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Long-term retrograde amnesia… the crucial role of the hippocampus

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Abstract

For patients with hippocampal pathology, disagreement exists in the literature over whether retrograde amnesia is temporally limited or very extensive depending on whether the anatomical damage is restricted to this structure or also involves additional temporal cortex. We report a comprehensive assessment of retrograde and anterograde memory functions of a severely global amnesic patient (VC). We found that he presented with a remarkably extensive and basically ungraded retrograde amnesia. This impairment profoundly affected four decades preceding the onset of his amnesia and encompassed both non personal and personal facts and events. VC also presented with a severe anterograde amnesia and a deficit in the acquisition of new semantic knowledge in the post-morbid period. Detailed MRI volumetric measurements revealed gross abnormalities in both hippocampi which were markedly shrunken. Of relevance to the debate on retrograde amnesia were the observations that the volumes of both entorhinal cortices and the remainder of both temporal lobes were normal. These data suggest that the hippocampus is critical not only for the efficient encoding and hence normal recall of new information but also for the recall of episodic information acquired before the onset of amnesia. Our results are compatible with the view that retrograde amnesia is both extensive and ungraded when the damage is limited to the hippocampus.

Keywords: Hippocampal pathology; Retrograde amnesia; Memory functions

1. Introduction

Organic amnesia caused by non-progressive brain damage is a selective impairment of memory that usually occurs in the absence of clear intellectual dysfunction and/or loss of general knowledge [43]. The memory impairment in amnesia is usually global, being both anterograde and retrograde [55]. Occasionally patients may present with severe anterograde amnesia (AA) but minimal retrograde amnesia (RA) [90,91]. Even less commonly, patients may present with what Kapur [26] named 'focal retrograde amnesia', namely severe RA in the context of very mild or completely absent AA [16,34,73]. Both the anterograde and the retrograde memory impairments cover complex sets of phenomena whose extent, nature and anatomical bases are still relatively poorly understood. Thus, the precise relationship between RA, AA and additional 'executive' cognitive deficits remains unclear (see for discussion [58]). Also different, often contrasting, cognitive theories have been put forward to account for the pattern of retrograde and anterograde memory loss [8,10,11,30,57].

The present paper focuses on the controversial issue of the structures involved in RA. It is generally accepted that severe amnesic states are only observed in patients with bilateral damage [42]. However, there is considerable debate over the role played in amnesia by

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several critical structures within the medial temporal lobe (hippocampus, entorhinal, perirhinal and parahippocampal cortices) and the related diencephalic midline structures (mammillary bodies, anterior thalamic nuclei, medial dorsal thalamic nuclei, thalamic nucleus and mammillothalamic tract). We will be primarily concerned with the role of the hippocampus. The role of the hippocampus in memory has been a topic of much debate and speculation. Different theories have been put forward regarding its function and its interaction with the neocortex. Those theories suggesting that only a particular kind of memory is dependent on the hippocampus will not be considered here [19,49,50].

Central to most of the theories focusing on the role of the hippocampus in RA is the notion expressed by Ribot [54] more than 100 years ago that the loss of memories from the past could be temporally graded. This phenomenon has influenced a number of accounts which have accorded to the hippocampus a relatively extended but nevertheless time limited role in memory tasks. Marr [36] was among the first to propose that the hippocampus acts as a temporary memory store for the storage of new information whilst the neocortex acts as a permanent memory store. On this type of theory, the hippocampus is viewed as a 'simple memory' temporarily storing traces and playing them back to be consolidated in the neocortex for permanent storage possibly during dream sleep. The view that the hippocampus plays a role in memory consolidation and in providing extra learning opportunities for the neocortical permanent memory store is also present in the work of Squire and colleagues [65,69–72]. The authors proposed that over a somewhat vaguely specified period of time, contents are assumed to become gradually independent of the hippocampus and dependent on neocortical storage sites. This is due to the action of the memory consolidation process.

Recently, a number of neuronal network models have also been based on this view ([39,40,45,76,77]; see for a review [67]). For example, on the Treves and Rolls [76,77] model there is detailed discussion of how the hippocampus might store information rapidly and have a crucial role in directing memory consolidation. In particular, in this model, when a partial cue is presented the hippocampus can reconstruct memory in the neocortex by activating neocortical sites. Across time and as a result of repeated reactivation, memories are fully established in the neocortex. Similar ideas are present in the model described by Murre [44,45] and Alvarez and Squire [2]. Murre's TraceLink model stressed the importance of hippocampus as a temporary 'scaffold' for new memories, serving as an intermediate 'link system' of connections, before they are well established at a neocortical level, the 'trace system'. In the Alvarez and Squire's neuronal network model of consolidation, information is first stored in a fast learning 'medial temporal lobe area' which then gradually strengthens slower-changing connections in a distributed 'neocortical' network. In the computational model proposed by McClelland and colleagues [40] it has also been suggested that recently experienced events are first stored through fast-changing synapses in the hippocampus in a 'condensed' form. This computational model offered a principled justification of why the consolidation process would require complementary learning systems in the hippocampus and neocortex. According to this view, rapid learning of new association would provoke fast changes in the cortical representations that would lead to so-called catastrophic interference. Thus, it is crucial to have a system that can learn rapidly independently of neocortex, but able to gradually modify it. So, on this model, repeated reinstatement of the hippocampal memory results in the accumulation of gradual and slow neocortical changes. This process allows the new memory to be integrated into existing neocortical networks. Remote memory is based on these accumulated neocortical changes.

All these theories would predict that if the pathology is restricted to the hippocampus, the RA should be temporally graded such that recent memory is more impaired than remote memory. The existence of an extensive and ungraded RA would only occur if the pathology also involves the neocortex and is not restricted to the hippocampus. Furthermore, if the damage is limited to the neocortex and the hippocampus is spared then the RA should primarily affect remote memories with recent memories being preserved. In support of this, several empirical studies have documented extensive and ungraded RA in patients whose pathology was NOT confined to the hippocampus but also extends to the neocortex [9,14,37,78]. Furthermore, relative preservation of more recent memories has been found in patients with semantic dementia, a pathology that is thought to mainly involve the temporal neocortex and much less so the hippocampus [21].

Even more compelling evidence for the view that the hippocampus has an important but temporally limited role in memory comes from studies reporting that hippocampal amnesics show selective memory deficits only for material acquired shortly before their lesion. Retrieval of more remote memories appears to be relatively preserved (see for review [66,67]). Among the best known examples, are four patients (RB, [92] and GD, WH and LM, [53]) who presented with RA limited to 1 or 2 years (RB and GD) or $\sim$15 years (WH and LM). Neurohistological data indicated that RB and GD had a bilateral lesion limited to the CA1 region of the hippocampus. WH and LM presented with a bilateral lesion involving all the cell fields of the hippocampus and the dentate gyrus. However, LM also had cell loss in layers II and III of the midportion of the entorhinal

cortex. WH had more substantial cell loss in the entorhinal cortex.

Recently four new patients (LJ, AB, EP and GT) have been reported whose RA has been investigated extensively [52]. In two patients (LJ and AB), the RA was limited to the decade preceding the onset of amnesia whilst in the other two (EP and GT) the RA was severe and extensive. MRI examinations revealed that LJ presented with a roughly 36% bilateral volumetric reduction of the hippocampus. In contrast EP and GT presented with severe bilateral temporal damage involving the hippocampus. For AB the authors presumed a circumscribed hippocampal lesion on the basis of the aetiology of his amnesia, a cardiac arrest. Thus, according to the authors, this study provides further compelling support for the position that damage to the hippocampus produces only limited RA and that additional temporal cortical damage is needed to produce severe and extensive RA. Moreover, the authors refer specifically in their discussion to the two patients (WH and LH; see [53]) who presented with an extensive RA of 15 and 25 years, respectively, in whom the additional temporal damage was located in the entorhinal cortex.

However, there are also on record a few patients in whom it is unclear what role any impairment in temporal cortical areas is playing in their extensive and ungraded RA. One example is patient NT. This patient was first reported in 1964 as presenting a severe memory impairment following a right temporal lobectomy for the treatment of epilepsy [15]. Formal investigation of her remote memories indicated an extensive and ungraded RA [56]. The neuropathological investigation revealed an old sclerotic lesion of the left hippocampus. Examination of the previously removed right temporal lobe revealed no clear abnormalities [84]. Thus, it is tempting to conclude that the RA in this patient was a consequence of the bilateral damage to the hippocampus, given that the left temporal lobe was pathologically intact. Patient HJ with a Korsakoff's psychosis presented with a severe amnesia in the absence of any other focal cognitive impairment [33]. His retrograde amnesia was of very long duration and not temporally graded on formal testing. The only abnormalities present at the neuropathological investigation involved the mammillary bodies and the medial dorsal nucleus of the thalamus. All other regions, including the neocortex, were normal.

In the context of these findings it is useful to consider the patient described by Kartsounis et al. [29]. The MRI findings on this patient showed a circumscribed abnormal signal in the CA1 and CA2 fields. An initial neuropsychological investigation suggested a severe amnesic syndrome. In particular, the patient was described as having an extensive retrograde memory loss, although no formal documentation of the extent of the RA was reported This study, therefore provided some preliminary clinical evidence of severe RA due to damage limited to the hippocampus.

Thus, attempts to identify the role of the hippocampus on RA have produced conflicting and controversial results, which have led to extensive debate in the literature. For example, suggestions have been made that the patients reported above with extensive and ungraded RA without clear cortical involvement must have had cortical 'hidden pathology' (see for further discussion [1,28,52,67]). One possible problem which is often mentioned is that the neuronal dysfunction caused by ischaemia may be more extensive than the region of gross pathology [3,20]. In line with this position, a recent PET study [35] has been held to highlight the limitation of relying on MRI to uncover functional damage, especially in cases of anoxia (for example see [1]). It should, however, be noted that the patient described by Markowitsch and colleagues to demonstrate this point performed poorly on non-verbal tests of general intelligence and had an MRI scan indicating subcortical and cortical atrophy with widening of the ventricles.

The problems of hidden cortical pathology, for example, apply to Kartsounis et al.'s [29] patient. However, they apply equally to the hippocampal patient LJ described by Reed and Squire [52]. Reed and Squire [52] also described patient AB as an hippocampal patient. However, this was based on an highly speculative inference based on the aetiology. No neuroradiological or post-mortem evidence was available. It should also be noted that the argument for hypothetical but undetected cortical pathology is one which allows theorists to select findings as they please. For instance, Reed and Squire [52] in the same paper quote the Kartsounis et al.'s patient as supporting their position that the hippocampus is central for learning new factual knowledge but reject the evidence from him on the role of the hippocampus in retrograde amnesia. On the basis of an inadequate argument from his neurological history, they conclude '…it seems unlikely that his damage could be limited to the CA fields of the hippocampus…'.

In addition, concerns have been expressed about the patients presenting with temporally limited RA where remote memories are spared. Often in these cases the severity of the amnesia [89] and the methodology employed for testing remote memories [60] have been criticised. For instance, consider the two hippocampal patients (AB and LJ) with temporally limited RA recently reported by Reed and Squire [52]. For the only patient (LJ) who we can be relatively sure had circumscribed hippocampus damage, there is a serious question over the severity of the amnesia. This patient's WMS-R verbal score was only one standard deviation below her IQ, although her WMS-R visual score was two standard deviations below her IQ. More critically, her performance on recall tests of public events and

famous faces was within the control range for all three time periods considered (1–10 years before amnesia; 11–20 years before amnesia; and 21–30 years before amnesia). Given these indications of only limited amnesia, the significance of her apparent temporal gradient in autobiographical memory is questionable.

Even more critically, the methodology used to test retrograde memory was inadequate. Tests were used in which the level of performance was equated across different retention intervals. However, it was shown mathematically by Shallice [60] that if one differentiates semantic from episodic memory processes, for which now there is strong neurological evidence, then this is methodologically inappropriate (see also [86]). One is comparing the retention of predominantly semantic, or personal semantic [9] information for longer time intervals with retention of predominantly episodic information over shorter time periods. No justification is provided by Reed and Squire [52] for the methodology used. It should be noted that a similar problem also applies to the investigation of the retrograde amnesia of patient RB reported by Zola-Morgan et al. [91].

