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Epilepsy-related long-term amnesia: Anatomical perspectives

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ABSTRACT

There are few clues as to the neural basis of selective long-term amnesia. We report group and single-case data to shed light on this issue. In a group study of patients with transient epileptic amnesia, there were no significant correlations between volumetric measures of the hippocampus and indices of accelerated long-term forgetting or longer-term autobiographical memory loss. Post-mortem investigations in a patient with temporal lobe epilepsy who showed accelerated long-term forgetting, together with a degree of autobiographical memory loss, yielded evidence of neuronal loss and gliosis in regions of both the right and the left hippocampus. Neuronal loss and gliosis were more evident in anterior than posterior hippocampus. These results indicate that the unusual forms of long-term forgetting seen in some patients with temporal lobe epilepsy have no gross anatomical correlate. The findings leave open the possiblities that subtle structural damage or subtle functional disturbance, perhaps in the form of subclinical epileptiform activity, underly epilepsy-related long-term amnesia.

1. Introduction

While the distinction between a shorter-term, labile consolidation process and a longer-term, more stable consolidation process is now an established feature of neurobiological thinking (Kandel, 2001; McGaugh, 2000), the fractionation of longer-term consolidation processes remains a relatively uncharted area in neuropsychological research. In recent years, a number of studies have challenged the traditional view that long-term memory consolidation is best viewed as a unitary process. In particular, there have been observations that have provided evidence for normal consolidation of information within time-frames of hours, coupled with accelerated forgetting of information over longer time periods. Such accelerated long-term forgetting (ALF) has been highlighted in several studies of patients with temporal lobe epilepsy. While there had previously been isolated reports which suggested the possibility of longer-term accelerated forgetting in patients with temporal lobe epilepsy (e.g. Martin et al., 1991), the first clear-cut case of very long-term accelerated forgetting appears to have been that reported by Ahern et al. (1994). Describing their patient, Ahern et al. noted that—"On many occasions, he was able to learn and retain new information across relatively long delay intervals ranging from 30 min to several hours. In marked contrast, JT was unable to remember major autobiographical and current events that had occurred days or weeks before each test session… JT's anterograde amnesia was characterized by an unusually rapid rate of forgetting over a time course of hours to days" (Ahern et al., 1994, p. 1271). Their patient subsequently had a right temporal lobectomy, though he continued to have seizure activity post-surgery. In a follow-up paper, O'Connor, Sieggreen, Ahern, Schomer, and Mesulam (1997) noted that JT's retention showed rapid decay after a matter of days, and that frequency of seizure activity appeared to play a role in his accelerated forgetting. They also found that the severity of retrograde amnesia, as indicated by performance on a test of memory for famous faces, increased over a three-year period. Lucchelli and Spinnler (1998) reported a patient with temporal lobe epilepsy that was accompanied by both an extensive retrograde amnesia and a selective impairment in the longer-term retention of new information. The contrast between this longer-term memory loss and intact performance on shorter-term memory tests was mainly evident for verbal material. Blake, Wroe, Breen, and McCarthy (2000) extended some of the findings from single-case studies to a group study of patients with temporal lobe epilepsy. They found that accelerated forgetting for verbal material was present over an eight-week period in patients with left temporal lobe epilepsy.

ALF has also been demonstrated in patients with a particular form of epilepsy known as transient epileptic amnesia (TEA). Patients with TEA experience brief, self-limiting episodes of isolated

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amnesia as a result of seizure activity, probably in the medial temporal lobes (Butler et al., 2007; Kapur, 1990; Zeman & Butler, 2010). These episodes typically cease upon treatment with anti-epileptic medication. Nevertheless, many patients complain of unusual persistent (interictal) memory difficulties. In particular, about 50% report that newly acquired memories fade rapidly over a number of days to weeks and 70% describe a patchy loss of memories for salient, personally experienced events of the remote past (Zeman & Butler, 2010). Patients typically perform normally on standard tests of anterograde memory but show ALF of new information over delays of days to weeks (Butler et al., 2007; Butler & Zeman, 2008; Muhlert, Milton, Butler, Kapur, & Zeman, 2010) and extensive impairment on tests of remote autobiographical memory (Manes, Hodges, Graham, & Zeman, 2001; Milton et al., 2010). We have previously demonstrated a subtle (~8%) loss of volume bilaterally in the hippocampus of patients with TEA, but did not identify any atrophy elsewhere in the brain using voxel-based morphometry (Butler et al., 2009). In this paper, we present the results of an investigation of interictal memory in TEA and its relationship with hippocampal volume.

