)
	COWAT	Total words produced for letters F, A and S	82 (>96%ile)
	WCST	Number of categories produced	6 (0.5 sds above control mean)
		Perseverative errors	0 (1.3 sds above control mean)
	BADS	Zoo map profile score	4 (Maximum profile score)
Attention	TEA	*Selective attention:*	
		Map search1	25-50 %ile
		Map search 2	75-90 %ile
		Telephone search	10-25 %ile
		Attentional switching:	
		Visual elevator	25 %ile
		Timing score	50-75 %ile
		Sustained attention:	
		Elevator counting	Normal
		Telephone search & counting	50-75 %ile
		Lottery	50-75 %ile
		Auditory verbal working memory:	
		Elevator	75 %ile
		Elevator counting & reversal	75 %ile

Legend: NART = National Adult Reading Test (Nelson, 1991); WAIS-R = Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981); SCOLP = Speed and Capacity of Language Processing (Baddeley et al., 1992); CET = Cognitive Estimates Test (Shallice and Evans, 1978); COWAT = Controlled Oral Word Association Test (Benton and Hamsher, 1976); WCST = Wisconsin Card Sorting Test (Heaton, 1981); BADS = Behavioural Assessment of the Dysexecutive Syndrome (Wilson et al., 1996); TEA = Test of Everyday Attention (Robertson et al., 1994).

TABLE II

JL's performance on standardised tests of perception and overlearned semantic information

Test	Subtest	JL's performance
BORB	Copying	normal
	Length Match (A)	30/30 (normal)
	Size Match (A)	29/30 (normal)
	Orientation Match (A)	25/30 (normal)
	Position of gap match (A)	37/40 (normal)
	Overlapping figures	25/25 (normal)
	Foreshortened match	24/25 (normal)
	Item match	32/32 (normal)
	Association match	30/30 (normal)
	Drawing from memory	normal
VOSP	Screening	20/20 (normal)
	Incomplete letters	19/20 (normal)
	Silhouettes	26/30 (normal)
	Object decision	20/20 (normal)
	Progressive silhouettes	9 (normal)
	Dot counting	10/10 (normal)
	Position discrimination	20/20 (normal)
	Number location	10/10 (normal)
	Cube analysis	10/10 (normal)
Benton Facial Recognition Test		41 (normal)
Boston Naming Test		57/60 (normal)
Graded Naming Test		21/30 (normal)
Pyramids and Palm Trees Test		96% (normal)

BORB - Birmingham Object Recognition Battery (Riddoch and Humphreys, 1993)
VOSP - Visual Object and Space Perception Battery (Warrington and James, 1991)
Benton Facial Recognition Test (Benton et al., 1983)
Boston Naming Test (Goodglass and Kaplan, 1972)
Graded Naming Test (McKenna and Warrington, 1983)
Pyramids and Palm Trees Test (Howard and Patterson, 1992)

superior range and there was no evidence that either her verbal or visuospatial intelligence had declined as a result of her head injury. Consistent with this, JL's injury had not slowed her information processing speed. All aspects of her attention and visual perception, including the ability to identify objects from different perspectives, were intact. Unlike the patient of De Renzi and Lucchelli (1993), JL's face perception was normal and she was able to identify faces from different perspectives. Her semantic memory for objects also seemed to be entirely normal.

JL's normal performance on the four tests of executive function is consistent with evidence that the dorsolateral prefrontal cortex, but not the orbitofrontal cortex is critical for good performance on these tests (e.g Duffy and Campbell, 1994). The former region appeared to be intact in JL whereas there was extensive damage to the right side of the latter region. Damage to orbitofrontal cortex has been associated with a disinhibition syndrome (Duffy and Campbell, 1994) and although JL did not exhibit most of the features that characterize this syndrome, such as poor impulse control, verbal lewdness and aggressive outbursts, she did demonstrate some lack of interpersonal sensitivity. For example, a friend who had been at school with JL, reported that, after her injury, JL was sometimes offhand and apparently uncaring, whereas she had not been so prior to the accident. However, JL met and married her husband after her accident and they have maintained a stable relationship for over 20 years.

There was some evidence that JL had some damage to her right amygdala region and such damage has been associated with a deficit in the perception of fear from faces (see Broks et al., 1998). JL was, therefore, administered a test of the ability to recognize emotional expression in faces. This test comprised 60 faces from the Ekman-Friesen series (Ekman and Friesen, 1976) with six emotional expressions each being portrayed by ten faces. For each face, subjects had to choose which of six expressions (happiness, sadness, anger, surprise, fear and disgust) was being portrayed. This test was conducted both with JL and ten matched control subjects (Age = 41.8 (SD = 3.0), FSIQ = 114.9 (SD = 10.6)). JL was able to recognize all the emotions apart from fear well within normal limits. She recognized fear in 5.0 faces in contrast to a mean number of 8.6 faces recognized by her control subjects. Her performance, which was 3.0 SDs below her control subjects' mean, was clearly impaired.

Assessment of memory for recently studied information

Patients with LTA should show relatively normal memory for recently experienced information, only beginning to show pathological loss of memory at delays well beyond those at which patients with the amnesic syndrome show clear deficits. In order to characterize to what extent JL showed normal memory for recently experienced information, she was given an extensive range of tests on which all global amnesics would be clearly impaired.

JL's performance on a number of standardised tests of new memory acquisition is shown in Table III. Her free recall and recognition seemed normal although there was some evidence that her visual recognition memory might be slightly impaired. Thus, JL's performance on the Doors subtest of the Doors and People test battery (Baddeley et al., 1994) was somewhat poorer than her scores on the other subtests of this battery. There was also a large discrepancy in JL's performance between the hard and easy components of the Doors subtest, which was greater than the discrepancy between the corresponding components of the verbal recognition subtest. In addition, there was a discrepancy, which fell at the 10th percentile, between her score on the Recognition Memory Test (RMT; Warrington, 1984) faces and words, her performance on the faces subtest being worse than her performance on the words subtest.

Although JL's face recognition was normal when assessed by the RMT, other evidence indicated that when it was made particularly hard to verbalize features of studied faces or use verbalized information to aid recognition memory, her face recognition was impaired. In order to show this, JL's performance was compared with that of a group of ten female controls matched for age and Full Scale IQ (Age = 45.7 (9.9), FSIQ = 109.3 (6.63)). Subjects studied a sequence of sixteen faces, which was presented to them on a computer monitor. Each face was that of a woman between the ages of 17 and 35. The hair of each woman was masked so that only the central features of the face were visible. Each face was randomly paired with a different digitised voice and remained on the screen while the voice said the sentence "When I was a child, every Sunday morning I used to go to the park with my parents and my little brother, Nigel". This presentation sequence was repeated three times and the procedure was repeated

TABLE III

JL's performance on standardised tests of memory function. The table presents JL's percentile scores for the Doors and People Test (Baddeley et al., 1994), the Recognition Memory Test (RMT: Warrington, 1984) and the topographical recognition memory subtest of the Camden Memory Test (Warrington, 1996); for the Weschler Memory Scale – Revised (WMS-R: Weschler, 1987) JL's index scores are presented; for the California Verbal Learning Test (Delis et al., 1987) a T-score (based on control norms with a mean of 50 and standard deviation of 10) and standard scores (number of standard deviations above or below the control mean) are reported.

Test	Subtest	JL's performance
Doors & People	People (verbal recall)	95.2 %ile
	Shapes (visual recall)	74.8 %ile
	Names (verbal recognition)	74.8 %ile
	Easy	90 %ile
	Hard	50 %ile
	Doors (visual recognition)	36.9 %ile
	Easy	75-90 %ile
	Hard	10 %ile
WMS-R	Verbal	100
(Index scores)	Visual	117
	General	104
	Delay	105
	Attention/concentration	112
RMT	Words	>75 %ile
	Faces	50 %ile
	Discrepancy	10 %ile
The Camden Memory Tests	Topographical RMT	50 %ile
CVLT	List A, trials 1-5 total	58 (T-score)
	List A, trial 1	0 (standard score)
	List A, trial 5	0 (standard score)
	List B	+1 (standard score)
	List A short delay FR	+1 (standard score)
	List A long delay FR	0 (standard score)
	Recognition hits	+1 (standard score)
	False positives	0 (standard score)

twice with a different set of faces and voices for each delay.