An alternative methodology is not subject to this criticism. This involves matching information retained over different time intervals by how well it was initially laid down, rather than by how well it is remembered. This was the procedure adopted in the initial investigation of retrograde memory by Warrington and Sanders [87]. The authors carried out an internal test of their assumption. They confirmed that the material used in their tests was not part of the general knowledge (semantic memory) of anyone in the culture by showing that intelligent teenagers could only retrieve the most recent events.

In this Introduction we have concentrated on the controversial issue related to the role of the hippocampus in retrograde memory. It seems likely that for this issue, detailed investigations of a large number of individual case studies are needed in order to determine the critical anatomical structures. Without such studies we will be unable to identify the roles not only of the hippocampus but also of a number of structures in the medial temporal lobe and diencephalic midline which may be of potential relevance for the processes involved in retrograde memory. For this purpose two types of patients are important: (1) those who show surprising sparing in memory skills given the relevant anatomical structures damaged; (2) those who despite restricted lesions show severe deficits in retrograde memory tasks.

In this study we report a further examination of a patient of the second type, namely the profoundly amnesic patient (VC) previously described by Kartsounis et al. [29]. Detailed MRI volumetric examinations were undertaken and revealed the presence of very restricted and quantifiable areas of neuronal damage. Comprehensive assessment of his amnesia revealed a remarkably extensive and ungraded RA affecting both personal and non-personal memories. These results assist in the understanding of the anatomical structures which are necessary for effective storing and retrieval of the mnestic traces.

2. Case report

The patient (VC) is a 73-year-old (born 1926) retired chief engineer in large ships such as liners who was reported by his wife as having an excellent memory. In May 1992 he developed an apparent severe migraine attack which was followed by a seizure. He was found to have a tachyrhythmia when admitted to hospital and recovered. In September 1993 he had two further seizures four days apart with a tachyrhythmia requiring cardioversion. Following these episodes, at the age of 67, he was profoundly amnesic. Since then he had no further epileptic episodes. His past history was unremarkable apart from mild reversible chronic obstructive airways disease. Whilst working at sea he had consumed considerable amounts of alcohol but this had never impaired his ability to function at a high level in his highly responsible position. Moreover, his memory functions were reportedly excellent during this period. For at least 15 years prior to his presentation he had never consumed more than 20 units per week, and often much less according to his wife. Neurological examination revealed a profound amnesia and a minor but variable impairment of pain assessed by pin prick over the left hand and foot. The remainder of the neurological examination was normal.

Extensive investigations were undertaken. Apart from the neuroradiological abnormalities (see below), the only abnormality was a mild impairment of left ventricular function of echocardiography. In particular, VDRL, liver function tests, full blood count, serum B12 and thyroid function were all negative or normal. Angiography of the extra-cranial vessels was normal.

3. Neuroradiological studies

3.1. Qualitative studies

3.1.1. MRI

T2-weighted images of the whole brain were obtained in the axial, coronal and sagittal planes (Signa 1.5 T MRI system, GE Milwaukee). Increased signal return was found throughout the length of both hippocampi (see Fig. 1). Formal measurement of the T2 relaxation time was in excess of 90 ms (greater than three standard deviations above normal) at all levels of both hippocampi. The hippocampi were atrophied and there was also abnormal signal return from the left amyg-

dala. There was no evidence of abnormal signal return from any other part of the brain. In particular both thalami were normal. In view of the report by Kapur et al. [25] of focal retrograde amnesia and bilateral temporal lobe pathology particular attention was paid to the appearance of the anterior temporal lobes. In this instance the temporal poles, anterior middle temporal gyri and anterior parahippocampal gyri of both sides were observed to be entirely normal.

3.1.2. PET

Resting PET scans (Siemens ECAT 951 scanner) were obtained; 250 Mbq of ^{18}FDG were administered. The field of view was 10 cm and the resolution 7 mm FWHM. Decreased tracer uptake was seen throughout the right thalamus and possibly the right parietal region compared to the left (see for further details [28]).

3.2. Quantitative studies

In order to measure more precisely the anatomical structures involved detailed MRI volumetric analysis was undertaken.

3.2.1. Volumetric MRI: methodology and regions of interest

The patient VC and six age-matched healthy control males (see Table 1) underwent high resolution volumetric T1-weighted MRI scanning. All images were obtained using a 1.5 T Signa scanner. Volumetric imaging was performed in the coronal plane using a spoiled gradient echo technique with a 24 cm field of view yielding 124 1.5 mm thick contiguous coronal slices through the head on a 256×128 image matrix with acquisition parameters (35/5/1/35_TR/TE/NEX/FLIP), which have been used previously in studies of hippocampal volumetric and morphometric studies [12]. This allowed regions of interest to be outlined with comparable landmarks and orientation in such way as to improve reproducibility. The MIDAS image analysis tools were used for regional segmentation [17]. These include semi-automated morphological operators which allow brain volumes to be extracted reliably from the volume data set. The editing tools allow simultaneous multiplanar display and editing, which permits viewing of sagittal sections through a region while the region is outlined in the coronal plane. Editing appears in real time on all planes and this improves the reproducibility of volumetric analysis. In order to compensate for different brain sizes between individuals all measurements were normalised to the total brain volume. All measurements were performed blind to the subject and to the left/right orientation of the measured region.

3.2.1.1. The hippocampus. Segmentation of the hippocampus was undertaken using the following guidelines. Rostrally, measurements commenced at its junction with the caudalmost portion of the amygdala. The caudalmost hippocampal measurement was taken at the point of the longest length of the fornix (the crus). Superiorly, medially and laterally the hippocampus was bounded by the cerebrospinal fluid (CSF) in the choroid fissure and the ambient cistern and inferiorly the hippocampus was bounded by the white matter separating it from the parahippocampal gyrus. This method excludes the tail of the hippocampus in order to achieve satisfactory reproducibility of segmentation, and has been documented elsewhere [62]. Mean intrarater (RS) variability for segmentation of this region was 3%.

3.2.1.2. The entorhinal cortex. Segmentation of the entorhinal cortex (EC) was undertaken using a protocol similar to that of Insausti et al. [23,24], which was based on cytoarchitectonic guidelines observed in the normal adult human brain. White matter was not in-

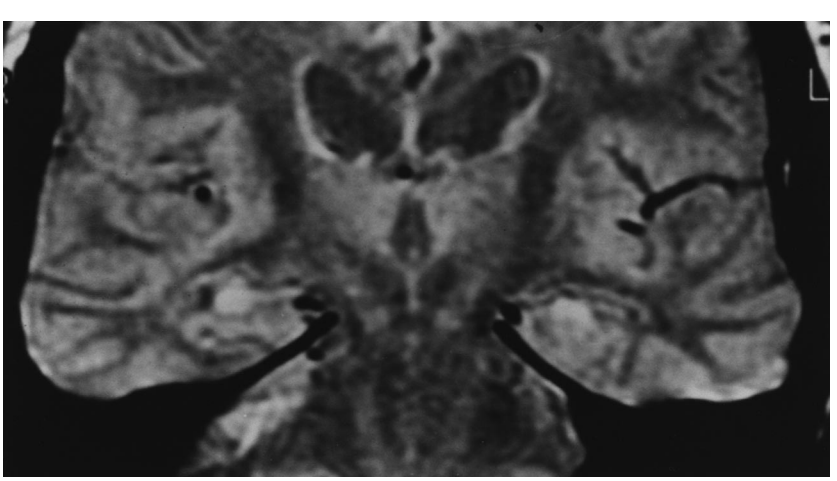

Fig. 1. Coronal sections through temporal lobe at the level of the body of the hippocampus. High signal return seen in each hippocampus (TR2000/TE30 ms and 5 mm thick).

Table 1
Volumetric MRI data on VC and six control subjects[a]

	Brain vol. (mm^3)	LHPC	RHPC	LENT	RENT	LPHG	RPHG	LTL	RTL	LSTG	RSTG	LMITG	RMITG	LFG	RFG
VC	1 056 528	0.124	0.134	0.041	0.047	0.263	0.292	5.478	5.928	1.826	2.000	2.034	1.935	0.434	0.568
No. of S.D. < CTR *X*	−0.96	−5.89	−4.16	−1.45	−0.18	−2.90	−0.96	−0.29	−0.38	0.87	1.45	−0.21	−0.98	0.30	1.60
Controls (CTR)															
C1	1 248 148	0.235	0.226	0.069	0.063	0.414	0.326	6.232	6.353	1.594	1.518	2.435	2.264	0.452	0.491
C2	1 054 070	0.244	0.273	0.051	0.054	0.341	0.495	4.970	6.233	1.362	1.696	1.805	2.296	0.272	0.418
C3	1 014 728	0.232	0.241	0.066	0.049	0.444	0.334	5.682	6.203	1.737	1.804	1.996	2.488	0.557	0.529
C4	1 198 406	0.263	0.257	0.038	0.030	0.338	0.339	5.720	6.045	1.646	1.701	2.238	2.437	0.379	0.500
C5	1 152 940	0.237	0.231	0.058	0.053	0.367	0.338	5.344	5.610	1.774	1.962	2.025	1.723	0.280	0.548
C6	1 275 186	0.204	0.200	0.062	0.045	0.367	0.317	5.649	5.782	1.891	1.908	1.988	2.056	0.461	0.491
Mean (*X*)	1 157 246	0.236	0.238	0.057	0.049	0.379	0.358	5.599	6.038	1.667	1.765	2.081	2.211	0.400	0.496
S.D.	104 730	0.019	0.025	0.011	0.011	0.040	0.069	0.421	0.287	0.182	0.162	0.221	0.283	0.112	0.045

[a] L, left; R, right; HPC, hippocampus; ENT, entorhinal cortex; PHG, parahippocampal gyrus; TL, temporal lobe; STG, superior temporal gyrus; MITG, middle and inferior temporal gyri; FG, fusiform gyrus. All volumes for the above regions are expressed as percentages of the total brain volume.

cluded within this measurement. Rostrally, the EC extended as far as the rostral extreme of the sulcus semiannularis and caudally the EC is found to end approximately 1mm beyond the end of the gyrus intralimbicus. However, for the purposes of reproducibility in this study the EC was not measured beyond the end of the gyrus intralimbicus. Superiorly, the EC was bounded by the white matter separating it from the amygdala (rostrally) and the hippocampus (caudally). Inferomedially, the EC was bounded by the CSF of the ambient cistern and laterally the EC extended as far as the collateral sulcus. As with Insausti et al. [24], the termination of the EC along the collateral sulcus was determined by the depth of the sulcus: if the sulcus depth was less than 1cm then the cytoarchitectonic border of the entorhinal and perirhinal cortices was located at the fundus; if the sulcus depth was between 1 and 1.5 cm then this border was found approximately halfway along the medial bank of the collateral sulcus; and if the sulcus depth was greater than 1.5cm then the border was located at the medial edge of the sulcus. Mean intra-rater (DC) variability for segmentation of this region was 4%.

3.2.1.3. The parahippocampal gyrus. A measurement was made of the parahippocampal gyrus corresponding to the rostrocaudal length of the hippocampus. This extended from the coronal section containing the most rostral part of the head of the hippocampus to the longest length of the fornix caudally. The white matter layer was included in the measurements. The superomedial border was the interface between the inferior boundary of the hippocampus and the white matter layer, and superolaterally the border was taken as the junction of the white matter layer with the inferior edge of the choroid fissure. Inferomedially the gyrus was bounded by the CSF of the ambient cistern and inferolaterally by the collateral sulcus. Mean intra-rater (RS) variability for segmentation of this region was 6%.