Post-mortem studies of amnesic patients (e.g. Duyckaerts et al., 1985; Gold & Squire, 2006; Mair, Warrington, and Weiskrantz 1979; Mayes, Meudell, Mann, & Pickering, 1988; Oxbury, Oxbury, Renowden, Squier, & Carpenter, 1997Rempel-Clower, Zola, Squire, & Amaral, 1996; Warrington & Duchen, 1992; Zola-Morgan, Squire, & Amaral, 1986) have pointed to neural structures that may have a critical role in the human amnesic syndrome. While most of these studies have implicated the hippocampus and neighboring structures in the limbic–diencephalic system, it is unclear if these structures also play a part in the very long-term accelerated forgetting shown by patients such as those described above. Is it the case, as is implied in some of the above studies (e.g. Luchelli & Spinnler, 1998), that left temporal lobe mechanisms are primarily involved, or is it possible that bilateral hippocampal pathology underlies such unusual memory loss? In this paper, we report post-mortem findings from a case of very long-term accelerated forgetting which we previously reported during the patient's life (Kapur et al., 1997).

The specific aims of this paper are to shed light on the role of medial temporal lobe structures in accelerated long-term forgetting by examining both group correlations of such forgetting with hippocampal volume measures and by a single-case study where the site and type of pathology could be more clearly delineated. As pointed out by Robertson, Knight, Rafal, and Shimamura (1993), converging evidence from single-case and group studies may provide a powerful tool to address key issues in Neuropsychology.

2. Group study: transient epileptic amnesia

2.1. Methods

Twenty-two patients with TEA and 20 matched, healthy controls were administered a battery of standard neuropsychological tests comprising the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999); the Logical Memory subtest from the Wechsler Memory Scale—third edition (Wechsler, 1997); copy and delayed recall of the Rey–Osterreith complex figure (Osterreith & Rey, 1944); the Recognition Memory Test (Warrington, 1984); the Graded Naming Test (McKenna & Warrington, 1983) and letter and category verbal fluency. A summary score for anterograde memory performance (zmem) was derived for each individual by averaging the *z* scores across delayed recall of the Logical Memory story, delayed recall of the Rey–Osterreith complex figure and performance on the words and faces components of the Recognition Memory Test.

A semi-structured interview, the Modified Autobiographical Memory Interview (MAMI), was used to assess memories for personally experienced events from each decade of the subject's life (Butler et al., 2007). For two topics (e.g. 'holiday') from each decade, subjects were asked to produce one detailed episodic memory (e.g. 'Can you recall any incident, even if minor, that occurred during a holiday in your 30s?'). Episodic memories were scored out of five according to their degree of specificity and experiential detail, based on the scheme described by Graham and Hodges (1997). An average score across all decades was calculated (avMAMI).

In a separate session, participants learned a 15 item word list from the Rey Auditory Verbal Learning Test (Schmidt, 1996) to a criterion of 90% accuracy. The word list was orally presented and recalled over a minimum of five and maximum of 10 trials. Free recall of the words was probed at delays of 30 min and one week after the final learning trial. Prior to the test session, symptoms of ALF were sought by asking "Do you find that new memories fade more rapidly than you would expect? If so, over what time period?". ALF symptoms were defined as complaints of memories fading rapidly over days or weeks. Ten of the patients reported symptoms of ALF (ALF+) in daily life and 12 did not (ALF−). No control subject reported ALF symptoms. All patients were on antiepileptic medication and seizure-free over the period of testing. 'Early forgetting' was defined as the difference between scores on the final learning trial and the 30 min probe, expressed as a proportion of the final learning trial score. 'Late forgetting' was defined as the difference between scores on the 30 min and one week probes, expressed as a proportion of the 30 min score. Repeated measures analyses of variance with factors of group and delay were used to compare forgetting rates between patients and controls across the first 30 min delay and across the 30-min to one-week delay.

Volumetric analysis of the hippocampus was carried out on 3D T1-weighted magnetic resonance images using the method described by Pruessner et al. (2000). A detailed account of the imaging, segmentation and analysis procedures can be found in a previous publication (Butler et al., 2009). Pearson's correlational analyses were used to investigate the relationships between hippocampal volume and memory performance on the standard neuropsychological instruments, autobiographical memory task and the long-term forgetting test.

2.2. Results

Demographic data and neuropsychological test results are shown in Table 1. No difference was detected between patients and controls on any of the standard neuropsychological tests. Compared with controls, patients were impaired on the autobiographical memory task (avMAMI: patient mean = 7.8 ± 1.1, control mean = 9.1 ± 0.7, $p < 0.001$).

