

Sparing of the familiarity component of recognition memory in a patient with hippocampal pathology

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Abstract

Subject KN has a persistent anterograde amnesia as a result of brain injury following meningitis in 1993. MRI scans reveal a bilateral decrease in the volume of his hippocampal region (dentate gyrus, CA1–4, subicular cortices) of approximately 45% in both the right and left hemispheres, although the volume of his perirhinal cortex appears normal. Aside from some changes to his occipital lobe and bilateral shrinkage of the amygdala, the rest of his brain appears normal on recent quantitative MRI scans. A striking feature of his memory loss is his ability to perform at normal levels on some tests of recognition, despite his consistent deficit on tests of recall. Two tests designed specifically to distinguish performance of two putative divisions of recognition memory (the Remember/Know procedure and the use of receiver operating characteristics to distinguish familiarity and recollection), provide evidence for a selective sparing of the familiarity component of recognition. The dissociation within recognition memory supports dual-process models of recognition, and also supports proposals that anatomically linked regions within the medial temporal lobe make qualitatively different contributions to recognition.

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1. Introduction

In recent years two opposing views have emerged concerning the relative importance of the hippocampus for recognition memory and for the recall of episodic information. One proposal is that the hippocampus is just as essential for recognition as it is for recall. This view arises from the notion that both aspects of memory are intrinsic components of the same class of memory (Knowlton & Squire, 1995). A second proposal is that the hippocampus is only essential for recollective aspects of recognition (Aggleton & Shaw, 1996; O'Reilly, Norman, & McClelland, 1998; Yonelinas et al., 2002). This second view can be traced back to dual-

process models of recognition memory (Mandler, 1980), and assumes that recognition is composed of two kinds of memory. One kind reflects a feeling of familiarity (sometimes called 'knowing') while the other reflects the actual recollection of events associated with the previously encountered stimulus (sometimes called 'remembering') (Gardiner, 1988; Yonelinas, 2002). It is supposed that each of these two forms of memory depend on one or more processes unique to it (Yonelinas, 2002). This second view predicts that patients with selective hippocampal pathology can still use their intact familiarity information to guide recognition and so show a relative sparing on many tests of recognition (Aggleton & Brown, 1999).

As the two proposals make very different predictions concerning the outcome of bilateral hippocampal pathology in humans this debate should be relatively straightforward to

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resolve. This has not, however, been the case. One major problem is that a likely source of familiarity information is the perirhinal cortex (Brown & Aggleton, 2001; Meunier, Bachevalier, Mishkin, & Murray, 1993; Murray & Richmond, 2001), which is subadjacent to the hippocampus. For this reason, lesion locus and extent become critical features in any test of these two different views. As a consequence, the most informative cases are those in which the pathology is both restricted to the hippocampus and sufficient to disrupt recall.

Most of the clinical evidence concerning this debate comes from the memory loss associated with hypoxic-induced hippocampal damage. The data on this condition are not, however, consistent. In one series of studies, Squire and his colleagues have repeatedly reported that recall and recognition are equivalently disrupted by hippocampal pathology following hypoxia (Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Manns & Squire, 1999; Reed & Squire, 1997; Stark, Bayley, & Squire, 2002). This series includes three hypoxic cases where post-mortem evidence has confirmed that cell loss is largely confined to the hippocampal formation (Reed, Hamann, Stedanacci, & Squire, 1997). For surviving patients MRI has been used to reveal bilateral hippocampal shrinkage of between 10 and 46% (Manns et al., 2003; Stark et al., 2002), while the parahippocampal gyrus volume is within normal limits ($\pm 15\%$). These cases, who are amnesic, are impaired on a variety of recognition memory tests at levels that seem comparable to their recall deficits (Manns & Squire, 1997; Manns et al., 2003; Reed et al., 1997). Of especial relevance is the report that six hypoxic patients with pathology thought to be primarily limited to the hippocampus, as determined by MRI, fail to show a preservation of familiarity when it is assessed by introspective judgements of 'remember' or 'know' responses in a yes/no recognition task (Manns et al., 2003). The authors conclude that the hippocampus is important for both recollection and familiarity (Manns et al., 2003).