3.2.1.4. The temporal lobe. Segmentation of the whole temporal lobe was achieved by using the difference in signal intensity between the grey matter of the temporal lobe and the surrounding CSF. Satisfactory outlining of this region was produced by setting a minimum threshold of 60% of the mean brain intensity. At this setting it was ensured that no parts of the temporal lobe were incorrectly excluded. The boundary between the temporal lobe and the remainder of the brain was defined by drawing a straight line across the temporal stem. The lateral extreme of this line was taken as the junction of the superomedial base of the superior temporal gyrus and the inferomedial extreme of the sylvian fissure. A line was drawn from this point to the most superior point of the temporal lobe on the medial side of the stem. This point corresponded to the juxtaposition of the stem to the superomedial portion of the amygdala rostrally, and to the superomedial extreme of the hippocampus at more caudal levels. Mean intra-rater (RS) variability for segmentation of this region was 3%.

4. Results

Summary of the results are reported in Table 1.

4.1. The hippocampus

The longest length of the hippocampus in midsagittal section, from the rostralmost extent of the head to the body of the hippocampus caudally at the level of the crus of the fornix, measured 32.4 mm for the left hippocampus and 31.4 mm for the right hippocampus. Both measures were well below the controls range (normal controls: left mean 39.3 mm, range 36.2–41.2 mm; right mean 37.6 mm, range 33.6–40.6 mm) Striking loss of hippocampal volume was noted throughout the length (see Fig. 2a, VC; and Fig. 2b, healthy control). The morphology of the head was strikingly abnormal, with a sharp demarcation from the caudomedial amygdala and near total loss of the digitationes hippocampi. At this level the cross-sectional area is markedly reduced, suggesting damage to the CA1 field. Both the uncal sulcus and the temporal horn are particularly prominent (see Fig. 3a and b). More caudally, the portion of the hippocampus superior to the uncal sulcus is reduced in cross-sectional area, reflecting damage not only to CA1 but also to the CA3 and CA2 fields (and possibly also the dentate gyrus). Beyond the caudal end of the uncus, the morphology of the hippocampal body was less distorted but still reduced in cross-sectional area (see Fig. 4a and b). At this level the left fimbria was so reduced it was virtually absent and the width of the right fimbria was severely reduced. At the level of the crus of the fornix the hippocampal body was still of small cross-sectional area, but it was not possible to relate this reduction in area to specific damage within the different hippocampal subfields. Both left and right fornices are also noted to be reduced in size, which again represents the loss of efferent fibres from the hippocampal formation, although it must be noted that the fornix also contains afferent fibres from the medial septum to the hippocampus.

The reduction in volume across the rostrocaudal length of the hippocampus is illustrated in Fig. 5a and b. Of particular interest is the observation that the volume loss in cross-sectional area is seen along the entire length of both hippocampi.

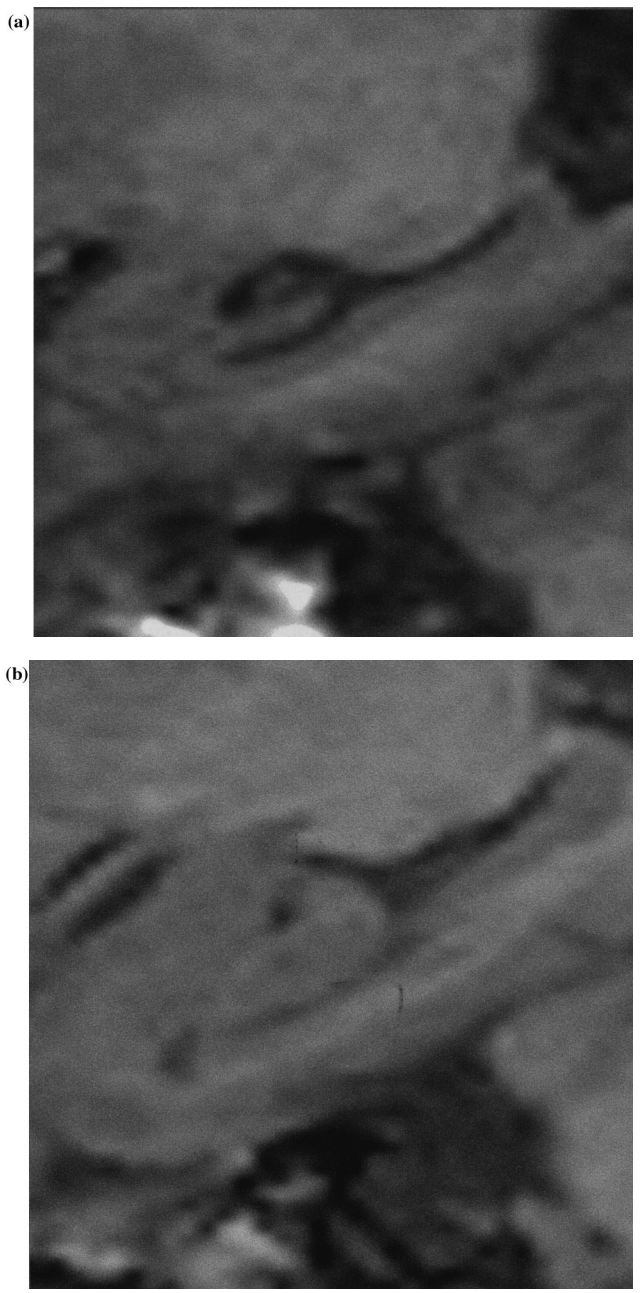

Fig. 2. Mid-sagittal sections through the left hippocampus of VC (a) and control subject (b) (T1-weighted MRI). In VC the uncal sulcus is prominent and there is a reduction in size along the entire length of the hippocampus.

4.2. The entorhinal cortex

There were no gross morphological abnormalities. In the case of VC, the greatest depth of the collateral sulcus was less than 1 cm and the border of the entorhinal cortex with the perirhinal cortex was therefore considered to be situated at the fundus of the collateral sulcus (see above). Of note is the fact that there was no widening of the collateral sulcus, and the thickness of the grey matter in this region appeared within normal limits (when compared with the control subjects), as did the length of the entorhinal cortex from its junction with the pre- and parasubiculum at its superomedial border to its inferolateral border with the perirhinal cortex. The volume of the left entorhinal cortex was less than 2 S.D. below the control mean and the volume of the right entorhinal cortex was less than 1 S.D. below the control mean. These measurements are provided in Table 1.

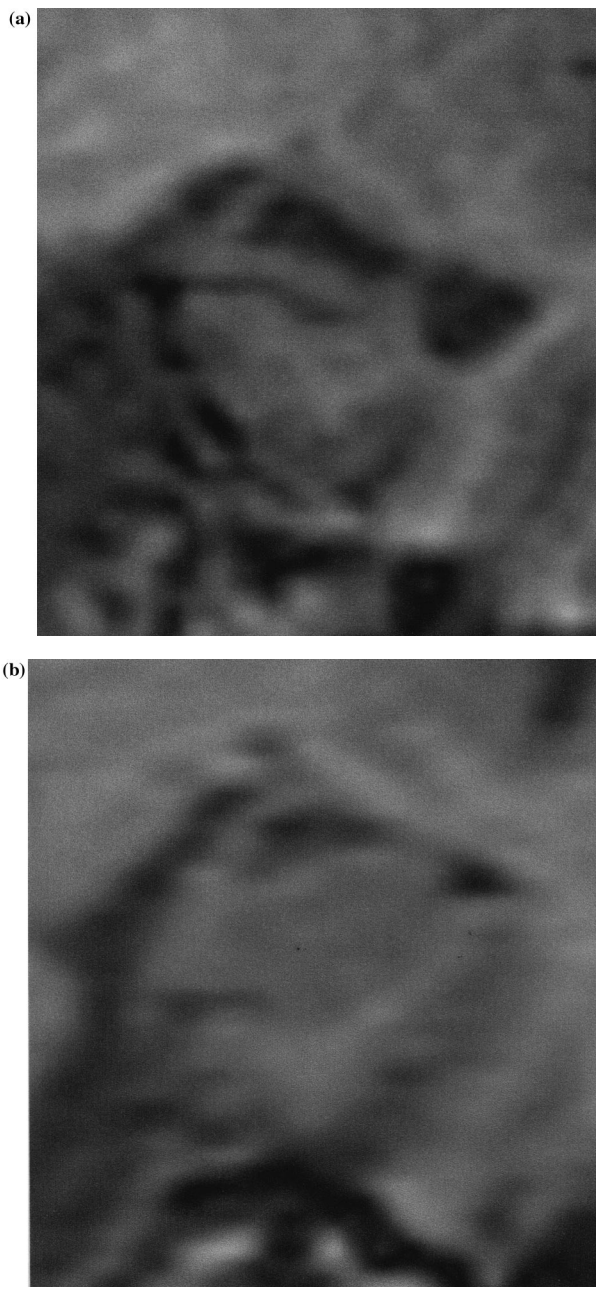

Fig. 3. Coronal sections through the head of the left hippocampus of VC (a) and the control subject (b) (T1-weighted MRI). In VC there is a near total destruction of the hippocampus (consisting primarily of the CA1 field) superior to the uncal sulcus.

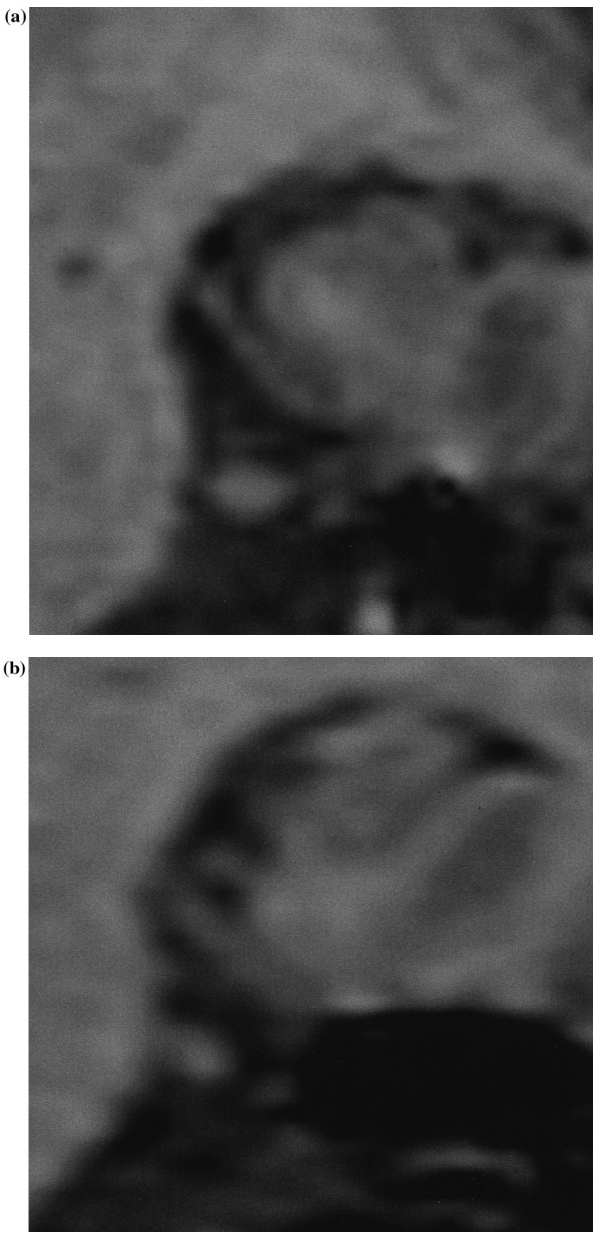

Fig. 4. Coronal section through the body of the left hippocampus of VC (a) and the control subject (b) (T1-weighted MRI). In VC there is a general reduction of cross-sectional area.