On the test of long-term forgetting, patients learned the word list at a similar rate to controls (trials to criterion: patient mean = 5.8 ± 1.1, control mean = 5.3 ± 0.9, $p = 0.084$). The patient group as a whole showed greater early forgetting (group × delay interaction: $F[1,40] = 4.3$; $p = 0.044$) and late forgetting (group × delay interaction: $F[1, 40] = 17.3$; $p < 0.001$) than controls. We separately examined the performance of patients who did and did not complain of ALF in daily life. ALF− patients showed greater early forgetting than controls (group × delay interaction: $F[1,30] = 5.9$; $p = 0.021$) but no difference in late forgetting (group × delay interaction: $F[1,30] = 2.4$; $p = 0.133$). ALF+ patients showed no difference in early forgetting from controls (group × delay interaction: $F[1,28] = 0.641$; $p = 0.430$) but a highly significant increase in late forgetting compared with both controls (group × delay interaction: $F[1,28] = 69.9$;

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Table 1.
Demographic data and test scores

	Patients ($n = 22$)	Controls ($n = 20$)
Age (years)	66.4 (8.8)	67.5 (8.6)
Sex distribution	12M/10F	8M/12F
Education (years)	13.2 (3.0)	13.0 (3.3)
Full scale IQ	124.7 (10.7)	121.2 (14.9)
Logical Memory delayed recall (25)	14.7 (2.8)	14.4 (3.7)
Rey figure delayed recall (36)	16.7 (5.6)	19.6 (6.2)
Recognition Memory Test (words) (50)	47.7 (2.0)	48.4 (1.7)
Recognition Memory Test (faces) (50)	43.4 (3.8)	45.2 (2.9)
zmem	−0.40 (0.6)	−0.05 (0.7)
Rey figure copy (36)	35.5 (1.3)	35.4 (1.2)
Graded Naming Test (30)	23.4 (3.0)	23.9 (3.8)
Letter fluency	48.2 (11.8)	45.0 (10.3)
Category fluency	22.5 (5.2)	22.7 (4.6)
avMAMI (10)	7.7 (1.1)**	9.1 (0.7)
Long-term forgetting task		
Number of learning trials to criterion	5.8 (1.1)	5.3 (0.9)
Recall at 30 min (%)	85.7 (8.7)*	92.8 (9.2)
Recall at 1 week (%)	30.1 (29.3)**	68.4 (23.8)

avMAMI, average score on the Modified Autobiographical Memory Interview.
* $p < 0.05$.
** $p < 0.001$.

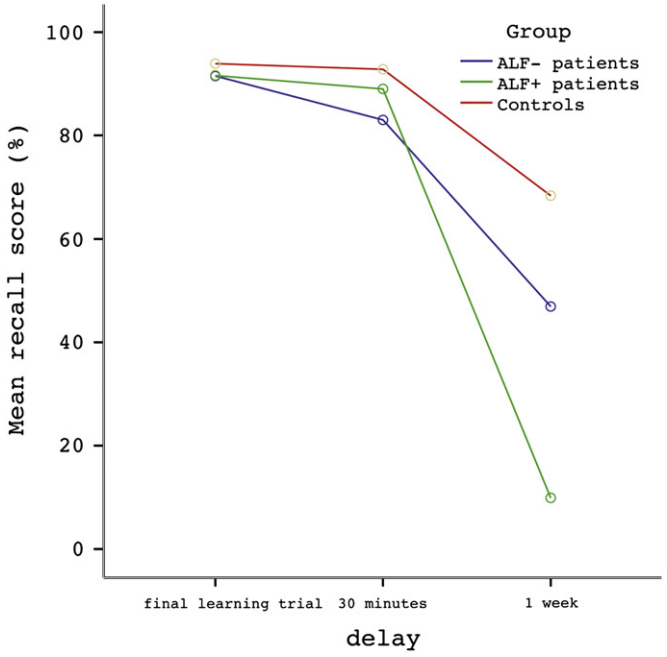

Fig. 1. Free recall performance on the word list at each of the three probes – final learning trial, 30 min and one week – is shown for healthy controls, TEA patients who do not complain of ALF (ALF−) and TEA patients who do complain of ALF (ALF+). ALF− patients differ from controls in the rate of early forgetting but not late forgetting. ALF+ patients differ from controls only in the rate of late forgetting.

$p < 0.001$) and ALF− patients (group × delay interaction: $F[1,20] = 32.7$; $p < 0.001$). These results are displayed in Fig. 1. Early forgetting rates did not predict late forgetting rates in either patients ($r = 0.168$, $p = 0.454$) or controls ($r = 0.343$, $p = 0.139$).

All MRI scans were clinically unremarkable. The volumes of the hippocampus in patients were not significantly different from controls (left hippocampal volume: patient mean = 2880 ± 378 mm^3, control mean = 3009 ± 274 mm^3, $p = 0.226$; right hippocampal volume: patient mean = 3129 ± 374 mm^3, control mean = 3201 ± 278 mm^3, $p = 0.490$). Despite this, the volumes of the hippocampus correlated with zmem in the patient group (left hippocampal volume: $r = 0.472$, $p = 0.031$; right hippocampal volume: $r = 0.497$, $p = 0.022$) but not in the control group (left hippocampal volume: $r = -0.156$, $p = 0.537$; right hippocampal volume: $r = -0.036$, $p = 0.888$).