At delays of 20 sec and 40 minutes, subjects were given a yes/no recognition test for each studied face. In each test, half the studied faces were presented. Thus, subjects were presented with a sequence of eight old and eight new faces in random order in each test and had to decide which faces they recognized. Recognition was scored using signal detection theory. JL's d' scores were 1.7 and 2.3 SDs below the mean scores of her control subjects on the 20 sec and 40 minute tests respectively. Thus, there was some evidence that JL's visual recognition memory was not normal, at least after a 40 minute delay, when verbalizable information was unlikely to affect performance appreciably.

To examine this hypothesis further and to determine whether it applied to materials other than faces, doors and perhaps voices, JL was given two further tests of recognition for visual stimuli. Each test comprised two subtests, which differed with respect to how easy it was to facilitate recognition by using memory for verbal re-codings of the visual stimuli. It was predicted that if JL had a problem in visual memory when this was only minimally facilitated by memories of verbal re-codings, then she should be more impaired when the chances of using memories of verbal re-codings were reduced.

The first test was one of recognition memory for visual patterns. This delayed matching-to-sample test for complex visual patterns was Experiment 2 in Holdstock et al. (1995). JL's performance was compared with that of the controls from that study (N = 12, 6 male, 6 female, mean age = 53, range 39-61, mean FSIQ = 110 range 99-122). Subjects studied one pattern at a time for four sec on a computer screen. Presentation of the stimulus was followed by an unfilled delay of 3, 10, 20 or 40 sec in a random sequence. A three-choice forced-choice recognition test was then given. There was a moderate and a hard version of the test. Each version was self-paced and each delay was used 15 times in a different random order for each subject.

The patterns were radially symmetrical and nonrepresentational and, therefore, difficult to verbalize. Furthermore, even if some verbal recoding was achieved, it was made hard to use this verbalized information at test in a way that related to task difficulty. This was because difficulty was defined operationally in terms of the number of features by which the studied pattern differed from the foil patterns. In both the moderate and hard condition, the performance of JL and her controls was collapsed across the four delays. The focus of interest was whether JL's performance relative to the control subjects declined significantly in the hard condition. Such a pattern would be consistent with the hypothesis that JL has a problem with remembering very recently experienced visual information that is hard to verbalize. Difference scores between performance in the moderate and hard conditions were calculated for each participant.

JL's recognition memory for the patterns is shown in Table IV.

Although her recognition in neither the moderate nor the hard conditions was significantly impaired, her discrepancy score was significantly greater than that of her controls. Her pattern of recognition memory for the patterns was, therefore, similar to her recognition memory for the doors. In both tasks, when foils and targets were very similar so that verbalized information was probably not very useful in discriminating between targets and foils, her performance became markedly more impaired.

TABLE IV

JL's performance on visual recognition tests. One task (Pattern recognition) involved recognition of abstract patterns when the targets and foils were moderately similar (Moderate) or very similar (Hard). The other task involved recognition of studied computer generated scenes which had to be selected from among totally new scenes (Old/New) or from among scenes in which studied furniture was recombined with other studied backgrounds and spatial configurations (Old/Recombined).

Task	Control mean (SD)	JL's performance
Abstract Pattern Recognition		
Moderate	51.8 (5.1)	54
Hard	38.6 (4.2)	32
Moderate-Hard difference	13.25 (4.0)	22
Scene Recognition		
Old/New (ON)	13.3 (4.0)	18
Old/Recombined (OR)	7.1 (2.4)	4
ON-OR difference	6.2 (3.12)	14

The second test was one of recognition for visual scenes of furniture in a room. The spatial layout of each scene was the same, but the 'furniture', which comprised a table, a lamp, two chairs, two windows, two walls, and a carpet, differed between scenes. During each study session, subjects examined 12 scenes, presented one at time on a computer screen, for five sec each. Subjects were told to look at the whole scene before judging how pleasant they felt it looked. Immediately after each study session, subjects were given one of two kinds of yes/no recognition test. In the first kind of test (old/new), each foil involved novel scenes of unstudied furniture arranged in the same spatial layout as the furniture in the studied scenes. The whole procedure was repeated so that old/new recognition was examined for 24 studied scenes and 24 completely new foil scenes. In the second kind of test, the foil scenes were re-combinations of studied scenes such that all the furniture had been seen at study, but in different studied scenes. Success depended on being able to identify which pieces of furniture had been presented together during the study phase. Success on the old/new test did not require this ability because subjects could identify studied scenes merely in terms of their memory for individual pieces of furniture. As with the old/new test, this whole procedure was also repeated so that subjects yes/no recognition was examined for 24 studied scenes and 24 recombined scenes.

JL's performance on this test was compared with that of 11 control subjects (age = 47.4, SD = 5.1; FSIQ = 111, SD = 10.8). In an attempt to match her performance to that of her control subjects on the old/new recognition test, JL was given a second study trial with each set of 12 scenes prior to test. On the second study trial, she had to judge how warm and cosy each room looked rather than how pleasant it was. A corrected recognition score for each test was constructed by subtracting the proportion of false alarms from the proportion of hits.

The profile of JL's recognition memory for the scenes, which is shown in Table IV, was very similar to the profile of her pattern recognition memory. Her discrepancy score between the old-new and the old/recombined tests was significantly greater than that of her control subjects. It is not possible to determine whether her performance on the old-recombination test was significantly impaired because she had been given double the study exposure of her control subjects. Given the poorer performance on this test by the controls, it is likely that the old/recombined test made more demands on visual memory. The test may also have made it harder to use memory for verbal re-codings of studied visual stimuli. As all the items of furniture had been seen before at study, verbal memories of these items would not have aided recognition. This would have had to rely on memory for which items went with which at study. It may have been much harder to give an effective verbal label to this associative information.

However, her recognition of neither the doors nor the visual patterns in the hard conditions, although well below the mean level of control subjects, was not 1.96 SDs below their mean scores, so one cannot confidently infer that she was impaired on these tasks. Similarly, JL's performance was not consistently impaired on another visual recognition test in which it seemed unlikely that memory of verbal re-codings could be easily used to help recognition. In this

test, four-choice forced-choice recognition memory was examined for two different sets of 12 objects that she had studied either 40 sec or 30 minutes earlier. The procedure is described by Holdstock et al. (2002a). Each object picture was seen twice for three sec on each occasion whilst subjects made a natural/manmade judgement and studied picture details respectively. The task was specifically designed to be extremely difficult by making the three foils of each studied object picture very similar to the studied object picture. Subjects were warned that this would be the case before studying the objects and examples of how similar the foils would be were given to them. This was done in order to ensure that subjects would try to encode sufficient numbers of details of each object picture to be able to perform the recognition task successfully.

JL was impaired at the shorter delay, but not the longer delay as is shown in Table V.

Possible reasons why JL performed so well on this extremely difficult task at the particularly demanding 30 minutes delay condition will be considered in the Discussion.

Assessment of forms of recent memory sensitive to hippocampal damage

JL's hippocampus appeared to be undamaged both on T1 and T2 weighted MR images and its volume was above the mean level of control subjects. However, there was some perirhinal cortex as well as extensive anterior temporal neocortex damage and this may have partially disconnected her hippocampus from processed sensory inputs. It was, therefore, of interest to assess whether her memory was intact on tests that are particularly sensitive to hippocampal damage. Selective hippocampal lesions have been shown to cause particularly severe impairments in the ability to recognize or recall recently studied object-location associations, and also in the ability to recall recently studied objects (as well as other items) (Holdstock et al., 2002a). There is also evidence that selective hippocampal lesions impair the ability to recognize recently studied face-voice pairings correctly (Vargha-Khadem et al., 1997).