4.3. The parahippocampal gyrus

There were no obvious morphological abnormalities of the grey matter of the parahippocampal gyrus but the white matter layer was noted to be reduced in size, particularly at the rostral end of the gyrus, between the head of the hippocampus superiorly and the entorhinal cortex inferiorly. The depth of the collateral sulcus was within normal limits, as was the mediolateral length of the gyrus, from the white matter medial to the pre- and parasubiculum to the lateral border of the gyrus at the fundus of the collateral sulcus. The volume of the right parahippocampal gyrus was less than one SD below the control mean while the volume of the left parahippocampal gyrus was slightly reduced (between two-three SD below the control mean; see Table 1). This mild degree of volume loss was clearly much less than that noted for the hippocampi.

4.4. The temporal lobe

There were no gross morphological abnormalities. In particular, there was no thinning of the temporal stem, no flattening of the gyri, and no widening of the sulci. The absence of obvious structural abnormalities was reflected in the volumetric analyses of the temporal lobe. The volumes of both left and right lobes were within normal limits as were the volumes of the gyri when measured individually (see Table 1).

4.5. Neuropsychological assessment

The patient was first referred to the Neuropsychology Department of the National Hospital for Neurology and Neurosurgery in September 1993 for evaluation of his memory difficulties. The results of this first assessment, together with an experimental investigation focusing on his amnesia, are reported elsewhere [28]. He has subsequently been reassessed on three different occasions. The experimental investigation that will be described here took place around the time of his fourth and last neuropsychological assessment (April 1998). The results of his four formal neuropsychological assessments are reported in Table 2.

When first assessed on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) in September 1993 he obtained an average verbal IQ and a high average performance IQ. This reflected only a very mild underfunctioning of his verbal skills with respect to his estimated high average pre-morbid optimum on the National Adult Reading Test [48]. His nominal skills, as assessed by the Graded Difficulty Naming test for both objects were intact (GNT [41]). Similarly, his visuoperceptual and visuo spatial skills were well within normal limits (incomplete letters and cube analysis from the visual object and space perception battery (VOSP) [85]). He also performed within normal limits on two tests sensitive to frontal lobe dysfunction (Weigl sorting test [88], and the cognitive estimates test [61]). By contrast, his memory functions were severely impaired, with deficits both in anterograde memory, affecting both verbal and visual material, and in retrograde memory, affecting both personal and non-personal memories.

In the second and third assessments, his cognitive profile remained static, except for a steady improvement of his performance on the non-verbal part of the WAIS-R. However, it seems likely that this improved performance was due to well-known ‘practice effect’

artefacts. The most notable feature remained his severe memory impairment (see Table 3). By the time of his fourth neuropsychological assessment (April 1998) his verbal IQ continued to remain static in the upper end of the average range while his performance IQ had further improved and was at a very superior level. His performance on the GNT remained at a high average level and his performance on the object decision test of visuoperception remained at a normal level. On two tests of frontal 'executive' skills (Wisconsin card sorting [47]; Hayling test [6]) his performance was entirely satisfactory. In particular on the Wisconsin card sorting test he obtained the 6 categories rapidly and made no perseverative errors. His attention and concentration abilities were clearly completely intact. The most notable feature at this time remained his global amnesia.

In summary, VC presented with an intact performance on general intelligence, focal language, perception and frontal 'executive' tasks which remained static over a 5-year period. This indicated that there was no

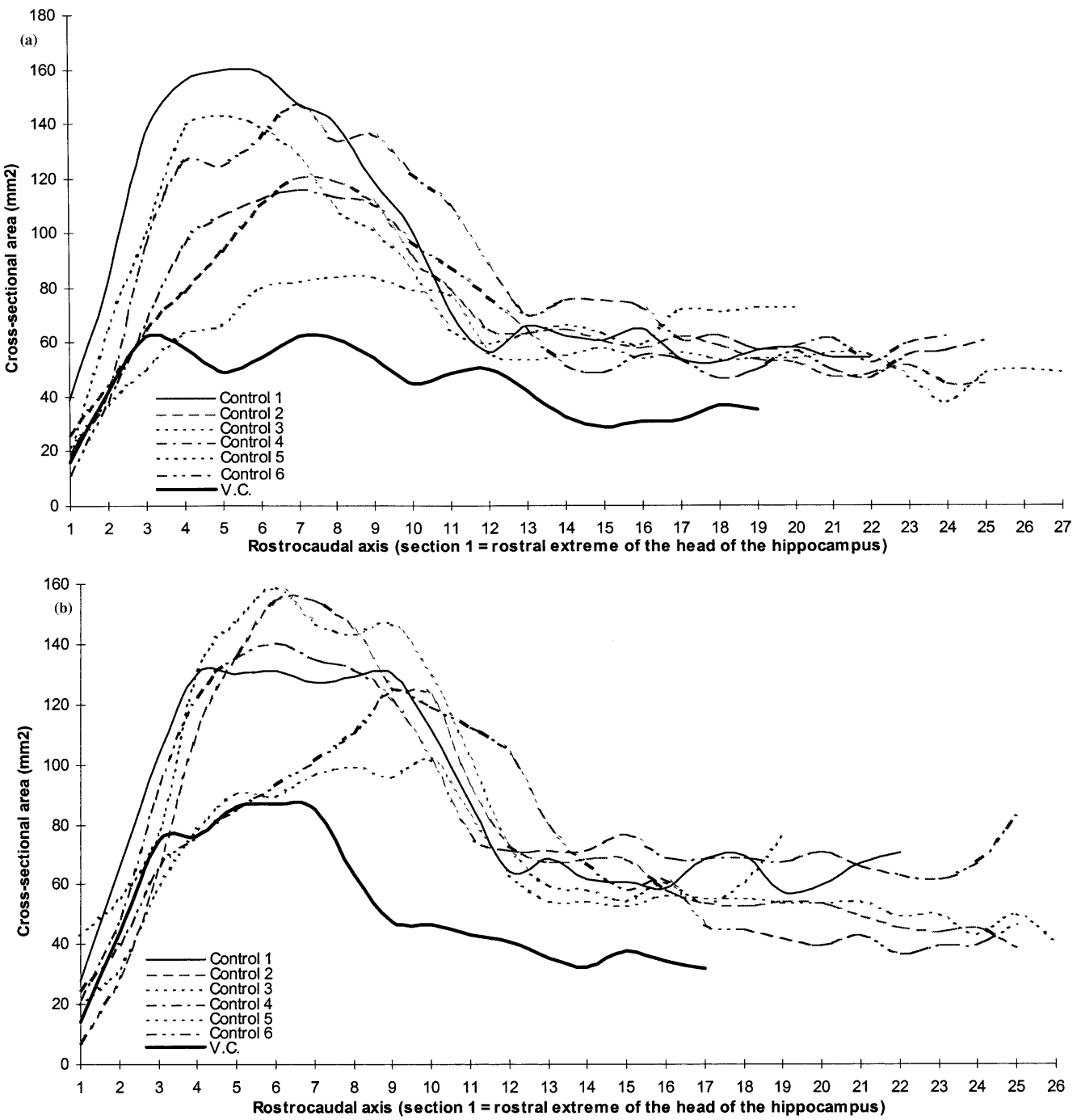

Fig. 5. Cross-sectional areas along the rostrocaudal length of left (a) and right (b) hippocampi.

Table 2
Cognitive test scores[a]

	March 93	March 96	Febuary 97	April 98
Verbal IQ	99	105	102	105
Performance IQ	111	120	136	141
GNT (O)	20/30 (25–50%ile)	17/30 (10–25%ile)	23/30 (75%ile)	23/30 (75%ile)
GNT (P)		n.t.	n.t.	20/30 (75%ile)
Incomplete letters	20/20	20/20	n.t.	n.t.
Cube analysis	10/10	10/10	n.t.	n.t.
Object decision	n.t.	18/20	17/20	17/20
Weigl	P	P	P	n.t.
Cognitive estimates	P	P	P	n.t.
Wisconsin card sorting	n.t.	n.t.	P	P
Hayling test	n.t.	n.t.	n.t.	17 (average)

[a] GNT (O), graded difficulty naming test — objects; GNT (P), graded difficulty naming test — proper nouns; %ile, percentile; n.t., not tested; P, passed.

Table 3
Anterograde memory test scores[a]

	March 93	March 96	Febuary 97	April 98
RMW	33/50 (<5%ile)	35/50 (5%ile)	35/50 (5%ile)	36/50 (<10%ile)
RMF	32/50 (<5%ile)	34/50 (<5%ile)	41/50 (25–50%ile)	39/50 (<25%ile)
TM	13/30 (<5%ile)	n.t.	14/30 (<5%ile)	13/30 (5%ile)
Famous faces	3/12 (<5%ile)	n.t.	3/12 (<5%ile)	3/12 (<5%ile)
Story recall				
Immediate	5 (<5%ile)	n.t.	n.t.	7.5 (<5%ile)
Delay	0	n.t	n.t.	0
List learning				18/95 (<5%ile)
Paired associates	n.t	n.t.	n.t	T1 = 4/24 (5%ile)
				T2 = 8/24 (5%ile)
Rey–Osterrieth figure				
Immediate	10/36 (<10%ile)	n.t.	n.t.	35/36 (90%ile)
Delay	0/36	n.t.	n.t	5/36 (<5%ile)
Door and peoples test				
Names test				
Immediate verbal recall				6/36 (<1%ile)
Delayed verbal recall				3/12
Verbal recognition test A				5/12 (<1%ile)
Verbal recognition test B				2/12 (<1%ile)
Doors visual recognition test				
Test A				7/12 (<1%ile)
Test B				1/12 (<1%ile)
Shapes test				
Immediate visual recall				13/36 (<1%ile)
Delayed visual recall				4/12

[a] RMW, recognition memory test for words; RMF, recognition memory test for faces; TM, topographical memory test; %ile, percentile; n.t., not tested.

progressive cognitive decline. An in depth assessment of his severe memory impairment is documented below.

4.6. Anterograde memory assessment: recognition and recall tests

Throughout the four neuropsychological investigations, VC was assessed on a variety of anterograde memory tests involving both recognition and recall paradigms (see Table 3). Verbal and visual recognition memory was assessed using alternative versions of the recognition memory test (RMT) [82] and on the topographical memory test of outdoor scenes recognition [83]. Verbal recall memory was assessed on the story recall and the list learning subtests of the adult memory and information processing battery [13] and on the

paired associates learning test [83]. Visual recall memory was assessed on the Rey–Osterreith complex figure [51] and on the current famous faces test. In addition, the doors and people test [4], which includes parallel recognition and recall based tests of verbal and non-verbal memory was administered at the time of his fourth neuropsychological assessment.

At the initial assessment (March 1993), his performance was globally impaired on recognition and recall memory tests. Through the second (March 1996) and third (February 1997) assessments only his verbal, visual recognition and visual recall memory were re-assessed. His verbal recognition memory, as assessed by the RMT, remained severely impaired whilst his performance had somewhat improved for visual recognition memory for unfamiliar faces. However, his visual recognition memory functions remained gravely impaired for outdoor scenes. Similarly, his visual recall memory for current famous faces remained profoundly impaired.

At the time of his fourth neuropsychological investigation (April 1998) it was clear that he remained severely amnesic. For example, he was never able to recognise the experimenters although he saw two of them (LC and PR) on several occasions for prolonged periods of time over a period of several years. It was noted, on one occasion, that when the experimenters left him alone for a few minutes, they were not recognised on their return. His amnesia was so severe that he was not able to recall even extremely poignant personal events. For example, the experimenters went to visit him at his home, very shortly after the funeral of his wife, with whom he had been happily married for 40 years. He had no recollection of her death nor of the funeral. Indeed, he asked on several occasions why she was not around the house.