Contradictory findings have, however, come from different cohorts of cases with hypoxic-induced pathology (Turriziana, Fadda, Caltragrione, & Carlesimo, 2004; Yonelinas et al., 2002). Here, recall is more disrupted than recognition. In addition, tests on a subgroup of hypoxic cases by Yonelinas et al. (2002) found impaired recollective aspects of recognition while familiarity-based responses appeared intact. Furthermore, analysis of recall and recognition performance in 56 hypoxic cases using covariance structural modelling found that the best fit for the data involved dual, independent processes within recognition, and that a single factor explanation for recall and recognition was insufficient (Quamme, Yonelinas, Widaman, Kroll, & Sauvé, 2004). Related to these findings are studies of people who suffered hippocampal damage at a young age, again due to hypoxia. These cases of 'developmental amnesia' can also show a relative sparing of recognition (Vargha-Khadem et al., 1997), which has been most detailed in the case Jon (Baddeley, Vargha-Khadem, & Mishkin, 2001). Unfortunately, attempts to compare levels of 'remember' or 'know' responses in Jon have proved problematic as he does not seem to have a typical con-

cept of what constitutes 'remember' (Baddeley et al., 2001). It has also been suggested that the early age of hippocampal pathology in cases like Jon could lead to compensation during development (Manns & Squire, 1999).

The apparent lack of consistency between studies of hypoxia, coupled with an unresolved debate over whether hypoxia might induce more generalised neural dysfunction (Bachevalier & Meunier, 1996; Caine & Watson, 2002; but see Squire & Zola, 1996), underlines the need for neuropsychological data from other causes of restricted hippocampal pathology. For these reasons case YR is especially interesting as she has an estimated bilateral volume decrease of 46% in her hippocampi while her entorhinal and perirhinal cortices appear intact and are of normal volume (Holdstock et al., 2002; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002). While her recall performance is consistently impaired, her recognition scores across a wide array of tasks are markedly better and usually fall in the normal range (Holdstock et al., 2002; Mayes et al., 2002). Thus, of 43 item recognition tests, on only four tests did her scores fall more than 1.96 S.D. below the mean score of her control group. This pattern of results has been interpreted as reflecting a sparing of familiarity memory, a view that receives some support from the 'Remember/Know' procedure (Holdstock et al., 2002). Although the onset of YR's amnesia coincided with the administration of an opiate drug, which may have led to an ischemic incident, there is some uncertainty about the precise aetiology of her pathology.

The present study concerns a man (KN) who suffered temporal lobe damage as a result of meningitis. This pathology occurred in 1993 when KN was 34. His MRI scans show evidence of bilateral hippocampal pathology while much of the remainder of his temporal lobes appear normal. The most obvious cognitive consequence of his pathology is severe anterograde amnesia, although he is able to learn and retain some new semantic knowledge (McKenna & Gerhand, 2002). As KN provides a rare opportunity to test the two opposing views concerning the effects of hippocampal pathology on recognition, the first goal was to compare more formally his performance on tests of recall and recognition. The second goal was to measure his performance on tests specifically designed to distinguish the putative 'recollective' and 'familiarity' components of recognition memory (Yonelinas & Kroll, 1998). In parallel with these cognitive tests we sought to quantify more precisely the locus and extent of his medial temporal lobe pathology. In describing his pathology, the term 'hippocampal region' is used throughout this text to refer to the dentate gyrus, hippocampal fields CA1–4, and the subicular cortices.

2. Methods

2.1. Participants

Approval for this study was provided by a Multi-Centre Research Ethics Committee (MREC). All partici-

pants gave their informed consent prior to inclusion in the study.

2.1.1. Case KN

Patient KN was an industrial biochemist who contracted meningoencephalitis at the age of 34, resulting in spinal cord damage and recurrent meningitis in July 1993. A lumbar puncture revealed the presence of group AB haemolytic streptococcus. Spinal cord damage in the regions D7–D9 has left him confined to a wheelchair. He does not have useful motor functions below T12. Although his IQ appears intact, his most obvious problem is a failure to learn new episodic information. For this reason he has been unable to resume work as a biochemist. Repeat testing indicates that the severity of his memory problems has now stabilised. In addition to his very clear memory problems, KN has suffered a loss of vision in the lower visual field. These visual problems are assumed to reflect the occipital lobe damage he sustained as a result of his illness.