There was no correlation between scores on the MAMI and volumes of the hippocampus in either the patients (left hippocampal volume: $r = -0.138$, $p = 0.551$; right hippocampal volume: $r = 0.211$, $p = 0.358$) or controls (left hippocampal volume: $r = -0.245$, $p = 0.378$; right hippocampal volume: $r = -0.391$, $p = 0.150$).

For the long-term forgetting task, there was no correlation between hippocampal volumes and early forgetting in the patient group (left hippocampus: $r = 0.301$, $p = 0.173$; right hippocampus: $r = -0.036$, $p = 0.889$) or control group (left hippocampus: $r = 0.250$, $p = 0.302$; right hippocampus: $r = -0.058$, $p = 0.813$). Similarly, no correlations were observed between hippocampal volumes and late forgetting in the patient group (left hippocampus: $r = -0.059$, $p = 0.794$; right hippocampus: $r = 0.032$, $p = 0.889$) or control group (left hippocampus: $r = -0.035$, $p = 0.886$; right hippocampus: $r = 0.005$, $p = 0.984$). There was no detectable difference in hippocampal volume between ALF+ and ALF− patients (left hippocampal volume: ALF+ mean = 3028 ± 400 mm^3, ALF− mean = 2757 ± 324 mm^3, $p = 0.094$; right hippocampal volume: ALF+ mean = 3150 ± 401 mm^3, ALF− mean = 3112 ± 0366 mm^3, $p = 0.817$). There was also no detectable difference between ALF+ and ALF− patients in the total number of seizures experienced (ALF+ mean = 24.0 ± 18.8, ALF− mean = 17.6 ± 20.0, $p = 0.208$) or seizure frequency (ALF+ mean = 13.3 ± 15.0, ALF− mean = 10.9 ± 6.2, $p = 0.811$).

3. Case report

3.1. Clinical history

This patient has been described in more detail elsewhere (Kapur et al., 1997). PA (d.o.b. July 31, 1932) initially presented in November 1991 with amnesia for holidays that she had taken in the previous 18 months. For example, she had been to France in September 1990, but she had no recollection at all of the holiday. A range of neurological, imaging and neuropsychological investigations carried out in 1992 and early 1993 were normal. Her memory symptoms persisted, and in 1994 she also developed minor absence attacks. In June 1994, EEG was carried out using a 29-electrode protocol that allowed for more focused mapping of the temporal lobes. Abnormal discharges were occasionally seen in the right temporal lobe, but the most frequent spikes were considered to arise from left inferior–anterior temporal lobe structures. An FDG PET scan was carried out, and no abnormalities could be detected.

MR scans were largely reported as normal, but in a scan carried out in February 1995, two neuroradiologists considered that there was a possible abnormality in the left anterior hippocampus. A further scan was carried out in October 1998 at Great Ormond Street Hospital, London, when volumetric indices were gathered, using procedures that have been described in detail elsewhere (Van Paesschen, Revesz, Duncan, King, & Connelly, 1997). The volume of the left hippocampus was 3942.01 mm^3 and the volume of the right hippocampus was 4316.01 mm^3. Taking into account the patient's age, these values represented a mild reduction in volume in the left hippocampus, consistent with the earlier MR findings.

Over the subsequent few years, PA remained on anticonvulsant medication and suffered several absence attacks a year. In June 1998, she underwent surgery for carcinoma of the rectosigmoid

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junction, and in October 1998 she developed secondaries in her liver and in her spine. She underwent a course of radiotherapy, but her condition deteriorated and she died in late October 1998. During the last two weeks of her illness, she refused to take anticonvulsant medication, and she consequently had two grandmal seizures in this period. Prior to her death, the patient gave written, informed consent for post-mortem investigations of her brain tissue to be carried out.

Neuropsychological investigations. Neuropsychological testing was carried out in 1994. On standard neuropsychological tests, PA displayed excellent performance, both on memory tests and on other cognitive tasks. Thus, on the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) she had a Verbal IQ of 133, a Performance IQ of 131, and a Full Scale IQ of 138. On the Wechsler Memory Scale-Revised (Wechsler, 1987), she had a General Memory Quotient of 116 and a Delayed Recall Quotient of 116. On other general cognitive tasks, including tests of naming (McKenna & Warrington, 1983), faces perception (Benton, Van Allen, Hamsher, & Levin, 1975), card sorting (Nelson, 1976) and verbal fluency (Lezak, 1983), she also performed well. Recognition Memory Test (Warrington, 1984) performance was excellent for words (49/50) and for faces (49/50).