Spatial recall and recognition memory and object recall memory were tested in the way described by Holdstock et al. (2002a). JL's performance was

TABLE V

JL's performance on recognition and recall tests for individual objects (Object memory) and for the studied locations of specific objects (Spatial memory) after delays of 40 seconds and 30 minutes

Test	Control mean (SD)	JL's performance	SDs from control mean
Object recognition 40s	9.5 (1.0)	6	–3.5
Object recognition 30m	9.7 (1.4)	10	0.2
Object recall 40s	9.8 (1.2)	12	1.8
Object recall 30m	7.0 (1.6)	5	-1.25
Spatial recognition 40s	10.9 (1.5)	12	0.7
Spatial recognition 30m	9.3 (2.0)	10	0.35
Spatial recall 40s	3.6 (1.5)	2.7	0.6
Spatial recall 30m	4.7 (1.6)	3.3	0.9

Negative SDs indicate performance which was worse than that of the control mean.

compared with that of a group of ten female matched control subjects (Age = 40.5, SD = 3.1; FSIQ = 111.6, SD = 7.6). At study, subjects examined 12 pictures of natural and manmade objects arranged in predetermined random positions on a plain white circular table. Subjects' attention was directed to each picture for three sec and a natural/manmade decision was made. The process was repeated a second time except that subjects were instructed to remember the objects' locations.

Object recall, and spatial recall and recognition were examined after filled delays of 40 sec and 30 minutes with different study materials in each condition. For object recall, subjects were asked to recall the names of as many of the studied objects as they were able. For the spatial memory tests, subjects were encouraged to use allocentric rather than egocentric cues by testing with circles of card that were 50% of the diameter of the table top. The test pictures were scaled down by a corresponding amount. In the spatial recall test, subjects had to place each picture on a blank circular card in the position the picture had occupied during study. The picture was removed before the subject placed the next picture. The score was the mean error of each subject in placing the object pictures back in their previously studied positions so higher scores indicated worse performance. In the recognition test, for each object-location association, subjects were shown a card with the corresponding object picture in four studied locations. Three of these locations had been occupied by other object pictures, and one had been occupied by the target picture. Subjects had to select the location in which that particular picture had been presented at study.

JL's performance on these tests is shown in Table V. Her spatial recall at both delays and her object recall at 40 sec were all above her control group's mean. Her object recall at 30 minutes was slightly below her control group's mean although well within the normal range. At both delays on the spatial recognition test, she scored slightly above the mean level of her control group. Overall, JL's performance on these three tasks, therefore, suggests that she did not have the pattern of memory deficits characteristic of selective hippocampal damage.

JL's ability to recognize recently studied face-voice pairings was also examined. The encoding task used to assess this ability was the one described above to test yes/no recognition when only the central regions of studied faces were visible. In the way described above, each of the 16 studied faces was associated with a particular voice. JL was then given a yes/no recognition test for half of these studied pairings after a delay of 20 sec, and for the other half after a delay of 40 minutes. Target items comprised faces and voices that had been studied together whereas foil items comprised re-combinations of studied faces and voices that had not been presented together. Subjects had to decide whether each face was presented with the same voice as the one with which it had been paired at study. JL was compared with the same control subjects with whom she had been compared on the yes/no recognition task for faces. Her d' scores were 2.0 and 1.60 SDs below those of her controls on the 20 sec and 40 minute tests respectively. Although JL was impaired on this task at least at the shorter delay, her impairment was comparable to that which she showed on the yes/no recognition for faces that was matched to it. Her pattern of performance

differs from that of some patients with selective hippocampal lesions, who show a deficit in face-voice recognition memory, but not in recognition of faces alone (Vargha-Khadem et al., 1997). JL's problem seems to have been a reflection of her difficulty in recognizing recently studied faces.

Assessment of remote pre- and post-morbidly acquired memories

Two tests were used to assess JL's remote memory for both pre- and post-morbidly acquired autobiographical information. Two further tests assessed her remote memory for pre-morbidly encoded autobiographical incidents and public information respectively. If JL's LTA developed in 1975 or shortly afterwards, then her post-morbidly acquired episodic and semantic memories should be impaired. Although patients with LTA usually show extensive retrograde amnesia, this is not a universal finding so determining the severity of JL's retrograde amnesia is an issue of some importance. Also, the relative severity of pre- and post-morbid remote memory impairments is of potential theoretical importance and has not previously been compared in LTA patients. To make such comparisons in an unbiased way requires the use of similar tests for the pre- and post-morbid periods. The first two tests, which were of autobiographical memory, met this condition.

JL's performance on two tests of autobiographical memory and one test of public information is shown in Table VI. In JL's case, memories tapped by the "childhood" section of the Autobiographical Memory Interview (Kopelman, 1990) fell in the pre-morbid period whereas memories from the 'early adult life' and 'recent life' sections fell in the post-morbid period. For the "childhood" section, she scored in the probably abnormal range for personal semantic information. In this section she was unable to remember details about her first school and her address at which she had lived only briefly. JL's memory for details from the childhood years from the age of 11 was much better. So her impairment in childhood personal semantic memories was almost certainly caused by brief exposure to and minimal rehearsal of these early personal facts. She scored in the acceptable range for the autobiographical incidents section from this period partially because she had an excellent memory for an encounter with the school bully. This was clearly something of great emotional significance, which she had rehearsed frequently over the ensuing years. The only other section on which her performance was normal was for personal semantic information from the 'early adult life' period on which she obtained a score of 18.5/21. Her factual memories about this period of her life were about details of her marriage, career and children and, like her memory about her primary school bully, these details had almost certainly been repeatedly rehearsed over many years. Both her autobiographical incident and personal semantic memory from the "recent life" period were in the definitely abnormal range.

In order to investigate JL's autobiographical memory in more detail, she and ten control subjects matched for age and Full Scale IQ (Age = 42.3, SD = 1.6; FSIQ = 118.1, SD = 9.4) were administered the autobiographical incident cueing procedure based on that described by Robinson (1976). Participants were presented with two sets of 24 words each, the first to be used in the

TABLE VI

JL's performance on tests of remote memory for pre- and post-morbidly acquired autobiographical and public information

Test	Subtest	JL's performance
Autobiographical Information		
AMI	Childhood semantic	13/21 (Probable abnormal)
	Childhood autobiographical	6/9 (Acceptable)
	Early adult semantic	18.5/21 (Acceptable)
	Early adult autobiographical	0/9 (Definitely abnormal)
	Recent semantic	14/21 (Definitely abnormal)
	Recent autobiographical	3/9 (Definitely abnormal)
Autobiographical Incident Cueing		
Unconstrained total	Total number of incidents recalled	2.1 SDs below mean of the matched controls
	Total number of details recalled	0.5 SDs below the mean of the matched controls
Unconstrained pre-morbid period	Number of incidents recalled	0.1 SDs above the mean of the matched controls
	Number of details recalled	0.6 SDs above the mean of the matched controls
Unconstrained post-morbid period	Number of incidents recalled	1.4 SDs below the mean of the matched controls
	Number of details recalled	1.1 SDs below the mean of the matched controls
Constrained to pre-morbid period	Number of incidents recalled	1.6 SDs below mean of the matched controls
	Number of details recalled	2.4 SDs below mean of the matched controls
Constrained to post-morbid period	Number of incidents recalled	2.4 SDs below mean of the matched controls
	Number of details recalled	3.1 SDs below mean of the matched controls
Public Information		
Famous Names	Recognition of very famous names	0.1 SDs above mean of the matched controls
	Recall of nature of fame for very famous people	1.7 SDs below mean of the matched controls
	Recognition of less famous names	0.7 SDs below mean of the matched controls (chance)
	Recall of nature of fame for less famous people	2.1 SDs below mean of the matched controls

AMI - Autobiographical Memory Interview (Kopelman, 1990)
Autobiographical Incident Cueing - procedure described by Robinson (1976)
Famous Names - questionnaire described in Hunkin et al. (1995)

'unconstrained' condition and the second to be used in the 'constrained' condition. For each of the words in the unconstrained condition, subjects were asked to think of a specific memory of which the word reminded them, which could have occurred during any period of their life, from early childhood to the present time. They were asked to describe this memory, in writing, in as much detail as possible. Participants were instructed that the memory should be specific to one event only and that it should be a personal memory and not something that happened to someone else. When they had completed this condition, the words for the 'constrained' condition were presented. In this condition, subjects were asked

to provide two memories associated with each word. The first memory was to come from the year 1975 or before (in JL's pre-morbid period) and the second was to come from 1976 or later (in JL's post-morbid period). Other than this, the instructions were the same as for the unconstrained condition. In the unconstrained and constrained conditions, the number of incidents recalled from JL's pre- and post-morbid periods, the total number of details recalled from each of these periods, and the mean number of details remembered for the recalled incidents from each of these periods were scored separately. The total number of incidents and details recalled, collapsed across pre- and post-morbid periods, were also separately scored in the unconstrained condition. Each detail about an incident comprised the amount of information that can be described in a simple sentence. For example, the cue 'letter' triggered one of the control subjects to recall "I remember receiving the letter containing my A level results. I had a temporary summer job at the time in a building society. My brother brought in the letter. So I had to open it with an audience of other staff." This was counted as the recall of four details.