KN complained of ‘tunnel vision’ which was worse inferiorly. He had worn spectacles since the age of approximately 25 years and did not experience any problems with his central vision. He had been diagnosed as diabetic 3–4 years previously and was receiving oral hypoglycaemics. Recent testing (7/2004) showed that his visual acuity with suitable corrective lenses in the right eye was 6/6- and in the left eye 6/5. Colour vision was essentially normal in each eye with The City University Colour Vision Test (2nd Edition, 1980) (Keeler Ltd., London, England) although each eye manifested a Tritan i.e., blue-yellow, abnormality to one plate, 9. Ocular motility was normal and the patient exhibited binocular vision. The visual field out to 30° eccentricity examined with the Humphrey Field Analyzer 750 (Carl Zeiss Meditec, Dublin CA) using Program 30-2 and the SITA Standard algorithm manifested a congruous absolute inferior altitudinal hemianopia in each eye together with some relative loss extending nasally over the horizontal midline. The pattern of visual field loss was indicative of an occipital lobe lesion. The anterior segments were normal and the ocular media clear in both eyes. The ocular fundi exhibited some tiny crystalline-like deposits scattered across the posterior poles. Both discs were pale. The intra-ocular pressure was 17 mmHg in the right and 18 mmHg in the left. Pupil responses, although sluggish, were normal.

2.1.2. Control subjects

A control group was used for those memory tasks for which the existing control data may be inappropriate (e.g., not age or IQ matched). The Control subjects consisted of seven biochemists/neurochemists who work at Cardiff University. The mean age of the controls was 46 years 3 months (ranging from 41 years 1 month to 53 years 11 months), while KN was 44–45 years old at the time of testing. The mean VIQ of the Controls predicted from performance on Wechsler Test of Adult Reading (Wechsler, 2001) was 114 ± 1.46 . The corresponding score for KN was 113.

2.2. MRI assessments of neuropathology

2.2.1. Previous MRI scans

Patient KN had a series of CT and MRI scans (1993, 1999, 2003). The last of these scans was specifically commissioned to permit direct comparisons with volume estimates from appropriate controls who had been scanned in the same machine with the same protocols. The first clinical scans after his meningitis (1993, CT and MRI) indicated changes to both white and grey matter in the right occipital region, suggestive of ischemic damage. Inspection of T1 and T2 images from his MRI scans in 1999 revealed bilateral abnormalities in the both grey and white matter of his occipital lobes, which were more evident in the right hemisphere. Although possible abnormalities in the left basal ganglia were reported in 1993, these were not evident on later scans. The MRI scans did, however, indicate an appreciable decrease in the volume of his left and right hippocampal region. The extent of this decrease could not be accurately measured without control data from scans using identical protocols. To rectify this shortcoming a new series of quantitative MRI scans were conducted in 2003.

2.2.2. New MRI scans (2003)

2.2.2.1. Acquisition. MR images were acquired using a 1.5 T SIGNA whole body imaging system (General Electric, Milwaukee, USA) at the MARIARC facility, University of Liverpool. One hundred and twenty four coronal T₁-weighted images were obtained using a 3D spoiled gradient echo (SPGR) pulse sequence (TE of 34 ms, TE of 9 ms and flip angle of 30°). The field of view (FOV) of the images was 20 cm, and each image refers to a contiguous section of tissue of 1.6 mm thickness. The images were reformatted along the long axis of the hippocampus using NRIA software (Brain Behaviour Laboratory, University of Pennsylvania), running on a SUN Ultra 10 Workstation (SUN Microsystems, CA, USA) to provide optimal visualisation of the temporal lobe structures. This software enabled the volume data to be re-sliced and re-sized according to multiple planes. The $256 \times 256 \times 124$ acquired voxels of side 0.78 mm \times 0.78 mm \times 1.6 mm were linearly interpolated from the mean pixel values of adjacent slices to $256 \times 256 \times 254$ cubic voxels of side 0.78 mm. All subjects (controls and patient) were imaged using identical protocol. The control subjects comprised 10 participants who provided a match for age (Table 1) and gender.