The performance of PA on tests of very long-term retention and on tests of public events memory is presented in detail elsewhere (Kapur et al., 1997). In summary, she scored within normal limits on immediate and 30-min delayed recall of story material, but was impaired at six-week delayed recall and recognition testing for the stories. Delayed recall of visual designs showed a similar pattern of scores, though 6-week design recognition memory was not impaired. Memory for news events and famous personalities showed a selective memory loss, with impaired performance for items from the 1990s, this corresponding to the period when her symptoms of memory loss and evidence of epilepsy first emerged. Thus, there was no evidence of a retrograde amnesia covering the period prior to the onset of her symptoms. On the *Autobiographical Memory Interview* (Kopelman, Wilson, & Baddeley, 1990), PA performed normally for Personal Semantic Items—20.5/21, 18.5/21 and 19/21 for Childhood, Early Adult and Recent Life time periods, respectively. In the case of incidents, there was evidence of a mild impairment for Early Adult Items—6/9, 3/9 and 6/9 for Childhood, Early Adult and Recent Life time periods, respectively. We examined PA's autobiographical memory further by the use of a modified Crovitz procedure. We asked her to retrieve specific memories in response to cues in the form of phrases, such as 'sitting a driving test', 'incident when swimming', 'a particular plane journey', 'a particular birthday party', and 'a holiday in Britain'. We did not specify any time period from which the memories were to be retrieved, but most of her recollections were in fact from before the presumed onset of her illness in 1990, when she was 58 years of age. Her recollections were transcribed and rated for clarity/vividness of the recollection by two independent raters, using a scale of 0–3, with the average of the ratings being taken. PA's performance was compared to that of four matched control subjects. Her score of 25/60 suggested a mild–moderate impairment, being below the mean of controls (37/60) and just outside the range of control data (26–42.5).

Although the above detailed assessments were carried out in the mid-1990s, more recent testing within the few years prior her death showed essentially the same pattern of performance.

4. Neuropathological findings

Both acute and chronic changes were seen in the brain. The acute changes were likely due to the two seizures that occurred in association with PA's terminal illness, and could be readily distinguished from the more neuropsychologically relevant chronic changes that were found.

Coronal sections through the brain were generally unremarkable, and showed the absence of major cerebral atrophy or ventricular dilatation. Sections of the left and right temporal lobe showed changes that were most likely age-related rather than representing significant pathology which was pertinent to our patient's memory loss. Such changes included atrophy of cortex and white matter, with large numbers of corpora amylaceae in the subpial cortex and around blood vessels in the deep white matter. These blood vessels had hyalinized walls. The cortical molecular layer was hypercellular with myelinated fibers in it.

Microscopic examination demonstrated that the left hippocampus showed loss of neurones and gliosis in CA1, CA2, CA3 and CA4 (Figs. 2–5). The dentate gyrus appeared intact. Remaining neurons showed acute ischemic damage, and there was acute edema. The changes were more severe in the anterior hippocampus. The right hippocampus showed much more severe acute damage, with marked edema in the pyramidal cell layer. There was also evidence of older cell loss and gliosis. There was a small infarct in the hilum, probably several weeks or months old.

A cluster of capillaries was seen in the mid-part of the right hippocampus, extending to all posterior levels examined. This was situated in the white matter of the stratum radiatum underlying Ammon's horn. It probably represented a small area of capillary hemangiectasis which had calcified, the significance of which is unclear but is occasionally seen in the general

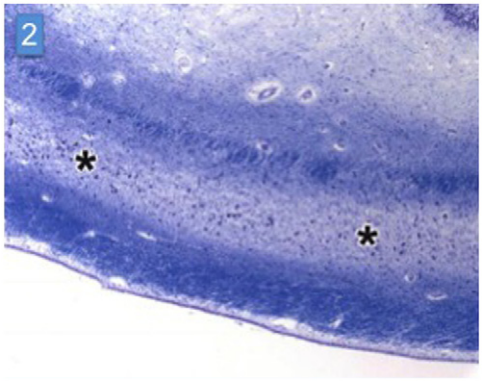

Fig. 2. Anterior hippocampus on the right side showing loss of neurons in CA1 (this figure between the asterisks), compared with CA1 in the posterior hippocampus (Fig. 3 between the asterisks).

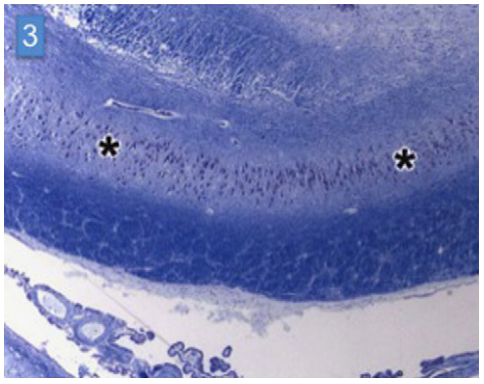

Fig. 3. Hippocampus on the right side showing neurons in CA1 in posterior hippocampus (this figure between the asterisks).