As Table VI shows, in the unconstrained condition of this test, JL recalled significantly fewer incidents in total than her control subjects (more than the standard criterion for impairment for a single patient of 1.96 SDs below the control mean) although she did recall almost as many details in total as her control subjects. Interestingly, the temporal distribution of the incidents she recalled was different from that of her control subjects because she recalled about equal numbers of incidents from pre- and post-morbid periods, whereas most of her control subjects' memories were drawn from the post-morbid period. In the constrained condition (tapping pre-morbid memory), JL recalled far fewer incidents than her control group although one cannot conclude with confidence that she was impaired. However, she was clearly impaired in the number of details that she recalled about her pre-morbidly acquired personal memories. Her recall of incidents and details from the post-morbid period was also clearly impaired. In the unconstrained condition, the number of details per recalled incident that JL remembered was close to the mean of her control subjects for both pre- and post-morbid periods. In contrast, in the constrained condition, the number of details per recalled incident that she remembered was 1.9 SDs below the mean of her control subjects for the pre-morbid period and 2.5 SDs below their mean for the post-morbid period. This reduction in the number of details recalled about each remembered incident in the constrained condition relative to the unconstrained was 3.9 SDs and 3.2 SDs greater for JL than her control subjects for the pre- and post-morbid periods respectively.

JL's autobiographical memory from the pre-morbid period was also examined by comparing her recall of certain personal episodes and personal facts with that of one of her old school friends. This friend provided and described in detail a number of incidents and personal facts that she thought JL should be able to remember. There were 14 such personal incident/fact items, which covered the period from when JL was aged around eight up until the time of her accident. The information covered involved mutual friends and teachers from school. Recall of each item was divided into component details, each of which comprised the amount of information that can be described in a simple

sentence. There were between four and ten such details for each item. Although the results from such questionnaires are difficult to interpret, there were very few details that JL failed to remember. In some cases, she was even able to clarify details and provide additional information about some of the incidents or facts that her friend had failed to include. Although the friend felt that JL's memory for this time period was somewhat poorer than her own, she could not think of any incidents or personal facts to support her feeling.

To investigate JL's memory for information that was publicly available during either the pre-morbid period or during both the pre- and post-morbid periods, she and ten matched control subjects (Age = 41.7, SD = 2.5; FSIQ = 117.1, SD = 9.6) were administered a questionnaire. The questionnaire assessed recognition of the names of people who had achieved prominence between 1960 and recent times. It is described fully in Hunkin et al. (1995). This questionnaire comprised a list of 95 names, 30 of which were fictitious. The remaining 65 names were of people who became famous during the period 1969 to 1974, i.e. in the five years leading up to JL's injury. About half of the names were those of very famous people (e.g. Edward Heath), who have maintained prominence since their period of peak fame. These people's names would have continued to be often heard and/or rehearsed until the present. The remaining names were of people whose fame was largely limited to the time between 1969 and 1974 when they came to public attention and were most prominent (e.g. Iain Macleod). For each name, subjects were asked to judge whether it was the name of a famous person, and if so, why the person was famous. Scores were expressed as the proportion of hits minus the proportion of false alarms.

JL's performance on this test is shown in Table VI. Her recognition of very famous names was entirely normal. However, she showed a trend towards impairment in her ability to recall the less rehearsed and more detailed information about why these very famous people were famous. JL's recognition of the less famous names was close to chance, although the control subjects' poor and highly variable performance meant that it was impossible to determine whether her recognition for this material was significantly impaired. However, she was impaired at recalling why the less famous people she recognized were famous. She, therefore, had a clear recall impairment for details about public information taken from the pre-morbid period.

The remote memory tests provide evidence that JL's autobiographical memory for the post-morbid period was clearly impaired, and probably more so than it was for the pre-morbid period. There was evidence that her autobiographical memory for the pre-morbid period was impaired, but this evidence was less clear-cut. The final test indicates that JL also showed a clear impairment for less rehearsed public information encountered in the pre-morbid period, but it also suggests that her memory for heavily rehearsed information that was first encountered in this period was relatively normal.

Assessment of long-term forgetting

Six tests were constructed to investigate JL's forgetting rate. Tasks were designed to measure free recall and recognition of both verbal and visual material

over delays of up to three weeks. JL's performance was compared with that of ten matched control subjects (Age = 40.6, SD = 2.7; FSIQ = 116, SD = 10.9).

A short story was constructed, similar to, although considerably longer than, those used in the WMS-R (Wechsler, 1984). It concerned a couple going to a restaurant for dinner on Valentine's day and the restaurant being raided by robbers. The story, which comprised one hundred units of information, was digitised for administration by computer. Presentation lasted three minutes.

A series of 36 questions about the story was constructed. For each question, a correct and three similar, but incorrect answers were devised. Questions were divided into three sets of 12. Within each set, care was taken to ensure that the questions addressed information from across the whole story. The sets of questions were piloted on a group of undergraduate students to ensure that recognition performance on each set was similar.

Figure recall was assessed using the Rey Osterrieth figure (Rey, 1941; Osterrieth, 1944). A series of 15 subunits was constructed to test recognition of the figure. For each subunit, three foils were devised that were similar to the target. The subunits were divided into three sets of five items each. The sets were piloted on a group of undergraduate students to ensure that recognition performance on each set was similar.

Word and face recognition tests were devised. These tests were constructed from three parallel versions of word and face recognition tests that were similar to the RMT (Warrington, 1984). The word recognition test comprised words of one and two syllables and the faces test comprised both male and female faces. For this study, the three presentation sets were amalgamated so that the presentation phase for both word and face recognition tests included 150 stimuli. Target stimuli for each of the three test sets were distributed evenly throughout the presentation set so that at test, items were drawn from across the presentation phase. The three tests comprised 50 items each for two-choice, forced-choice recognition.

Testing took place in two experimental sessions. In the first, all the tasks were presented and tested at the 20-sec and 30-minute delay. The third set of recognition tests was given in a second session three weeks later. After the first session, participants were not told that their memory for the material would be tested again in order to make rehearsal of the material during the three week delay improbable.

The order of presentation and test of the tasks in session one was: Presentation of the story, 20-sec story recall and recognition, presentation of figure, 20-sec figure recall and recognition, presentation of 150 words, immediate word recognition, presentation of 150 faces, immediate face recognition, 30-minute story recall and recognition, 30-minute figure recall and recognition, 30-minute word recognition and 30-minute face recognition. This order was the same for all participants.