A further formal reassessment of his memory functions was undertaken. His verbal and visual recognition memory skills remained severely impaired. He obtained a borderline defective score on the verbal version of the RMT and a low average score on the visual version. His somewhat improved performance on the RMT could have arisen through practice effects (Cipolotti et al., in preparation). On a further and more stringent visual recognition memory test (the topographical memory test) his performance remained gravely impaired. On the famous current faces test his score remained as gravely impaired as at the time of his first assessment. Interesting paramnesic errors were noted in this test. For example he named Clinton as 'Nixon… no… he followed Nixon… I think he is Kennedy' and he named Terry Wogan, an Irish TV personality, as 'Eamon Andrews', an Irish TV personality famous in the 60s. When asked to recall the Coughlan and Hollows' Story and the Rey–Osterreith figure, following a 30-min delay, he was unable to remember even being exposed to them. Similarly, his performance was very impaired on the list learning and the paired associated learning test. On the doors and people test [4], he did not achieve the cut-off for an overall age-scaled score of 1. Analysis of his performance on the various subtests revealed that he presented with a marked verbal and visual memory impairment. Interestingly, this grave impairment equally affected recognition and recall processes.

In summary, the results of the anterograde memory assessment indicate the presence of a severe global memory impairment affecting both recognition and recall which remained static over a 5-year period.

5. Experimental investigation

In the following experimental investigation we investigated VC's memory functions further. We assessed systematically the severity and the temporal extent of VC's retrograde memory using four different tests: the dead or alive test, the famous public events questionnaire test, the famous faces test, and the famous people names familiarity test. The status of VC's autobiographical memory and semantic knowledge in both the anterograde and the retrograde domains was also explored.

For the novel tests, groups of normal control subjects matched to VC on the basis of age and educational level were used. Different groups of control subjects are reported for the different tests. Their biographical details and performance will be reported below.

5.1. Retrograde memory

5.1.1. Experiment 1: dead or alive test

This test of retrograde memory [27] assesses memory for personalities who have been famous over the last 30 years. In this test the patient is required to indicate whether a famous personality was dead or alive, whether he/she had been killed or had died of natural causes and to indicate when the person died by choosing between eight time periods, sampling 4 years between 1950 and 1989. VC's performance was compared with that of the control subjects reported in the Kapur et al., [27] study. These controls were comparable to VC in terms of age and optimal level of pre-morbid functioning. VC performed extremely poorly on this test. His percentage of overall correct answers was only 47%, which is severely impaired relative to the controls. Thus, this result provides the first formal evidence that VC showed a marked memory loss for public events.

5.1.2. Experiment 2: famous public events questionnaire test (recall and three alternative forced choice)

Following the procedure used by Sanders and Warrington [56] a questionnaire test of famous public

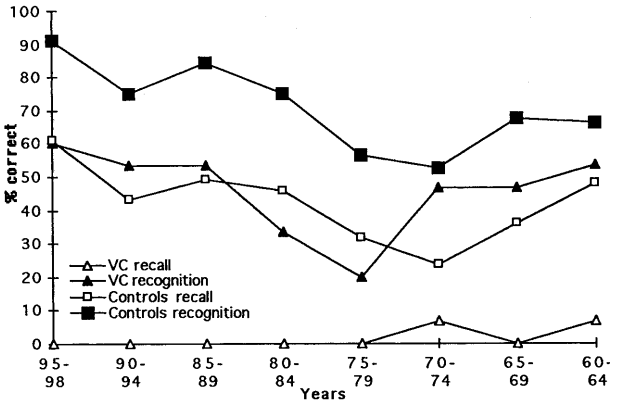

Fig. 6. Results on the famous public events questionnaire test.

events was constructed with the aim of matching the measurability of events at the time of their occurrence (for discussion of the importance of this procedure, see [38,60]). The test consisted of 120 questions about public events which were deemed to be of major importance. The Chronicle of the 20th Century 1995 and widely distributed British newspapers (Times, Daily Telegraph, Independent and the Guardian) were used as source of items. There were eight sets of 15 questions sampling events for each 5-year period between 1960 and 1998. The questions required a mixture of place names (e.g. Where in India was the chemical leak which killed 2000 and affected a further 200 000?), people's names (e.g. Which female tennis player was stabbed in the back by a rival's fan?) and a description of an event as the response (e.g. What caused the fire at York Minster?). The questions were matched as far as possible across the eight different time periods. For each time period an effort was made to choose questions judged to be most striking at the time of the event, this was subject to the constraint that in the case of the more remote events only those which were no longer discussed in public life were included. Thus, every attempt was made to avoid events subject to repeated review in the media, movies and books. For example, events such as the Watergate scandal were excluded. These types of event, being regularly re-discussed in the media, have effectively become part of general knowledge.

The test was first administered in a recall format (e.g. Where in India was the chemical leak which killed 2000 and affected a further 200 000?), and then immediately afterwards in a three-alternative multiple choice format. This consisted of the correct answers and two plausible alternative answers (e.g. Bhopal, Kanpur or Bombay?). Alternatives which were phonologically similar or related to another similar event were, for the most part, avoided. The patient was asked to choose the correct one, guessing if necessary. The questions were presented in a random order, with contemporary events mixed in with more remote events.

A normal control sample of 24 subjects, age (mean age = 67.31 years; S.D. = 4.56) and matched educationally (mean age left full time education = 17.2 years; S.D. = 3.3) were also given this test. The results for VC and the control subjects are shown in Fig. 6. This shows mean percentage correct for each 5-year period sampled.

VC's performance on the recall version of the test was at floor. He was virtually unable to recall any event from all the time periods sampled. On three alternative forced choice version of the test his performance was also markedly impaired. Indeed, his performance was at chance for two time periods (1980–84 and 1975–79) and only marginally above chance level for the remaining time periods.

For the purposes of statistical analyses the eight time periods were collapsed into four decades (1960s, 1970s, 1980s and 1990s). For the recall condition, raw scores were first converted using a square root transformation, because the distribution was skewed upwards with a long tail. As shown in Table 4(a) there was a significant difference between VC and the normal control group for recalling all four time periods.

Table 4
Famous public events questionnaire test: (a) recall and (b) multiple choice recognition

	VC percentage score (%)	Controls mean percentage score (%)	*Z*	*P*
(a) Comparison of square root transform of raw scores (/30) for VC and controls				
1960s	3.3	42	2.61	<0.005
1970s	3.3	28	1.97	<0.025
1980s	0	47	4.37	<0.001
1990s	3.3	53	3.31	<0.001
(b) Comparison of arcsin transform of raw scores (/30) for VC and controls				
1960s	50	67	1.03	<0.2
1970s	30	54	1.41	<0.08
1980s	43	81	2.98	<0.002
1990s	56	84	2.1	<0.02

For the three alternative forced choice condition, prior to analysis raw scores were converted using arcsin transform, as scores were distributed binomially. As shown in Table 4(b), there were significant differences between VC and the control group on the performance for the 1980s and 1990s. However, no statistical significance was found for the 1960s and 1970s. This may have been simply due to decreasing power of the tests for the later time periods. The controls were performing less well and thus the probability of finding a significant difference with VC was reduced. In this context, it should be noted that if one collapse together the 60s and 70s decades his performance did not significantly differ from chance. VC's performance was less than two standard deviations above chance for those two decades. In contrast, the performance of the controls for both decades was well above two standard deviations from chance.

The performance of the control subjects showed the expected superiority of the three alternative forced choice condition over the recall condition. Furthermore, there was a clear decline both on the three alternative forced choice and the recall versions of the test, as the questions referred to events that were more remote in time (see for similar results [87]). This was confirmed by a page test for ordered alternatives. This test was carried out on both recall and three alternative forced choice conditions for the normal controls scores. For both conditions significant trends were found, ($N = 24$, $K = 4$, recall $- ZL = 4.24$, $P < 0.001$, recognition $- ZL = 5.44$, $P < 0.001$), indicating that more recent events were more likely to be answered correctly than more remote events. This suggests that our selection criteria for the construction of the test were methodologically sound and the questions for the different time periods were balanced.

In summary, the performance of VC on the famous events questionnaire provides no evidence that more remote memories were spared or less impaired than more recent memories. The time span covered by this test antedates the onset of VC's amnesia by more than 30 years and post-dates the onset of VC's amnesia by ~ 5 years. Nonetheless, VC was grossly impaired in the more sensitive version of the test, i.e. the recalling of both very remote and very recent events. Thus, VC exhibited an equally severe anterograde and retrograde memory loss. The severe retrograde memory loss appears to cover a period of more than 30 years.

5.1.3. Experiment 3: famous faces test (recall and three alternative forced choice)

Using principles and techniques similar to those utilised for the public events questionnaire test, a retrograde memory test for famous faces was constructed. This test included 145 monochrome photographs of public figures, judged to be the most striking at a particular period of time. There were four sets of photographs sampling famous faces of four decades, between 1960 and 1998. In each decade there were the following number of photographs: 1960s = 31, 1970s = 32, 1980s = 43 and 1990s = 39. It would be inappropriate to attempt to limit faces to a 5-year period as is possible for events. The famous public figures where a mixture of British and American politicians (e.g. Clinton), actors, singers and TV personalities (e.g. Oprah Winfrey), sportsmen (e.g. the footballer Paul Gascoigne), and people associated with a famous event (e.g. Louise Woodward, recently involved in the death of a child). An effort was made to ensure that the different types of professions were as matched as possible across the four different time periods. As in the case of the 'remote' events only those famous personalities whose public life was no longer much discussed in the media, were included. Thus, for example photographs of someone like Jacqueline Kennedy–Onassis who rose to fame in the sixties but continued to remain so until the nineties were excluded. A pilot study on seven young people (mean age = 19.9 years; S.D. = 3.5) revealed that the chosen personalities of the 60s and 70s were unknown to them (0 for both decades). This confirmed that our chosen personalities were indeed famous only within that period.

As with the famous public events questionnaire test, there were two versions of the famous faces test: recall and three alternative forced choice. On the recall version VC was presented with each photograph and requested to orally name the famous person (e.g. William Hague, current leader of the UK Conservative Party). On the three alternative forced choice version each unrecalled famous face photograph was presented together with three multiple choice names (e.g. Which of the following is the name of the person? Michael Portillo, William Hague or Chris Patten?; all are well-known UK Conservative politicians). The alternatives were other names of famous people. The patient was asked to choose the correct one, guessing if necessary. The recall condition was tested first, followed immediately by the recognition condition, which was given while the patient was inspecting the photograph. The famous faces photographs belonging to different time periods were presented in a random order.

VC's performance was compared with that of 20 control subjects, age (mean age = 68.6 years; S.D. = 10.8) and educationally matched (mean age left full time education = 16.8 years; S.D. = 2.4). The results for VC and the control subjects are shown in Fig. 7. This shows the percentage correct for each decade sampled.

Similar results were obtained on the famous faces test as with the famous events questionnaire test. Thus, VC's performance was at floor in the recall version. He was virtually unable to recall any famous personality for all the time periods sampled. On the three alterna-

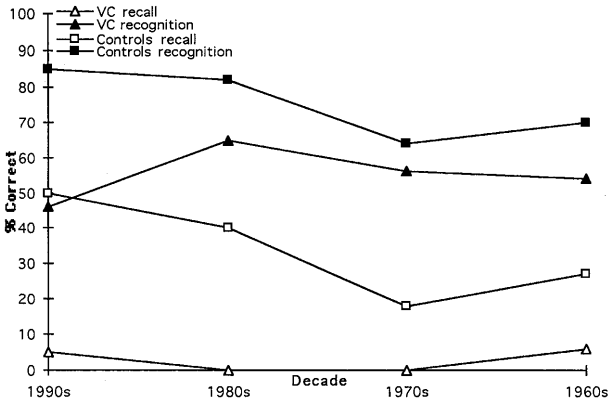

Fig. 7. Results on the famous faces test.

tive forced choice version of the test his performance was superior to his performance on the recall version. However, his performance in this condition, although above chance, was also impaired.

For the recall condition, raw scores were first converted using a square root transformation, as the control distribution was skewed upwards with a long tail. As shown in Table 5(a) there was a significant difference between VC and the normal control group for the recall of famous faces for all the four decades tested.

For the three alternative forced choice condition prior to analysis raw scores were first transformed using an arcsin transform, as scores were distributed binomially. As shown in Table 5(b) there was a significant difference between VC and the control group for the recognition performance in the 1990s and a strong trend in the 1980s result. However, no statistical difference was found for the other two decades.