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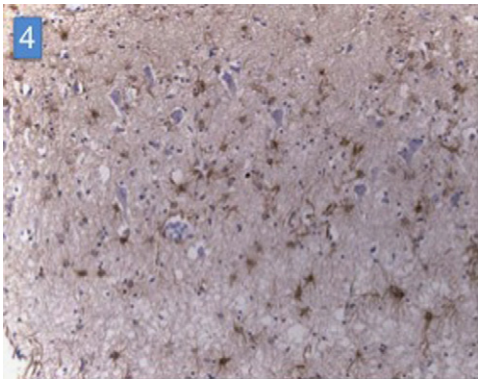

Fig. 4. CA1 in the anterior portion of the left hippocampus, showing reactive astrocytosis (this figure, brown staining of cells), compared with the subiculum at the same level (Fig. 5) in which there is no apparent loss of neurons and no significant astrocytosis. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

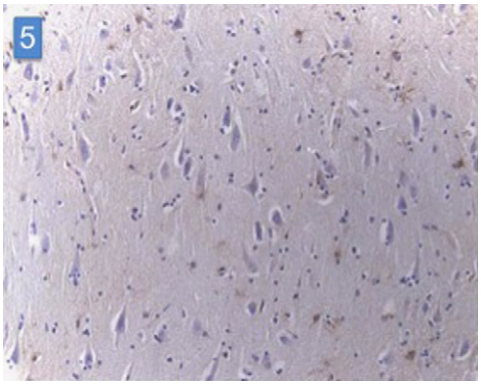

Fig. 5. Subiculum at the same level as CA1 shown in Fig. 4.

population. Both amygdalae were free of any significant pathology. The parahippocampal region (entorhinal cortex, perirhinal cortex, parahippocampal cortex and subiculum) was found to be normal in routine light microscopic examination. The cerebellum was macroscopically intact, but Purkinje cells and neurones of the dentate nucleus showed acute necrotic changes.

In summary, post-mortem investigations showed both acute and chronic changes bilaterally in the hippocampus, with chronic neuronal loss and gliosis in CA1, CA2, CA3 and CA4 regions, this pathology being more marked in anterior regions.

5. Discussion

In our group study of patients with transient epileptic amnesia, there were no significant correlations between volumetric measures of the hippocampus and indices of accelerated long-term forgetting or longer-term autobiographical memory loss. In our single-case study of selective very long-term anterograde memory impairment, post-mortem investigations showed neuronal loss and gliosis in regions of both the right and the left hippocampus. Neuronal loss and gliosis were more evident in anterior than posterior hippocampus. There was no evidence of significant pathology in parahippocampal structures such as the entorhinal cortex, perirhinal cortex and parahippocampal cortex. Evidence from both single-case and group studies converged to demonstrate that there is no gross structural abnormality that underlies selective long-term memory loss.

The group of TEA patients investigated here performed normally on a range of standard neuropsychological measures including tests of anterograde memory. Concordant with their subjective complaints, however, they were impaired on a test assessing remote autobiographical memory. Furthermore, on a task of very long-term memory, the patients learned at a normal rate but showed accelerated forgetting over a one week delay. Forgetting over the first 30 min was greater in patients compared with controls, but only amongst patients who did not complain of ALF in everyday life. Importantly, these patients did not differ from controls in the rate of forgetting over the subsequent week. In contrast, patients who did complain of ALF in everyday life did not differ from controls in their early forgetting rates, but showed a dramatic decline in memory over the one week delay. This late forgetting component appears, therefore, to doubly dissociate from early forgetting and as such may reflect a deficit in a distinct cognitive process—perhaps a later stage of memory consolidation.

No group differences in hippocampal volume were detected between patients and controls. However, in patients only, both right and left hippocampal volumes correlated with a summary score of anterograde memory performance. This finding suggests that the patients had a degree of hippocampal atrophy below the sensitivity threshold of the group comparison but which nonetheless affected memory performance, or covaried with other (unmeasured) brain regions that affected memory performance. Indeed, in a previous investigation we demonstrated a volume reduction of approximately 8% in a much larger group ($n = 41$) of TEA patients (Butler et al., 2009). Importantly, no relationship was found between hippocampal volume and late forgetting in either patients or controls. This negative finding does, of course, not rule out a structural cause for ALF. It may be that explorations beyond the hippocampus or alternative imaging techniques looking at, for example, white matter integrity, will find an explanation in the future. An alternative possibility is that ALF is due to the physiological disruption of memory networks by recurrent (subclinical) seizure activity in the brains of patients with TEA.

An important and outstanding question is whether ALF relates to a deficit of memory encoding, consolidation or storage. Despite the fact that TEA patients learn at a normal rate, encoded memories may be less robust and thus susceptible over the long-term to, for example, the effects of retroactive interference (Dewar, Cowan, & Sala, 2007). Alternatively, the encoded memory traces may initially be normal but then subsequently disrupted by a failure of consolidation or storage processes.