At the beginning of the first session, subjects practiced the distractor task that intervened between story presentation and recall. This was an odd/even judgement task in which subjects were instructed to read aloud a series of one, two or three digit numbers appearing on the screen and say whether they were odd or even as quickly as possible. The rate at which subjects could perform this

task was stored and the numbers appeared at this predetermined rate following story recall in order to prevent, as far as possible, rehearsal of the story during the 20-sec delay. Following this the instructions for story recall were displayed on the screen. Subjects were instructed that they would hear a short story that was about three minutes long and that they should try and remember as much about it as possible. They were instructed that, following presentation of the story and the distractor task, they would be required to tell the experimenter everything they remembered about the story and that where possible they should use the same words used in story presentation. They were told that when they had recalled as much about the story as possible they would be presented with a set of multiple-choice questions about the story. When the experimenter had confirmed that the subject had understood the instructions, the story was played to the subject. Following presentation of the story and the 20-sec distractor task, an audio tape recorder was switched on and the subject was asked to recall as much about the story as possible. The test was untimed and each subject was given enough time in order to exhaust their recall. When it had been confirmed that the subject could recall no more details about the story, the tape recorder was switched off and the subject was presented with the first set of 12 questions. Each question was presented one at a time on the screen with the target answer and the three foil answers displayed underneath in a vertical arrangement. The position of the target answer was varied pseudorandomly across questions so that it appeared equally often in each of the four positions. The subjects' response to each question was recorded manually.

Following story recognition the subjects practised the distractor task for the 20-sec delay between figure copy and recall. This was similar to the odd/even judgement task described above. Subjects were presented with arrays of 12 symbols including @, £, &, %. For each array, subjects had to count the number of £ signs and tell the experimenter how many there were in each array, as quickly as possible. The rate at which subjects performed this task was stored and the arrays were presented at this predetermined rate in the delay between figure copy and recall. Subjects read the instructions from the screen. They were informed that they would see a complex figure presented on the screen and that they should copy the figure from the screen onto a sheet of paper and try to remember it. They were also instructed that following recall of the figure they would be given a recognition test for subunits of the figure. When it had been confirmed that the subjects understood the instructions, the Rey figure was displayed on the computer screen. No time limit was set on this task and the figure remained on the screen until the participant had completed their copy. They then performed the distractor task for 20-sec before being asked to draw the figure from memory. After this, subjects were given the first subunit recognition test. During the test, the target subunit and its three foils were displayed on the screen, the position of the target subunit was varied across the test. Subjects were asked to say which of the subunits comprised part of the figure. The subjects' response was recorded manually.

Following figure recognition, subjects were shown the set of 150 words one at a time. Each word was presented for four sec and subjects were required to say whether they found each word pleasant or unpleasant. Immediately

following word presentation the first test was administered which tested recognition of 50 of the 150 words. The face recognition test was then presented and tested in the same way as the word recognition test. Following this, subjects were administered the 30-minute condition for each of the tests in the order described above. In the second session three weeks later, subjects were tested in the same order as in the first session.

JL's recall of the story at the 20 sec and 30 minute delays, although numerically below the mean of the controls, was well within the control range. At the three-week delay, however, JL recalled nothing about the story that she had heard. When questioned further she had no recollection of having heard a story and could not even remember that it had been presented on the computer. The story recall and other LTA results are shown in Table VII.

At the 20-sec delay, JL's recognition of the story was impaired although her score was just within the control range. At the 30-minute delay, however, her recognition performance was only slightly below her control group's mean. In comparison, she was significantly impaired in comparison with the control group at the three week delay.

JL's recall of the Rey Osterreith figure at both the 20-sec and 30-minute delays was above the mean level of her control subjects. However, at the three-week delay, her score was almost three SDs below the mean level of her control group.

Similarly, JL's figure recognition score was numerically superior to the mean level of her control subjects at the 20-sec delay and was markedly superior to their mean score at the 30-minute delay. At the three-week delay, her score had fallen to below the mean of the control group although a significant impairment was not demonstrated.

On the word recognition tests, JL's performance was normal at the 20-sec

TABLE VII

JL's performance and the mean performance of her matched control group (standard deviation in parentheses) for each of the tests of long term forgetting

Test		Delay		
		20 seconds	30 minutes	3 weeks
Verbal Recall	JL	24.0	19.0	0.0
	Control mean	32.8	34.2	22.4
	SD	(13.1)	(13.9)	(9.8)
Verbal Recognition	JL	9.0	9.0	5
	Control mean	10.9	9.4	8.4
	SD	(0.9)	(1.1)	(1.6)
Visual Recall	JL	27.0	27.0	4.0
	Control mean	22.4	23.6	15.3
	SD	(3.5)	(3.0)	(4.0)
Visual Recognition	JL	5.0	5.0	2.0
	Control mean	4.1	4.0	2.9
	SD	(0.7)	(0.5)	(1.4)
150 Word Recognition	JL	47.0	45.0	24.0
	Control mean	47.6	46.5	33.4
	SD	(2.3)	(2.4)	(3.8)
150 Face Recognition	JL	35.0	33.0	25.0
	Control mean	44.2	42.4	35.3
	SD	(2.7)	(3.2)	(2.9)

and 30-minute delays, but clearly impaired at the three-week delay. For the face recognition tests, JL's performance was significantly impaired at all three delays. Her performance at the two shorter delays was above chance, but by three weeks had fallen to chance levels.

Discussion

Patients with LTA show relatively preserved memory for recently experienced episodic and factual information, but impaired memory for such information when tested at delays of some weeks. JL showed a memory deficit of this kind. With a single case, it is hard to be sure whether memory is completely normal because one does not know precisely how well the patient performed pre-morbidly. Nevertheless, overall JL's ability to recall or recognize quite a few kinds of information that she had studied up to 30 minutes previously was close to the mean level of her control subjects, sometimes being clearly above and sometimes clearly below this level. In contrast, her ability to recall and recognize verbal and visual materials that she had studied three weeks before was clearly impaired relative to the performance of her control subjects.

Although JL's ability to remember most kinds of recently studied information was good, she was usually impaired at face recognition memory. The deficit was most apparent when it was made harder for JL to discriminate between target and foil faces either by removing distinctive surrounding features of faces or by exposing her to a large number of faces. These manipulations would probably have made it harder for her to boost her ability to discriminate studied from novel faces using memories for her verbal re-codings of facial characteristics. This deficit was not caused by an impairment in face perception because JL showed no such deficit. She did, however, have an impaired ability to identify fear in faces. Although this deficit seemed to be specific to fear, it may have been associated with reduced arousal when studying faces. There is evidence that the amygdala, which was partially damaged in JL, plays an important role in modulating the initial consolidation of emotional memories (Mayes and Roberts, 2001). Consistent with this view, amygdala lesions remove the memory advantages usually found for emotionally salient relative to neutral information (Phelps et al., 1998). It has also been argued that amygdala lesions may impair face, but not word, recognition memory on the RMT (Aggleton and Shaw, 1996). If this is correct and amygdala lesions do impair face recognition memory, it is unclear whether they have this effect because they disrupt modulation triggered by the perception of relatively emotional stimuli such as faces. Although JL had some amygdala damage, she also had extensive anterior temporal neocortex damage, which may have also contributed to her impairment in recognizing recently studied faces. In support of this possibility, Counsell et al. (1994) have reported that superior temporal gyrus lesions impaired face, but not word, recognition on the RMT in two patients. Further supporting evidence from functional neuroimaging indicates that the anterior temporal neocortex is activated bilaterally when normal subjects perform a face recognition memory task (Sergent and Signoret, 1992).

However, JL's deficit in recognizing recently studied information may not have been confined to faces. There was also evidence that her recognition of recently studied doors, patterns, room scenes, and possibly objects was more impaired either when foils were very similar to targets or when subjects were forced to rely on memory for which visual components were seen together at study. When targets and foils are very similar, it is plausible to argue that it is hard to use memories of verbal re-codings of stimuli to aid recognition. Similarly, it is plausible to argue that it is quicker and more automatic to verbalize which items one is viewing than verbalize that several items are occurring together. As with faces, therefore, subjects may have only been able to make minimal use of verbal memories of such stimuli when discriminating between studied and unstudied exemplars. So JL may not have had a selective deficit in recognizing recently studied faces, but a more general deficit in recognizing recently studied visual information when this was hard to encode verbally in a useful fashion. It will be important to obtain further support for this proposal. It needs to be shown that visual recognition becomes progressively more impaired in JL as the verbal contribution to performance is reduced systematically over several stages in a controlled fashion. It also needs to be shown that verbal recognition does not show similar increasing deficits in JL as task difficulty is progressively increased to levels corresponding to those of the hard visual recognition tasks. The limited evidence available from the hard and easy recognition tasks of the Doors and People Test is that JL's recognition may be slightly disrupted by increasing the difficulty of verbal tests, but that the disruption is less than that caused by increasing the difficulty of visual tests.