Control subjects showed the expected decline in performance as the photographs were of people that were famous at an earlier period in time, both on the recall and on the three alternative forced choice version of the test. This was confirmed by a page test for ordered alternatives which demonstrated the expected decrement in performance with more remote faces. A significant trend was indeed found both for recall and three alternative forced choice conditions ($n = 4$, $k = 20$, recall $- ZL = 6.66$, $P < 0.001$, recognition $- ZL = 5.42$, $P < 0.001$).

In summary, these results replicated and extended those obtained in the previous task. VC has a profound memory impairment for recent and remote famous faces. In particular in the recall condition he was gravely impaired for items from his period of anterograde amnesia as well as for items from the three decades preceding his stroke. Thus, in the recall condition there was again a lack of evidence for the preservation of remote memories. This indicated that VC suffered from an extensive and ungraded retrograde amnesia. The three alternative forced choice condition will be considered further in the discussion.

5.1.4. Experiment 4: famous people names familiarity test

In experiments 1, 2, and 3 we demonstrated that when assessed with recall and alternative forced choice techniques VC had an extensive loss of retrograde memories involving both events and famous people. The aim of this experiment was to investigate whether VC might have implicitly retained retrograde memories by using a familiarity judgement test. Familiarity judgement tests have been shown to be performed within normal limits by some densely amnesic patients who presented with preserved implicit knowledge of public figures [89].

Four sets of 15 names of famous people were assembled; one set was of personalities who were prominent in the 60s; one set was of personalities who were prominent in the seventies; one set was of personalities who were prominent in the 80s and; one set was of personalities who were prominent in the 90s. As in the case of the 'remote' famous faces test only those names of famous people whose public life was no longer much discussed in the media were included. Each famous name was paired with two unknown distractors (e.g. Boris Chronnell, Paul Chenier, Konstantin Chernenko). In the list of three names (the target and the two distractors) the target name occurred equally often in each position. The triplets of names were presented in a

Table 5
Famous faces test: (a) recall and (b) multiple choice recognition

	VC percentage score (%)	Controls mean percentage score (%)	Z	P
(a) Comparison of square root transform of proportional scores for VC and controls				
1960s	6	27	1.98	<0.02
1970s	0	18	2.20	<0.01
1980s	0	40	4.19	<0.001
1990s	5	50	3.78	<0.001
(b) Comparison of arcsin transform of proportional scores for VC and controls				
1960s	54	70	1.10	<0.15
1970s	56	64	0.46	<0.4
1980s	65	82	1.41	<0.08
1990s	46	85	2.91	<0.002

Table 6
Famous people names familiarity test: comparison of arcsin transform of raw scores (/15) for VC and controls

	VC raw score	Controls mean raw score	Z	P
1960s	9	10.77	0.82	<0.21
1970s	10	12.03	0.98	<0.17
1980s	9	11.84	1.42	<0.08
1990s	6	10.42	1.61	<0.06

pseudorandom order with contemporary famous names alternating with more remote names. VC was told that in the list only one of the three names was famous. He was asked to indicate which was the most familiar name from the list of three names, guessing if necessary. After he chose the most familiar name he was requested to provide information that would allow the identification of the public personality.

A normal control sample of 31 subjects, age (mean age = 58.4 years; S.D. = 7.88) and matched educationally (mean age left full time education = 17.69 years; S.D. = 3.13) were also given this test. The results of VC and the control subjects for each decade sampled, are shown in Table 6.

For the purposes of the statistical analysis the raw scores were converted using an arcsin transform, as scores were distributed binomially. As shown in Table 6, there was no significant difference between VC's performance and the control performance over the four decades period. VC's scores were within normal limits in all four decades tested. Thus, these findings indicated that VC had retained some implicit knowledge of public figures despite the severe loss of explicit knowledge.

Table 7
Autobiographical memory performance

Autobiographical memory interview	No. correct	Comment
Autobiographical		
Childhood	1/9	Definitely abnormal
Early adult life	2/9	Definitely abnormal
Recent life	0/9	Definitely abnormal
Semantic		
Childhood	11/24	Definitely abnormal
Early adult life	15/24	Probably abnormal
Recent life	3/24	Definitely abnormal

Table 8
Pre-and post-morbid vocabulary scores

	VC	Controls mean (S.D.)
Vocabulary subtest score (WAIS-R)	12 (age-scaled score)	
New vocabulary test (recall)	4/20	14.9 (2.08)
New vocabulary test (recognition)	12/20	18.0 (1.15)

5.2. Autobiographical memory

5.2.1. Autobiographical memory interview

This test of autobiographical memory [32] requires the patient to generate information concerning three periods of his life (childhood, early adult life and recent life). For each time period, the patient is requested to recall both personal semantic knowledge (for example, 'What was your home address when attending high school?') as well as autobiographical episodes (for example, 'Describe an incident which occurred in the period when you were attending elementary school'). VC's scores are presented in Table 7.

Inspection of Table 7 demonstrates that VC was completely unable to recall autobiographical episodes from his recent life and almost completely unable to recall autobiographical episodes from childhood and early adult life. Although he was able to produce a few pieces of personal semantic knowledge (e.g. his address when starting school but his address has remained the same throughout his life), he scored in the abnormal range for all three periods of life. This shows that he had severe impairment of both autobiographical and personal semantic memory from his childhood, early adult life and recent life. Thus, in this task there was no indication of a temporal gradient in his recall of personal memories just as for the retrograde non personal memory tasks.

5.3. Retrograde and anterograde semantic memory

5.3.1. Pre-morbidly acquired vocabulary: WAIS-R vocabulary subtest

Knowledge of vocabulary from the retrograde period was evaluated from the vocabulary subtest of the WAIS-R. His age-scaled scores are reported in Table 8. VC's performance in this test was in the high average range. This indicates that VC's knowledge of semantic information from the pre-morbid periods is clearly intact. Thus, there is a remarkable contrast between VC's intact ability to store and retrieve old lexical-semantic knowledge and his severe and pervasive impairment in retrieving remote personal and non personal memories.

5.3.2. Post-morbidly acquired vocabulary: new vocabulary test

In order to assess VC's ability to acquire new vocabulary we selected 20 words (from the Oxford Dictionary of New Words) which had entered the British lexicon subsequent to his becoming amnesic. This dictionary includes the date of entry of words into the British lexicon. There were two conditions of testing: (a) recall — he was presented with a word and asked to define it and; (b) multiple-choice — the words that he was unable to correctly define were re-presented using an alternative multiple two-choice format. This consisted of the correct definition of the word and a plausible false definition (e.g. BSE — 'Is it an incurable brain condition in cattle that can cause neurological disorders and results in death?' or 'Does it stand for the British Society for Epilepsy?'). VC was asked to choose the correct one, or guess if necessary. Ten control subjects were also given this test (mean age = 57.8 years, S.D. = 10.42). VC's and controls' scores are given in Table 8.

VC performed extremely poorly both in the recall and in the multiple choice conditions by comparison with the performance of the control subjects. The good performance of the control subjects especially in the recognition version suggests that our new vocabulary test was relatively easy and therefore VC's severely impaired performance (recall 5.2 S.D.s below the normal mean; recognition 5.2 S.D.s below the normal mean) cannot be attributed to a task difficulty artefact. Thus, his inability to update his vocabulary reflects a remarkable degree of impairment in comparison with his excellent lexical-semantic knowledge from the premorbid period. In summary, VC was unable to acquire new semantic knowledge in the post-morbid period.

6. Discussion

The neuroanatomy of the different aspects of the amnesic syndrome is the subject of intense and extensive debate. In the Introduction we have argued that detailed analysis of neurological patients presenting with restricted lesions and severe memory impairments are of great theoretical interest. In this series of experiments we have reported our investigation of the profoundly globally amnesic patient VC, whose intellectual and cognitive skills were otherwise entirely satisfactory. In particular, we have focused on the retrograde component of his global memory impairment and on the status of his semantic fact learning skills. Detailed anatomical measurements were undertaken in an attempt to clarify the functional role of the hippocampus and related anatomical structures in these mnestic processes.

As far as the extent of VC's anatomical lesion is concerned the high resolution volumetric MR scans provided unequivocal evidence of damage to both hippocampi, with significant bilateral loss of volume and abnormal signal return. This volume loss was noted throughout the length of both hippocampi. The magnitude and distribution of loss makes it inevitable that the CA1 field sustained considerable damage. This is shown by the near-total loss of the digitationes hippocampi at the rostral end which contains only the CA1 field and also by the fact that the most severely affected portion of the hippocampus was the head in which CA1 is the predominant cell field. In addition, the outflow tracts of the CA1 fields to subcortical regions — the fimbriae — were reduced markedly in size. Damage to the CA3 field is suggested by the global reduction in the cross-sectional area of the hippocampus at more caudal levels, although the degree of pathological involvement of each subfield is difficult to quantify. Similarly, the loss of grey matter in the region between distal CA1 and the superomedial border of the entorhinal cortex strongly suggests damage to the subiculum and to the pre- and parasubiculum. However, at present methods for quantitative measurements of these areas are relatively unreliable.

Could lesions external to the hippocampus be playing a causal role in VC's amnesia? In this respect the entorhinal cortex is the most critical structure. The entorhinal cortex is the major supply of cortical afferents to the hippocampus and damage to this area has been associated with extensive RA [53]. Moreover, Reed and Squire [52] contrasted hippocampal patients with and without damage to the entorhinal cortex with respect to the length of their RA. However, in the case of VC the volume of this anatomical structure was in the normal range. The left parahippocampal gyrus was slightly reduced in volume (between 2 and 3 S.D. below the control mean). The right parahippocampal gyrus was less than 1 S.D. below the control mean. The difference between the two sides was not significant.

At present there is no reliable technique for quantitative analysis of the subdivisions of the parahippocampal gyrus other than the entorhinal cortex. However, it is estimated that a significant proportion of the decrease in parahippocampal gyrus volume in VC may be attributable to a reduction in the white matter, comprising the efferent fibres from the hippocampus (particularly CA1) to the cortical regions within the parahippocampal gyrus [5]. The efferents from CA1 to subcortical and cortical sites consist of collaterals arising from the primary axons that contribute to the fimbria [74,79]. Given the marked reduction in the size of the fimbriae in VC one would expect a concomitant diminution in the number of cortically-directed efferent fibres from CA1 which comprise in part the white matter layer of the parahippocampal gyrus. Qualitative analysis in this instance reveals that there is attenuation of the white matter bilaterally involving the portion of

the anterior parahippocampal gyrus that is subjacent to the head of the hippocampus and superior to the entorhinal cortex. In this context it is of note that the entorhinal cortex receives more inputs from CA1 than from the subiculum in the rat [75] and in the primate CA1 is found to provide the majority of the direct hippocampal projections to the parahippocampal gyrus, with a particularly strong projection to the anterior portion [5]. Some comments on other parahippocampal regions are also possible. The small fraction of the perirhinal cortex contained within the parahippocampal gyrus, namely the portion located at the fundus of the collateral sulcus, appeared qualitatively to be intact, as does the remainder of the perirhinal cortex. Finally, it is worth mentioning that areas TF and TH in the posterior parahippocampal gyrus are believed to represent visual association areas and there is little evidence linking these regions directly to mnemonic function.

In addition to the hippocampal damage, there was abnormal signal return from the left amygdala. This damage is unlikely to be of importance for three reasons. First, isolated lesions of the amygdala do not impair memory in lower primates [92]. Secondly, in man the resection for epilepsy of the amygdala, sparing the hippocampus, does not cause amnesia [59]. Thirdly, Cahill and colleagues [7] have previously demonstrated in a patient with Urbach–Wiethe disease that amygdala lesions impair the encoding of emotionally salient episodic memories (dealing with mutilation) but not those involved with more emotionally neutral material.