One potential limitation of the present results is that they may have been subject to ceiling effects in the early stages (final learning trial and 30 min probe) (Bell, Fine, Dow, Seidenberg, & Hermann, 2005). Such effects may have masked or reduced the size of differences between patients and controls in early forgetting, so that what was in fact a uniformly accelerated forgetting rate looked instead like an increase specifically in late forgetting. We acknowledge the potential for ceiling effects to have influenced the forgetting rates observed in this study. Indeed, they may have been responsible for the absence of any correlation between early and late forgetting rates in either patients or controls. However, we believe that our finding of a distinct pattern of accelerated long-term forgetting is robust for the following reasons. First, patients and controls performed at a similar level on a range of standard anterograde memory tasks and learned the word list at a similar rate, suggesting that, as a group, patients do not have a marked learning or early retention deficit. Second, we were able to detect increased early forgetting in the ALF− subgroup, who were therefore clearly not at ceiling at 30 min, but their late forgetting proceeded at the same rate as controls. In contrast, the ALF+ subgroup showed increased late forgetting in the absence of any (detectable) difference in early

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forgetting. This finding represents a double dissociation between early and late accelerated forgetting in TEA and thus implies the existence of two distinct psychological processes. Nevertheless, given the potential importance of the phenomenon of ALF for theories of long-term memory, it would be wise for future studies definitively to rule out ceiling effects, perhaps using a lower learning criterion. It is worth noting that in a previous investigation of ALF (Muhlert et al., 2010), we used an 80% criterion with a word list and still found accelerated forgetting in patients. Moreover, in that study, early forgetting rate predicted late forgetting rate in controls but not in patients.

In our single case study, it would seem that hippocampal pathology was related to the presence of intermittent, bilateral subclinical seizure activity (c.f. Binnie, 2001). It is possible that this epileptiform activity disrupted very long-term memory formation and thus contributed to the unique profile of our patient's memory disorder. It is not possible to say with certainty whether the hippocampal cell loss was the cause or the consequence of the epileptic activity that occurred as part of our patient's condition. Our patient did not show the significant medial temporal lobe atrophy that has been associated with prolonged seizure activity (O'Brien, So, Meyer, Parisi, & Jack, 1999). Regardless of the particular cause and effect relationships surrounding the hippocampal abnormalities that we found in our single-case study, our data support recent observations from functional imaging studies in normal individuals which indicate that the hippocampus plays a role in the consolidation and retrieval of new memories over a time frame that is measured in weeks and longer, rather than just a few hours (Stark & Squire, 2000).

The presence of neuronal loss in hippocampal regions such as CA1, both in our patient and in other patients such as RB (Zola-Morgan et al., 1986), mirrors the abnormality that is seen as an accompaniment of common forms of temporal lobe epilepsy associated with hippocampal sclerosis (Mathern, Babb, & Armstrong, 1997). It therefore raises the question why our patient, and others with temporal lobe epilepsy, do not show the pattern and severity of memory loss that was shown by patients such as RB. Compared to the amnesic patient RB – who had an acute, hypoxic etiology – cell loss in our patient appeared milder in the CA1 region. However, across the anterior hippocampus as a whole it seemed somewhat more extensive, in that it also involved other CA regions, whereas the pathology in patient RB was largely restricted to the CA1 sector. Compared to what is commonly seen in patients with temporal lobe epilepsy, our patient's brain showed relatively mild macroscopic shrinkage of the hippocampus as a whole, and in particular there was no significant gliosis in the dentate gyrus, as is often seen in hippocampal sclerosis. It is possible that only bilateral severe CA1 neuronal loss, as was found in patients RB (Zola-Morgan et al., 1986) and GD (Rempel-Clower et al., 1996), results in major memory impairment on standard anterograde memory tests. Up to the present, there are only a few published cases of patients with a history of temporal lobe epilepsy who have bilateral CA1 lesions and well-documented memory loss. Most of these case reports (e.g. Oxbury et al., 1997; Penfield & Mathieson, 1974; Warrington & Duchen, 1992) have reported marked anterograde memory loss, with a variable degree of retrograde amnesia. The differing etiologies (acute hypoxia in patients RB and GD contrasting with milder, more temporally distributed, changes in our patient) may have played a part, allowing for greater involvement of compensatory mechanisms in our patient. In terms of common neuropsychological features, it is worth noting that in all three patients – PA (our case), RB and GD – there was an absence of any major retrograde amnesia.