It may be hard to demonstrate that JL does have the kind of recognition deficit proposed because she is an intelligent woman, who has suffered from LTA for around 25 years and, in that time, has developed excellent coping strategies. Normal subjects probably rarely use, and are, therefore, likely to be less skilled at, these strategies. The use of high-level verbal re-coding strategies by JL could explain her above average recognition of the Rey figure at short delays, and also her above average ability to discriminate between pictures of objects that had been studied 30 minutes previously and extremely similar foil pictures. The skilled use of such strategies could also explain why JL's ability to recall recently studied visual stimuli was never found to be impaired. Such a deficit might only become apparent if great care was taken to score for accuracy of reproducing hard-to-verbalize information. However, if JL is using verbal re-coding strategies, she cannot be doing so on all occasions. If she was doing so, she would not have performed inconsistently on the 40-sec and 30-minute object recognition tests that have equivalent degrees of similarity between targets and foils.

If JL does have a visual memory deficit of the kind just outlined, this would be consistent with the view that large perirhinal cortex lesions impair recognition memory severely even at short delays (Aggleton and Brown, 1999). Volumetric measurements showed that destruction of the anterior half of JL's right perirhinal cortex was nearly total whereas damage to her left perirhinal cortex was so minimal as to be impossible to quantify with current procedures. The relative normality of her verbal memory when tested at short delays is, therefore, consistent with her largely intact left perirhinal cortex. However, if the right

perirhinal cortex plays a dominant role in initially putting non-verbalized visual information into memory, extensive lesions to this structure should cause recognition memory deficits even at very short delays. The effects on memory of largely unilateral perirhinal cortex lesions have not been reported before. Our study suggests that, at least for right-sided lesions, these effects on memory for recently studied information may be very subtle perhaps because of her excellent coping skills.

The neuroradiological evidence that JL suffered damage to the right, but not the left, orbitofrontal cortex strengthens this conclusion. Frey and Petrides (2000) have noted that the orbitofrontal cortex is strongly interconnected with the anterior medial temporal lobe region and that lesions to it can disrupt recognition memory in monkeys (e.g. Meunier et al. 1997). They found that, in humans, blood flow into the orbitofrontal cortex increased when abstract visual information was encoded and that this increased blood flow correlated with that found in the right entorhinal and perirhinal cortex region. If both the right perirhinal and orbitofrontal cortices are parts of a system that mediates recognition memory for visual objects and patterns, then partial damage to both sites should usually be more disruptive than either kind of partial damage alone. There is another way of determining whether the processing contribution to recognition memory of the right perirhinal and orbitofrontal cortices is impaired relative to the contribution of their left sided equivalent structures. This would involve testing recognition for the same kinds of stimuli after presenting them briefly either in the left or right halves of visual space. As JL's left anterior temporal neocortex damage overlaps with and is more extensive than her right sided damage, this test would be conservative.

Our evidence indicates, however, that this extensive anterior temporal neocortex damage on the left may have minimal effects on memory for recently studied information. The damage might have been expected markedly to reduce the flow of processed visual object and verbal information into JL's largely intact left perirhinal cortex and thus impair its memory processing. As verbal recognition is believed to depend in part on intact perirhinal cortex processing, JL's only slightly affected recognition of recently presented verbal inputs was contrary to this expectation. There was no evidence that JL's hippocampus was damaged. Its volume was entirely normal and its appearance on a T2 weighted image was normal. Despite this, the extensive anterior temporal neocortex and right perirhinal cortex damage that JL has suffered might have been expected to have reduced the level of visually processed verbal and object information reaching her hippocampus so that its memory processing should have been impaired. As recall is very sensitive to selectively impaired hippocampal function, JL's good recall of recent visually presented object and verbal information was clearly contrary to this expectation. JL's good spatial memory was less puzzling because spatial information may input into the hippocampus mainly via intact more posterior neocortical and medial temporal cortex routes. Her one apparently 'hippocampal' deficit was in recognizing recently studied face-voice pairings. This, however, was almost certainly a reflection of her impaired recognition of faces, and some patients with hippocampal lesions show relatively normal face recognition (Vargha-Khadem et al., 1997; Mayes et al., in

press). JL, therefore, provides evidence that sufficient object and verbal information must be able to reach the memory processing structures of the medial temporal lobes despite very marked structural damage to the anterior regions of the temporal neocortex. The finding suggests that other intact routes must still be available in JL's brain.

As indicated in the Introduction, it is unknown how long after study memory remains relatively intact in LTA patients and how much, if at all, this period of relative preservation of memory differs across patients. In the work described in this paper, JL only showed relatively preserved memory out to delays of 30 minutes. This was the longest delay less than three weeks that was used. In a parallel study of semantic memory acquisition (Holdstock et al., 2002b), however, we found that JL could recognize newly learned word definitions normally after a delay of one day although she was clearly impaired after a delay of three weeks. JL, therefore, showed accelerated forgetting of the newly learned word definitions at some time between one day and three weeks following study. This is consistent with what was found in the current study and fits with anecdotal reports of JL and her husband that her autobiographical memories begin to fade at delays of around one week.

An extreme view about this pattern of forgetting is that LTA of the kind shown by JL is merely a mild form of the amnesic syndrome. If this is correct, then a milder form of the functional deficit(s) that underlie the amnesic syndrome cause LTA. In defence of this view, it might be argued that patients like JL may have very mild memory impairments for some kinds of information when these have been encoded within the previous 30 minutes. Precisely when LTA patients begin to show clear signs of accelerated forgetting would depend on the severity of the underlying functional deficit(s). It might also be argued that global amnesics, who ex hypothesi are more impaired, continue to show pathologically accelerated loss of the memories that underlie recall for up to weeks following encoding, but this cannot be measured because the patients' recall rapidly drops to chance.

There are, however, three strong arguments against this view. First, JL does not have the lesions associated with global amnesia. This is particularly true of the lesions in her left hemisphere, which, as far as we have been able to determine, do not significantly involve the medial temporal lobes, the midline diencephalon, the basal forebrain, the pre-frontal neocortex or the fibre tracts that connect these regions. Second, there is no evidence that patients with the amnesic syndrome show pathologically fast loss at least of the ability to recognize information at delays between 30 minutes and several weeks following encoding (see Isaac and Mayes, 1999a and b). In contrast, LTA patients, such as JL, show exactly this pattern of accelerated loss of recognition as well as of recall. Third, in a study that examined the acquisition of new semantic memories, Holdstock et al. (2002b) found that JL showed a partial double dissociation with another patient, YR, who had a selective amnesia that primarily affected her recall. YR's deficit was caused by a relatively selective hippocampal lesion. When semantic memory was tested at a short delay, JL recalled normally whereas YR was clearly impaired, but when recall of repeatedly encountered public information was tested after delays of months or

years (but this information was still first encountered in the post-morbid period of both patients), JL was clearly more impaired than YR although YR was still mildly impaired. This pattern should not have been found if JL had a milder form of the same functional deficit as YR. Kapur (1994) has also reported a similar pattern of dissociation. It is, therefore, extremely unlikely that LTA constitutes a mild form of amnesia.