Some students of amnesia have argued that functional imaging studies may show more extensive abnormalities than anatomical sectional scans and therefore they can be considered a more reliable indicator of the extent of the damage. In our patient the resting ^{18}FDG PET scan showed less signal return from the right thalamus and possibly right parietal region. By contrast there was no sign of structural abnormality on the thalamus on the MRI. Functional imaging is not an anatomical parameter; it is, as the name implies, a functional variable. Once an anatomical abnormality had occurred at one point in a functional pathway areas downstream will also probably be abnormal. This does not mean that there are anatomical abnormalities downstream. Indeed the functional imaging abnormality is consistent with the variable superficial sensory impairment in his left limbs but does not indicate where the lesion is located. Moreover, even if the right thalamic abnormality on PET were to reflect a hidden structural lesion this could hardly account for the verbal memory impairment of VC. VC's impairment on the verbal memory domain was if anything worse than the visual memory domain (see [63,64] for relevant unilateral thalamic patients).

Turning to the nature of VC's memory impairment, our investigation on the retrograde component of VC's global amnesia revealed severe memory loss. On a test of retrograde memory [27] requiring him to indicate whether personalities who had been famous at some time over the last 30 years were dead or alive, he obtained a very poor score. However, not only was VC's retrograde amnesia severe it was also found to be extensive and ungraded. We have constructed two new retrograde memory tests which measured solely episodic memory retrieval at all time periods. On the questionnaire designed to probe recall and multiple choice recognition of famous public events, his scores were extremely poor. Of particular relevance is the finding that his scores remained equally poor over the four decades tested (1990s; 1980s; 1970s; and 1960s). On the recall version he was virtually unable to score at any decade. The multiple choice recognition version has less power for the earliest decades but his poor scores did not indicate any sparing for the most remote events. Similarly, on a task requiring him to recall and recognise photographs of famous personalities, his performance was very severely impaired. On the recall version of the test he was found again to be virtually unable to identify the famous faces across four decades. In the multiple choice recognition version again we obtained an extensive, 'flat' gradient of retrograde amnesia but problems with statistical sensitivity were greater at earlier decades because of the poorer performance of the controls. Nonetheless, there may have been a marginal saving of his face recognition performance for the 1960s and 1970s decades. However, his recall performance with this material, which was equally bad to that of Reed and Squire's [52] post-encephalitic patients, indicate that retrieval of face memory from the earlier decades is profoundly abnormal. Together with his even poorer performance on multiple choice recognition and recall of remote public events these results suggest that Ribot's law of forgetting claiming 'that the dissolution of memory is inversely related to the recency of the event' is not confirmed in our amnesic patient.

These findings have implications for those theories sharing the idea that the hippocampus has only a temporary role in memory storage and that ultimately the neocortex is responsible for long-term memory storage (e.g. for a review [65]). These theories, although different in detail, predict extensive and ungraded RA only when the damage is not restricted to the hippocampus but also involves temporal neocortex. However, VC had lesions which were principally confined to the hippocampus and yet showed extensive and ungraded RA. This suggests that the role of the hippocampus is not limited to the temporary consolidation of memory traces. On the position of Squire and colleagues, one has to assume that the recall performance of no more than 10% of that of normal controls and a public events recognition performance at chance

for the 1960s and 1970s decades results from hidden pathology in the temporal lobe.

The hidden pathology argument is of course a very popular [1]. The claim that cortical deficit resulting from hidden pathology would not show up on MRI or comprehensive cognitive testing is often based on the study of Markowitsch [35]. The authors reported an amnesic patient whose PET investigation revealed widespread regions of hypoactivity that, according to him, could not be predicted from the MRI scans. However, the MRI report on this patient refer to non specific cortical/subcortical atrophy, with widening of the lateral ventricle. Moreover, the patient, an office clerk, who had been in coma for 14 days, had a FIQ of 85 and showed other deficits on cognitive testing, for example performing very poorly on attention and concentration tests. By contrast, VC's MRI showed no atrophy compared with intact control subjects of his age, has not been in a coma and apart from the episodic memory abnormality his performance on a series of cognitive tests was in the expected average/high average range.

Instead our findings are much more easily explained on the view that the hippocampus provides a form of representation (or learning or processing) which is not available to the neocortex and that is critical for effective retrieval of both recent and remote episodic memories. According to this view and in keeping with our findings retrograde amnesia is not temporally graded following a hippocampal lesion, given appropriate testing for retrograde amnesia.

It is noteworthy that our patient was also incapable of autobiographical recollections. His performance on the AMI was very poor both for personal semantic memory and autobiographical memory. His very poor performance equally affected all the periods of his life spanning from very recent times to his childhood. These findings count against an idea suggested by Verfaellie and colleagues [81] and recently favoured by Reed and Squire [52] that '…learning of any kind, whether it be episodic or semantic, may be more impaired in amnesia when information was acquired recently rather than remotely…' (p. 451). Instead, our data implicates that the hippocampus is needed to retrieve autobiographical memories throughout life [46]. Thus, overall our findings indicate that retrieval of event memory requires the processing provided by the hippocampus.

It is also worth noting that despite VC's exceptionally severe retrograde deficit, there was evidence that his performance did not differ from that of the control group on a test designed to assess simple familiarity for famous people names. Using a variant of a multiple choice recognition memory test in which the names of famous people were paired with two unknown distractor items his performance was within normal limits for three decades (1960; 1970; 1980). Only for the 90s was his performance slightly worse than the controls. In this respect, his performance was similar to the post-encephalitic patient described by Warrington and McCarthy [86] who exhibited no deficit on this type of task. However, it should be noted that 4 further post-encephalitic patients, although presenting a somewhat improved performance in the familiarity for famous names test, were distinctively impaired [52,68]. Warrington and McCarthy [83] suggest that this type of familiarity judgement depends on lexical-semantic processes. In this case this would fit with these processes not involving the hippocampus.

Finally this study provides interesting results on the status of post-morbid semantic learning. VC's semantic knowledge from the post-morbid period is clearly abnormal. He demonstrated no post-morbid semantic acquisition on our tests of public knowledge both for famous events as well as for famous personalities. He was also unable to acquire new terms and novel concepts, despite having maintained excellent pre-morbid word knowledge. Evidence of no new vocabulary acquisition has been previously reported in long-standing amnesia [18,79]. However, our patient together with patient LJ reported by Reed and Squire [52], appear to be the only instances in which impaired vocabulary acquisition has been established following damage restricted to the hippocampal structure. This evidence suggests that new fact learning is impaired by hippocampal pathology. Recently Vargha-Kadhem et al. [80], in order to explain the relatively normal acquisition of semantic knowledge by three teenage amnesic patients who had suffered early hippocampal damage, stressed the role of the perirhinal and entorhinal cortices in the acquisition of new context-free semantic memories. It remains possible that the age at which damage to these systems occurs is a critical feature and thus, important factors such as developmental reorganisation must be considered.

Alternatively other authors have implicated sparing of the left and right inferolateral temporal cortices to account for the acquisition and storage of post-morbid semantic knowledge in amnesic patients [22,31]. In particular, the patient (RS) recently described by Kitchener et al. [31] was found to have acquired new information of rather limited amount about famous people, public events and new vocabulary during the 13-year period since he became amnesic. VC, despite normal left and right inferolateral temporal cortices, was unable to learn new semantic material. A critical difference may be that the patient of Kitchener et al. [31] suffered a much more asymmetrical lesion. The MRI showed multifocal limbic damage on the left involving the hippocampal complex, posterior thalamus and medial frontal lobe. In contrast the lesion in the right hemisphere was much more circumscribed. In particular only the posterior part of the right hippocampus was

involved. Perhaps the relative sparing of the remainder of the right hippocampus may be sufficient to allow the very limited semantic acquisition shown by their patient. Alternatively, the computational model of McClelland et al. [40] explicitly postulates that in the absence of a functioning hippocampal system the neocortex can learn (albeit slowly), in isolation, through repeated exposure to the information. Given the unspecified 'slow' interval of time necessary for such an isolated neocortex to learn it is possible that VC's 6-year post-morbid period was not of sufficient length. In contrast, the 13 year post-morbid period of the Kitchener et al. [30] patient might have allowed the slow learning of vocabulary and semantic facts. Only further re-assessment of our patient could serve to resolve this issue. Nevertheless, our findings emphasise the point that learning of new semantic factual knowledge does not accrue to normal levels in the face of hippocampal pathology.

In summary, our patient represents one of the first instances in the amnesia literature where the involvement of key anatomical structures was quantitatively verified and extensive and theoretically motivated cognitive tests have been carried out. We are aware that quantitative analysis of structural lesions cannot irrefutably eliminate the possibility of hidden cortical pathology. Nevertheless the best quantitative analysis so far available has failed to detect further anatomical lesions. Our findings suggest that retrograde amnesia both for personal and non-personal events can be both extensive and ungraded when the damage is limited to the hippocampus. Thus, these findings are not consistent with those theories claiming that the hippocampus plays a critical role only for the retention of events which have occurred relatively recently.

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References

[1] Aggleton JP, Brown MW. Episodic memory, amnesia and the hippocampal-anterior thalamic axis. Behavioral and Brain Sciences 1999;22:425–90

[2] Alvarez P, Squire LR. Memory consolidation and the medial temporal lobe: a simple network model. Proceedings of the National Academy of Sciences of the USA 1994;91:7041–5.

[3] Bachevalier J, Meunier M. Cerebral ischemia: are the memory deficits associated with hippocampal cell loss? Hippocampus 1996;6:553–60.

[4] Baddeley AD, Emslie H, Nimmo-Smith I. Doors and People. Bury St. Edmunds, UK: Thames Valley Test Company, 1994.

[5] Blatt GJ, Rosene DL. Organization of direct hippocampal efferent projections to the cerebral cortex of the Rhesus monkey: projections from CA1, prosubiculum, and subiculum to the temporal lobe. Journal of Comparative Neurology 1998;392:92–114.

[6] Burgess P, Shallice T. The Hayling sentence completion test. Neuropsychologia 1996;34:263–73.

[7] Cahill L, Babinsky R, Markowitsch H, McGaugh JL. The amygdala and emotional memory [letter]. Nature 1995;377:295–6.

[8] Cermak LS. The episodic-semantic distinction in amnesia. In: Squire LR, Butters N, editors. Neuropsychology of Memory. New York: Guilford, 1984.

[9] Cermak LS, O'Connor M. The anterograde and retrograde retrieval ability of a patient with amnesia due to encephalitis. Neuropsychologia 1983;21:213–34.

[10] Cohen NJ. Preserved learning capacity in amnesia: evidence for multiple memory systems. In: Butters NL, Squire L, editors. The Neuropsychology of Memory. New York: Guilford, 1984.

[11] Cohen NJ, Squire LR. Preserved learning and retention of pattern analyzing skill in amnesia: dissociation of knowing how and 'knowing that'. Science 1980;210:207–9.

[12] Cook MJ, Fish DR, Shorvon SD, Straughan K, Stevens JM. Hippocampal volumetric and morphometric studies in frontal and temporal lobe epilepsy. Brain 1992;115:1001–15.

[13] Coughlan AK, Hollows SE. The Adult Memory and Information Processing Battery. Leeds, UK: St. James's University Hospital, 1985.

[14] Damasio AR, Eslinger PJ, Damasio H, Van Hoesen GW. Multimodal amnesic syndrome following bilateral temporal and basal forebrain damage. Archives of Neurology 1985;42:252–9.

[15] Dimsdale H, Logue V, Piercy M. A case of persisting impairment of recent memory following right temporal lobectomy. Neuropsychologia 1964;1:287–98.

[16] Evans JJ, Breen EK, Antoun N, Hodges JR. Focal retrograde amnesia for autobiographical events following cerebral vasculitis: a connectionist account. Neurocase 1996;2:1–11.

[17] Freeborough PA, Woods RP, Fox NC. Accurate registration of serial 3D MR brain images and its application to visualizing change in neurodegenerative disorders. Journal of Computer Assisted Tomography 1996;20:1012–22.

[18] Gabrieli JDE, Cohen NJ, Corkin S. The impaired learning of semantic knowledge following bilateral medial temporal-lobe resection. Brain and Cognition 1988;7:157–77.