Although our case PA bears some similarities to previously described cases of selective hippocampal pathology, and would seem to fit with some models that highlight preserved recognition memory (Brown, Warburton, & Aggleton, 2010), it is worth noting critical difference with earlier cases. While at face value the differences between WAIS and Wechsler Memory Scale Quotients are similar between PA and RB (22 and 21, respectively), quotient values in themselves can be misleading, as highlighted in the seminal paper by Lezak (1988). Thus, the 30 min delayed recall scores for both stories and visual designs were markedly impaired in the case of RB (Zola-Morgan et al., 1986, Fig. 2), but were within normal limits in the case of PA (see Kapur et al., 1997, Table 1).

Our observations are in harmony with animal lesion studies that have found differential effects of hippocampal lesions on short-term and long-term memory functioning (e.g. Alvarez, Zola-Morgan, & Squire, 1994). They also support findings of post-training hippocampal stimulation resulting in a form of delayed-onset anterograde amnesia, where long-term memory rather than short-term memory is adversely affected (Kesner & Conner, 1972). In addition, animal studies have reported that various seizure intensities of hippocampal stimulation will have differential effects on short-term and long-term memory functioning. Allowing for some negative findings (Roman & Soumireu-Mourat, 1988), Bierley, Kesner, and Novak (1983) noted that subthreshold electrical stimulation of the dorsal hippocampus applied during learning disrupted retention at 20-min delay, but had no effects at 1-min or 12-min delays, whereas seizure-level stimulation disrupted retention at all intervals. If one assumes that retention intervals are 'stretched' when comparisons are made with human subjects, and that subthreshold stimulation may mimic subclinical seizure activity of the sort that we suspected occurred in our patient and in other similar reported cases, then the pattern of findings reported by Bierley et al. (1983) may provide an animal model for the mechanisms that underlie the occurrence of some forms of long-term accelerated forgetting.

The pattern of memory disorder displayed by our patient, where the predominant presenting symptom was the inability to 'reminisce' about past holidays, and lack of recollection of places she had visited even when she revisited them, is reminiscent of symptoms described in cases of transient epileptic amnesia (Manes et al., 2001; Zeman & Hodges, 2000). It is also in keeping with reports of impairments on tests of longer-term memory in patients with temporal lobe epilepsy. Similar observations were noted in an early study by Barr, Goldberg, Wasserstein, and Novell (1990) in a group of patients who had undergone temporal lobectomy. In a study of a group of patients that included both those with temporal lobe epilepsy and those who had undergone temporal lobectomy, Viskontas, McAndrews, and Moscovitch (2000) found impaired memory for autobiographical events. This was based on performance on the Autobiographical Memory Interview (Kopelman et al., 1990) and yielded a pattern of performance whereby there was little in the way of any temporal gradient of autobiographical memory loss. In a study that focused on memory for public events, and that was restricted to patients who had temporal lobe epilepsy but who had not undergone surgery, Bergin, Baxendale, Thompson, Fish, and Shorvon (2000) also found evidence of significant impairment in remote memory performance in patients with temporal lobe epilepsy.

Two broad neuropathological possibilities that may explain the presence of memory disorder in our patient—a permanent structural abnormality in the hippocampus that resulted in the absence of biochemical processes that contribute to the stable consolidation of long-term memories and a more intermittent physiological abnormality that interfered with long-term consolidation on an occasional basis. Some of the clinical features of our case would point to the latter explanation. Thus, our patient thought that her memory loss since the onset of her symptoms was patchy rather than global for events over recent years. It is possible that the presence of bilateral, intermittent, epileptiform

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activity in the region of the hippocampus and related neural networks acted over a period of time to disrupt very-long term consolidation of new memories. In an animal model of retrograde amnesia, Laurent-Demir and Jaffard (1997) have shown that afterdischarges induced by electrical stimulation of the dorsal hippocampus will result in temporally extended retrograde amnesia. The disruptive effects of ongoing epileptic activity on trace formation for an event, often without any awareness by the individual, has been well documented (Gloor, 1997; Palmini et al., 1992). Peri-ictal disruption of traces is therefore one likely candidate mechanism for the type of very long-term memory loss in patients such as the one reported here. It is also possible that a particular temporal pattern and severity of clinical/subclinical epileptic activity may result in the type of retrograde amnesia seen in patients such as those described by O'Connor et al. (1997) and by Lucchelli and Spinnler (1998), and thus provide a human analogue to the retrograde amnesia demonstrated in mice by Laurent-Demir and Jaffard (1997). It is unlikely that there is a simple relationship between an epileptic event and erasure of immediately preceding memories, in view of the findings of Bergin, Thompson, Fish, and Shorvon (1995) that seizure activity does not disrupt memory for word-list or story material that was acquired 48 h earlier.

In summary, our findings suggest the existence of a distinct phase of very long-term memory consolidation that can be disrupted in patients with subtle hippocampal damage and epilepsy. We did not identify any relationship between accelerated long-term forgetting or autobiographical amnesia and the degree of hippocampal atrophy, raising the possibility that these abnormalities are caused by structural damage elsewhere, or by subclinical seizure activity.

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