Further confirmation that JL's memory was clearly impaired after long delays was obtained by examination of her remote memory for personal facts and episodes that she had learned or experienced post-morbidly. This impairment was found even though these memories would have received some rehearsal in the time period of up to many years between initial encoding and our test. The one exception to the pattern of clear impairment was JL's good recall of personal semantic information from her early adult life. This information, which included basic facts about JL's marriage, children and job, was of great emotional significance to her and would, almost certainly, have been more extensively rehearsed by her over the ensuing years than was the personal information for which her memory was impaired. In a parallel study, Holdstock et al. (2002b) found that JL's recall of detailed factual information about post-morbidly encountered neologisms, public events, and famous people was also clearly impaired. These memories would also have received some degree of re-exposure and rehearsal in the long period after initial encoding and our test. However, the number of details recalled about the items on Holdstock et al.'s test determined the score that subjects obtained. These details, for which JL's remote memory was impaired, would have been much less rehearsed than the general facts about her marriage, children and career, for which JL's remote memory was relatively intact. Post-morbidly acquired memories may, therefore, be protected from the functional deficit(s) underlying LTA when they have been frequently rehearsed.

What level of rehearsal, if any, is sufficient to render a memory completely immune to the functional deficit(s) underlying LTA is unclear. However, JL's normal semantic memory, some of which may have been acquired during the post-morbid period, also suggests that prolonged rehearsal can produce immunity. Similarly, JL also seemed to have acquired immunity for her memory of very famous names that were first encountered in the pre-morbid period. Memories of such names would have been frequently rehearsed over a very long time period that included both pre- and post-morbid periods. As a result, her recognition was close to the mean level of her control subjects. In relative contrast, however, her recall of why these people were famous was 1.7 SDs below the mean level of her control subjects, perhaps reflecting the reduced frequency of rehearsal of detailed information. Similarly, whether or not JL showed a deficit in pre-morbidly acquired personal memories seemed to depend on how frequently and for how long the memory was likely to have been rehearsed. How frequently memories need to be rehearsed, and for how long a time period, before they become immune to the functional deficit underlying LTA needs to be systematically investigated.

One possibility is that unless memories continue to be regularly rehearsed for as long as they last, they remain susceptible to the degradation caused by the

functional deficit(s) underlying LTA. If this was the case, then LTA would not be a disorder of slow consolidation, but one in which memories continue to be liable to degrade to an abnormal extent however long they last. Degradation could occur because, in LTA, an active process necessary to maintain even consolidated memories is blocked or because noisy neural activity (such as seizures) actively degrades memories that would otherwise be stable. If one or both of these kinds of degradation underlie LTA, then all LTA patients should show extensive retrograde amnesia at least for memories that do not continue to be rehearsed with sufficient regularity.

JL's retrograde amnesia was not as extensive as has been reported in some patients with LTA (e.g. De Renzi and Lucchelli, 1993; Kapur et al., 1996). Nevertheless, she did show some impairment in her detailed recall of pre-morbid personal experiences as well as in her recall of why people, whose fame was mainly confined to the pre-morbid period, were famous. It has been suggested that more extensive retrograde amnesia is triggered by more posterior superior, middle and inferior temporal gyrus damage than JL had (Kapur et al., 1994). It could also be that more extensive retrograde amnesia is triggered by predominantly right-sided temporal neocortex damage (e.g. Markowitsch et al., 1993). Consistent with this suggestion, two of the cases of LTA with extensive retrograde amnesia showed either structural or EEG evidence of damage to the right temporal cortex (De Renzi and Lucchelli, 1993; O'Connor et al., 1997). However, the patient reported by Kapur et al. (1996), who had an extensive retrograde amnesia, showed a similar pattern of damage to JL. Like JL, this patient had damage to the left temporal pole and anterior portions of superior, middle and inferior temporal gyri on the left. In other words, the damage was greater on the left and anterior. In addition, the patient reported by Lucchelli and Spinnler, also appeared to have left rather than right temporal lobe involvement. The evidence is weak, therefore, that extensive retrograde amnesia in LTA is only found in cases with more posterior and predominantly right-sided temporal neocortex damage.

It is possible, however, that the severity of JL's retrograde amnesia has been underestimated. As a teenager she kept extensive diaries that she still often reads and talks about. This may explain why she was able to remember the details of some relatively prominent pre-morbid personal facts and experiences as well as the friend who provided the memories for the third remote memory study. The possibility is also consistent with the results of the second remote memory study, which examined detailed autobiographical incident cued recall and found that JL, relative to her control subjects, showed a significantly greater reduction in the number of details recalled about remembered pre-morbid incidents in the constrained than in the unconstrained condition. This pattern has a plausible interpretation. In the unconstrained condition, subjects probably recalled their strongest and perhaps best rehearsed memory related to a specific cue, and, in JL's case, almost equal numbers of incidents were recalled from pre- and post-morbid periods. In the constrained condition, it is likely that about half the incidents recalled from each period would have been based on less dominant and probably less rehearsed memories. Unlike with her control subjects, for JL, this meant that reduction in the strength and probably the level of rehearsal of

recalled memories greatly reduced the amount of detail she could remember even when she showed cued recall of an incident (and she also showed less incident cued recall from the pre-morbid period). If this interpretation is correct, then JL's retrograde amnesia is reduced for more rehearsed incident memories. In other words, these results suggest that her retrograde amnesia may be extensive for less rehearsed incident memories, but is reduced although perhaps not abolished for more rehearsed memories. The suggestion needs to be checked by examining JL's retrograde amnesia for memories, the level of rehearsal of which has been directly assessed.

If LTA is caused either by a problem in maintaining memories regardless of their age and level of rehearsal or by a problem with temporally limited slow consolidation, then patients must show some retrograde amnesia at least for less rehearsed pre-morbid memories. A common functional deficit may underlie both the anterograde and the retrograde amnesia in the LTA patients so far reported. If so, only retrograde amnesia with a very steep temporal gradient for well rehearsed memories would refute the 'continuous maintenance problem' explanation whilst being consistent with the 'slow consolidation problem' explanation of these patients' LTA. JL's data do not provide such a refutation because the autobiographical incident cueing study does not prove that well rehearsed incident memories are only impaired when the incidents occurred shortly before the onset of JL's impairment. They merely suggest that there is less retrograde amnesia overall for JL's better rehearsed pre-morbid incident memories. Equally, however, the fact that most LTA patients show relatively extensive retrograde amnesias does not prove LTA to be a continous maintenance problem. This is because the brain dysfunctions that cause extensive retrograde amnesia and LTA may be different, but always, or nearly always, occur together.

The current evidence, therefore, allows that any one of four main functional deficits could be causing LTA. Furthermore, more than one of these deficits could be operating in single patients and perhaps the functional deficit(s) that cause LTA differ across patients. First, disruption of the slow consolidation of episodic and semantic memories could be causing LTA. Once a memory has undergone sufficient slow consolidation, it should no longer be vulnerable to LTA. Second, slow consolidation may be unaffected in LTA, but before episodic and semantic memories have undergone sufficient slow consolidation, they may be disrupted by noisy and repetitive neural activity in critical brain sites. Whether LTA is caused by a deficit in slow consolidation or by the disruptive effects of noisy neural activity on unconsolidated memories, retrograde amnesia should show a steep temporal gradient. Third, even if episodic and semantic memories have undergone slow consolidation, their survival may require certain kinds of neural activity to be regularly repeated. If this activity is blocked by brain dysfunction in LTA, then the memories should be lost. Fourth, even if episodic and semantic memories have undergone slow consolidation, they may be disrupted in LTA by noisy and repetitive neural activity in critical brain sites. If LTA is caused by a disorder that affects even memories that have been slowly consolidated, the patients should show extensive retrograde amnesia even for very strongly learned memories. It remains a possibility that rehearsal makes

memories increasingly immune to brain dysfunction even when slow consolidation has been completed. If slow consolidation causes the links that bind the components of episodic and semantic memories together to be stored in the neocortex (Alvarez and Squire, 1994), continued rehearsal may lead to these neocortical links being stored more redundantly. Alternatively, if Nadel and Moscovitch (1997) are correct, slow consolidation at least of episodes is never complete as long as memory lasts and the links that bind the components of episodes are stored with increasing redundancy in the medial temporal lobes through continued rehearsal. In both cases, more extensive neural dysfunction in these regions would be needed to disrupt more rehearsed memories.