[19] Gaffan D. Recognition impaired and association intact in the memory of monkeys after transection of the fornix. Journal of Comparative and Physiological Psychology 1974;86:1100–9.

[20] Gaffan D, Lim C. Hippocampus and blood supply to TE: parahippocampal pial section impairs visual discrimination learning in monkeys. Experimental Brain Research 1991;87:227–31.

[21] Graham KS, Hodges JR. Differentiating the roles of the hippocampal complex and the neocortex in long term memory storage: evidence from the study of semantic dementia and Alzheimer's disease. Neuropsychology 1997;11:77–89.

[22] Hodges JR, Graham KS. A reversal of the temporal gradient for person knowledge: Implications for the neural organisation of long-term memory. Neuropsychologia 1998;36:803–25.

[23] Insausti R, Runon T, Sobreviela T, Insausti AM, Gonzalo LM. The human entorhinal cortex: a cytoarchitectonic analysis. Journal of Comparative Neurology 1995;355:171–98.

[24] Insausti R, Juottonen K, Soininen H. MR volumetric MRI analysis of the human entorhinal, perirhinal, and temporopolar cortices. American Journal of Neuroradiology 1998;19:659–71.

[25] Kapur N, Ellison D, Snith MP, McLellan DL, Burrows EH. Focal retrograde amnesia following bilateral temporal lobe pathology. Brain 1992;115:73–85.
[26] Kapur N. Focal retrograde amnesia in neurological disease: a critical review. Cortex 1993;29:217–34.
[27] Kapur N, Young A, Bateman D, Kennedy P. Focal retrograde amnesia: a long term clinical and neuropsychological follow-up. Cortex 1989;25:387–402.
[28] Kapur N, Thompson P, Kartsounis LD, Abbott P. Retrograde amnesia: clinical and methodological caveats. Neuropsychologia 1999;37:27–30.
[29] Kartsounis LD, Rudge P, Stevens JM. Bilateral lesions of CA1 and CA2 fields of the hippocampus are sufficient to cause a severe amnesic syndrome in humans. Journal of Neurology, Neurosurgery and Psychiatry 1995;59:95–8.
[30] Kinsbourne M, Wood F. Short-term memory processes and the amnesic syndrome. In: Deutsch D, Deutsch JA, editors. Short-term Memory. New York: Academic Press, 1975.
[31] Kitchener EG, Hodges JR, McCarthy RA. Acquisition of post-morbid vocabulary and semantic facts in the absence of episodic memory. Brain 1998;121:1313–27.
[32] Kopelman MD, Wilson BA, Baddeley AD. The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. Journal of Clinical and Experimental Neuropsychology 1989;11:724–44.
[33] Mair WGP, Warrington EK, Weiskrantz L. Neuropathological and psychological examination of two patients with Korsakoff's psychosis. Brain 1979;102:749–83.
[34] Markowitsch HJ, Calabrese P, Haupts M, Durwen HF, Liess J, Gehlen W. Searching for the anatomical basis of retrograde amnesia. Journal of Clinical and Experimental Neuropsychology 1993;15:947–76.
[35] Markowitsch HJ, Weber-Luxemburger G, Ewald K, Kessler J, Heiss W-D. Patients with heart attacks are not valid models for medial temporal lobe amnesia. A neuropsychological and FDG-PET study with consequences for memory research. European Journal of Neurology 1997;4:178–84.
[36] Marr D. Simple memory: a theory for archicortex. Philosopichal Transactions of the Royal Society of London, Series B 1971;262:23–81.
[37] McCarthy RA, Warrington EK. Evidence for modality-specific meaning systems in the brain. Nature 1988;334:428–30.
[38] McCarthy RA, Warrington EK. Cognitive Neuropsychology. New York: Academic Press, 1990.
[39] McClelland JL, McNaughton BL, O'Reilly RC, Nadel L. Complementary roles of hippocampus and neocortex in learning and memory. Society for Neuroscience Abstracts 1992;18:1216.
[40] McClelland JL, McNaughton BL, O'Reilly RC. Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. Psychological Review 1995;102:419–57.
[41] McKenna P, Warrington EK. Testing for nominal dysphasia. Journal of Neurology, Neurosurgery and Psychiatry 1980;43:781–8.
[42] Milner B. Amnesia following operation on the temporal lobe. In: Whitty CWM, Zangwill OL, editors. Amnesia. Cambridge, MA: MIT Press, 1966.
[43] Milner B. Disorders of learning and memory after temporal lobe lesions in man. Clinical Neurosurgery 1972;19:421–46.
[44] Murre JMJ. Categorization and Learning in Modular Neural Networks. Hillsdale, NJ: Lawrence Erlbaum, 1992.
[45] Murre JMJ. TraceLink: a model of amnesia and consolidation memory. Hippocampus 1996;6:675–84.
[46] Nadel L, Moscovitch M. Memory consolidation, retrograde amnesia and the hippocampal complex [review]. Current Opinion in Neurobiology 1997;7:217–27.
[47] Nelson HE. A modified card sorting test sensitive to frontal lobe defects. Cortex 1976;12:313–24.
[48] Nelson HE. National Adult Reading Test, 2nd edn. Windsor, UK: NFER-Nelson Publishing Co. Ltd., 1991.
[49] O'Keefe J, Nadel L. The Hippocampus as a Cognitive Map. Oxford, UK: Clarendon Press, 1978.
[50] Olton D, Becker J, Handelmann GE. Hippocampus, space, and memory. Behavioural and Brain Sciences 1979;2:313–65.
[51] Osterreith PA. Le test de copie d'une figure complexe. Archives de Psychologie 1944;30:206–356.
[52] Reed JM, Squire LR. Retrograde amnesia for facts and events: findings from four new cases. Journal of Neuroscience 1998;18:3943–54.
[53] Rempel-Clower NL, Zola S, Squire LR, Amaral DG. Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. Journal of Neuroscience 1996;16:5233–55.
[54] Ribot TA. Les Maladies de la Memoire. Paris: Germer Baillere, 1881.
[55] Russell WR, Nathan PW. Traumatic amnesia. Brain 1946;69:280–300.
[56] Sanders HI, Warrington EK. Memory for remote events in amnesic patients. Brain 1971;94:661–8.
[57] Schacter DL, Tulving E. Amnesia and memory research. In: Cermak LS, editor. Human Memory and Amnesia. Hillsdale, NJ: Lawrence Erlbaum, 1982.
[58] Schmidtke K, Vollmer H. Retrograde amnesia: a study of its relation to anterograde amnesia and semantic memory deficits. Neuropsychologia 1997;35:505–18.
[59] Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. Journal of Neurology, Neurosurgery and Psychiatry 1957;20:11–21.
[60] Shallice T. From Neuropsychology to Mental Structure. New York: Cambridge University Press, 1988.
[61] Shallice T, Evans ME. The involvement of the frontal lobes in cognitive estimation. Cortex 1978;14:294–303.
[62] Soininen H, Partanen K, Pitkanen A. Volumetric MRI analysis of the amygdala and the hippocampus in subjects with age-associated memory impairment: correlation to visual and verbal memory. Neurology 1994;44:1660–8.
[63] Speedie LJ, Heilman KM. Amnesic disturbance following infarction of the left dorsomedial nucleus of the thalamus. Neuropsychologia 1982;20:597–604.
[64] Speedie LJ, Heilman KM. Anterograde memory deficits for visuospatial material after infarction of the right thalamus. Archives of Neurology, Chicago 1983;40:183–6.
[65] Squire LR. Memory and Brain. New York: Oxford University Press, 1987.
[66] Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychological Review 1992;99:195–231.
[67] Squire LR, Alvarez P. Retrograde amnesia and memory consolidation: a neurobiological perspective. Current Opinion in Neurobiology 1995;5:169–77.
[68] Squire LR, Cohen NJ. Memory and amnesia: resistance to disruption develops for years after learning. Behavioral and Neural Biology 1975;25:115–25.
[69] Squire LR, Cohen NJ, Nadel L. The medial temporal region and memory consolidation: a new hypothesis. In: Weingartner H, Parker E, editors. Memory Consolidation. Hillsdale, NJ: Lawrence Erlbaum, 1984:185–210.
[70] Squire LR, Haist F, Shimamura AP. The neurology of memory: quantitative assessment of retrograde amnesia in two groups of amnesic patients. Journal of Neuroscience 1989;9:828–39.
[71] Squire LR, Amaral DG, Press GA. Magnetic resonance measurements of hippocampal formation and mammillary nuclei distinguish medial temporal lobe and diencephalic amnesia. Journal of Neuroscience 1990;10:3106–17.

[72] Squire LR, Ojemann JG, Miezin FM, Petersen SE, Videen TO, Raichle ME. Activation of the hippocampus in normal humans: a functional anatomical study of memory. Proceeding of the National Academy of Sciences of the USA 1992;89:1837–41.
[73] Stracciari A, Ghidoni E, Guarino M, Poletti M, Pazzaglia P. Post-traumatic retrograde amnesia with selective impairment of autobiographical memory. Cortex 1994;30:459–68.
[74] Swanson LW, Sawchencko PE, Cowan WM. Evidence for collateral projections by neurons in Ammon's horn, the dentate gyrus, and the subiculum: a multiple retrograde labelling study in the rat. Journal of Neuroscience 1981;1:548–59.
[75] Tamamaki N, Nojyo Y. Preservation of topography in the connections between the subiculum, field CA1, and the entorhinal cortex. Journal of Comparative Neurology 1995;353:379–90.
[76] Treves A, Rolls ET. Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. Hippocampus 1992;2:189–99.
[77] Treves A, Rolls ET. Computational analysis of the role of the hippocampus in memory. Hippocampus 1994;4:374–91.
[78] Tulving E, Schacter DL, McLachlan DR, Moscovitch M. Priming of semantic autobiographical knowledge: a case study of retrograde amnesia. Brain 1988;8:3–20.
[79] Van Groen T, Wyss JM. Extrinsic projections from area CA1 of the rat hippocampus: olfactory, cortical, subcortical, and bilateral hippocampal formation projections. Journal of Comparative Neurology 1990;302:515–28.
[80] Vargha-Kadhem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M. Differential effects of early hippocampal pathology on episodic and semantic memory. Science 1997;277:376–80.
[81] Verfaellie M, Reiss L, Roth HL. Knowledge of New English vocabulary in amnesia: an examination of premorbidly acquired semantic memory. Journal of International Neuropsychological Society 1995;1:443–53.
[82] Warrington EK. Recognition Memory Test. Windsor, UK: NFER Nelson Publishing Co. Ltd., 1984.
[83] Warrington EK. Studies of retrograde memory: a long-term view. Proceedings of the National Academy of Sciences of the USA 1996;93:13523–6.
[84] Warrington EK, Duchen LW. A re-appraisal of a case of persistent global amnesia following right temporal lobectomy: a clinico-pathological study. Neuropsychologia 1992;30:437–50.
[85] Warrington EK, James M. The Visual Object and Space Perception Battery. Bury St. Edmunds, UK: Thames Valley Test Company, 1991.
[86] Warrington EK, McCarthy RA. The fractionation of retrograde amnesia. Brain and Cognition 1988;7:184–200.
[87] Warrington EK, Sanders HI. The fate of old memories. Quarterly Journal of Experimental Psychology 1971;23:432–42.
[88] Weigl E. On the psychology of so-called processes of abstraction. Journal of Abnormal and Social Psychology 1941;36:3–33.
[89] Weiskrantz L. On issues and theories of the human amnesic syndrome. In: Weinberger NM, McGaugh JL, Lynch G, editors. Memory Systems of the Brain. New York: Guilford Press, 1985.
[90] Whitty CWM, Zangwill OL. Amnesia: Clinical, Psychological and Medicolegal Aspects, 2nd edn. London: Butterworth, 1977.
[91] Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CAI of the hippocampus. Journal of Neuroscience 1986;6:2950–67.
[92] Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. Journal of Neuroscience 1989;9:4355–70.