At least in JL, however, greatly over-rehearsed semantic memories were invulnerable to the effects of LTA, and it seems probable that most, if not all, patients with LTA have normal semantic memory. JL had extensive bilateral damage to her anterior temporal neocortex that was particularly severe on the left. It is, therefore, puzzling that atrophic damage to a similar region, particularly including the inferior and middle temporal gyri, has been related to the severe loss of semantic memories that characterizes semantic dementia (e.g. Simons et al., 1999). One possibility is that the distributed system in which much semantic information is represented and stored long-term is very widely disrupted in semantic dementia. Although the major damage is to the anterolateral temporal neocortex regions, there may also be subtler damage to other neocortical regions, which causes a severe degradation of long-term storage of semantic memories. If this is correct, then patients with acute lesions that extend beyond anterolateral temporal neocortex (where the damage is located in patients like JL) into the posterior temporal neocortex should not only show LTA and extensive retrograde amnesia, but these symptoms will be overlaid with some loss of heavily overlearned semantic memories.

It is currently unclear whether storage of the links that bind episodic as well as semantic memory components together transfers from the medial temporal lobes to the neocortex through a process of slow consolidation. Even if this does happen, it is uncertain whether continued rehearsal makes memories that have already undergone slow consolidation increasingly immune to brain dysfunction. These uncertainties must be removed if the functional deficits underlying particular cases of LTA are to be identified. At what stage if any, a memory becomes immune to LTA needs to be addressed by difficult experiments that control the frequency of rehearsal over long periods of time in LTA patients and their control subjects.

If the neural dysfunction(s) that underlie LTA were known, this knowledge would carry implications about the functional deficit(s) responsible for the disorder. Knowledge of these functional deficits together with their determinants, would, in turn, carry implications about theoretically important issues concerning the neural bases of memory. For example, abnormalities might be confined to the neocortex and propagated only minimally to the medial temporal lobes. If older much rehearsed memories become relatively immune to LTA, this would imply that the condition is caused by a functional abnormality in which slow consolidation is prevented by dysfunction in the neocortical sites where memories would otherwise have eventually been stored. Such a deficit is

consistent with the view that storage of both episodic and semantic memory transfers to the neocortex through a process of rehearsal over a limited time period (see Alvarez and Squire, 1994), but inconsistent with the view that episodic memory storage remains critically dependent on the medial temporal lobes (Nadel and Moscovitch, 1997).

It seems likely that episodic and semantic information is represented in other neocortical sites as well as the anterolateral temporal neocortex. However, when slow consolidation is completed, this latter region may store the links between the components of episodes and facts that have been stored from the point of acquisition in the other neocortical sites. Damage to the anterolateral neocortical sites might make it impossible to store the links so that memories fade as the links cease to be stored in the medial temporal lobes. Such damage would be expected to impair some pre-morbid memories that had already undergone slow consolidation if it destroyed sites where links had been stored. If the damage to the neocortical regions in which links are stored is sufficiently extensive, it should cause an extensive retrograde amnesia affecting even very strongly rehearsed memories for which the componential links are redundantly and diffusely stored. If damage extends into neocortical regions in which episodic and factual components are represented and stored, then patients may even be unable to represent new episodic and semantic information normally. In other words, the extent of neocortical damage may change the qualitative features of LTA.

As JL had minimal left-sided perirhinal cortex damage, but showed striking long-term forgetting of verbal materials, it is unlikely that damage to the perirhinal cortex is critical for her verbal (and probably also her visual) LTA. This conclusion is supported by evidence from two other patients with LTA. Neither the patient described by De Renzi and Lucchelli (1993) nor the one described by Kapur et al. (1996) appeared to have either damage or disruption of this area of cortex.

It is also unlikely that structural damage to the hippocampus directly contributed to JL's LTA. Her hippocampus appeared to be intact and she did not show the kind of anterograde amnesia found in some patients with relatively selective hippocampal lesions (e.g. Vargha-Khadem et al., 1997; Mayes et al., 2001). It is more likely that extensive damage to the anterior temporal neocortex, perhaps particularly on the left, played a key role in her LTA. However, it remains possible that the particular kinds of partial complex seizures, associated with JL's temporal lobe epilepsy, were responsible for her LTA. JL had fairly frequent seizures, but the frequency of these has remained constant since their onset so it was not possible to determine whether the severity of her LTA correlated with seizure frequency. De Renzi and Lucchelli (1993) reported an LTA patient without epilepsy although the possibility of sub-clinical seizure activity cannot be excluded.

Particular kinds of seizures could disrupt organized interactions between the medial temporal lobes and the neocortex that are essential for producing neocortical storage of the links that bind memories together (Alvarez and Squire, 1994). Such seizures might continue to disrupt interactions that increase the redundancy of neocortical storage even when slow consolidation is complete. Alternatively, seizures might disrupt the medial temporal lobe-neocortical

interactions that may be essential for storing links in the medial temporal lobes with increasing redundancy as Nadel and Moscovitch (1997) have argued. These seizure effects would probably be exacerbated if the anterior temporal neocortex is also damaged. It is also possible that certain kinds of temporal lobe seizure actually disrupt memories either before slow consolidation has occurred or at any stage in a memory's history. Seizure explanations of LTA, however, have difficulty explaining why patients do not show mild forms of organic amnesia with immediate impairments of memory because the seizures should disrupt the normal operation of the medial temporal lobes.

Although JL showed the symptoms of LTA, it is remarkable how preserved her cognition otherwise was considering the extent of her structural damage and her epilepsy. In addition to her preserved intelligence, processing speed, executive functioning, attentional processes, and well-established semantic memory, she showed apparently well preserved visual perceptual abilities. The fact that JL showed completely normal visual perception does not refute Murray and Bussey's (1999) proposal that perirhinal cortex damage disrupts high-level visual processing. It does, however, suggest that even if the proposal does apply to humans, damage may have to be quite extensive and bilateral before a clear deficit appears. JL's preserved semantic memory also suggests that the atrophy found in the perirhinal cortex in patients with semantic dementia (Simons et al., 1999) makes at most a very minor contribution to their semantic memory impairment.

In summary, JL showed the relative preservation of newly encoded memories and impaired memory for episodic and semantic information encoded some weeks previously that is characteristic of LTA. There was evidence that memories which had been more rehearsed over long periods of time were relatively preserved regardless of whether they had been acquired pre- or post-morbidly. We argue that damage to JL's right perirhinal cortex, perhaps in combination with her right orbitofrontal cortex damage, probably explains why she showed a mild recognition impairment of recently encountered visual stimuli when her recognition of these stimuli could not easily benefit from memory of any verbal re-codings. Further work is needed to confirm this proposal. JL's LTA included verbal memories, which are likely to be mediated primarily by left hemisphere structures. Although we have experimental and anecdotal evidence that JL's memory may be normal for as long as one week, we need to test her verbal and autobiographical memory systematically at several delays to determine better when her forgetting of verbal and autobiographical information begins to become pathologically accelerated. As her left orbitofrontal and perirhinal cortices were relatively intact, it seems most likely that her LTA was caused by her extensive anterior temporal neocortex damage and/or her temporal lobe epilepsy. The possible role of anterior temporal neocortex lesions in LTA can be explored by fully characterizing further cases of LTA in which there is no evidence of epilepsy. The possible role of epileptic seizures in LTA can be further explored by determining whether there is a relationship between severity of memory impairments and frequency of certain kinds of clinical or subclinical seizures before and during the delay period. As has been discussed, identification of the neural and functional underpinnings of LTA is a goal of considerable theoretical importance, but one that still remains to be achieved.

Acknowledgements. This work was supported by a Programme Grant from the UK Medical Research Council. We are grateful to Daniela Montaldi for help with the preparation of the manuscript, to Clare Mackay for making the volume measurements of medial temporal lobe structures and preparing the figures, and to Qiyong Gong for preparing the figure legends.

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A.R. Mayes, Department of Psychology, University of Liverpool, Eleanor Rathbone Building, PO Box 147, Liverpool, L69 3BS, UK.
e-mail: A.Mayes@liverpool.ac.uk