2.2.2.2. Volume estimation. Unbiased estimates of structure volume were obtained from ANALYZE image analysis software (MAYO Foundation, Minnesota, USA) running on a SUN Ultra 10 workstation. Volume estimates of the hippocampal region, amygdala, perirhinal and entorhinal cortices, temporal lobes, lateral ventricles and whole hemispheres were performed using the Cavalieri method of modern design stereology in combination with point counting. The Cavalieri method functions by taking the total section

Table 1
Volume estimates for KN and 10 age-matched controls

Control	Age	R. hpc	L. hpc	R. amyg	L. amyg	R. peri	L. peri	R. ent	L. ent	R. t. lobe	L. t. lobe	R. hemi	R. hemi	R. l. vent	L. l. vent	ICV
1	48.8	2.11	1.93	1.62	1.50	4.1	3.8	1.3	1.1	56.5	52.3	397.5	420.1	14.0	17.7	1038.8
2	42.1	2.34	2.27	2.08	1.99	6.0	5.2	1.2	1.4	75.6	74.2	540.8	521.5	11.2	11.0	1299.7
3	45.1	3.10	2.96	2.26	2.26	4.8	3.9	1.5	1.3	84.5	80.4	593.9	582.6	10.1	14.0	1308.1
4	44.3	3.12	3.04	2.34	2.15	5.3	4.5	1.2	1.2	92.0	87.4	598.9	574.6	6.0	7.23	1322.6
5	40.9	2.57	2.51	1.84	1.88	3.4	3.1	1.3	1.4	69.4	77.2	592.3	560.1	28.8	30.3	1608.1
6	40.4	2.08	2.16	2.01	1.89	5.5	4.6	1.5	1.7	66.5	66.8	365.4	378.2	23.6	18.2	1021.6
7	40.3	2.35	2.18	2.04	2.10	3.6	3.0	1.4	1.4	61.5	60.3	452.3	437.8	10.5	13.3	1137.5
8	40.4	2.41	2.37	2.11	2.14	3.7	4.3	1.2	1.3	72.8	71.3	501.3	501.3	14.7	10.9	1224.3
9	40.0	2.70	2.78	1.86	1.94	3.9	3.3	1.4	1.1	72.9	61.4	487.6	493.3	7.1	8.84	1330.0
10	49.9	3.21	3.17	2.00	1.93	4.2	4.7	1.2	1.3	81.6	77.0	574.3	542.9	7.0	6.85	1213.9
Mean	43.2	2.60	2.54	2.02	1.98	4.45	4.04	1.32	1.32	73.3	70.8	510.4	501.2	13.3	13.8	1250.5
S.D.	3.68	0.42	0.43	0.21	0.21	0.90	0.74	0.12	0.18	10.7	10.6	84.5	69.5	7.5	6.99	169.0
Patient KN 44*		1.4	1.3	1.6	1.3	4.5	4.3	1.2	1.1	72.5	64.8	493.2	485.2	14.1	13.0	1131.1

All volume estimates are in cm³. Age is age at time of scanning. Abbreviations: L., left; R., right; amyg, amygdala; ent, entorhinal cortex; hemi, hemisphere; hpc, hippocampal region; ICV, intracranial volume; l. vent, lateral ventricle; peri, perirhinal cortex; t. lobe, temporal lobe.

area of a compartment and multiplying by the section interval (or slice thickness) to estimate the volume of the compartment without bias (Gundersen & Jensen, 1987). The volume of the structure was estimated by counting the number of points falling inside the region of interest and multiplying the total number of points by the area per point, to provide an unbiased estimate of the section area. The data acquired from point counting were then input into a computer, the volume calculated and the CE predicted using S-plus statistical software (StatSci, Washington, USA).

2.2.3. Anatomical landmarks for the structures of interest

2.2.3.1. Perirhinal cortex. The landmarks for the medial temporal cortices matched those of Insausti et al. (1998). The appearance of the collateral sulcus marked the transition of the temporopolar cortex into the perirhinal cortex and was, therefore, the first slice volume from which estimates were taken. The medial boundary of the perirhinal cortex was the entorhinal cortex while the lateral boundary included the medial bank of the collateral sulcus. The superior boundary was the hippocampus, with the inferior boundary being the ventral edge of the parahippocampal gyrus. The caudal limit of the perirhinal cortex was located two sections behind the end of the uncus.

2.2.4. Entorhinal cortex

The rostral margin of the entorhinal cortex was associated with the appearance of the limen insulae, the medial border of the entorhinal cortex being the ventral border of the gyrus semilunaris. The medial portion of the entorhinal cortex forms the gyrus ambiens, which extends caudally to the anterior limit of the hippocampal fissure. The ventral limit of the gyrus ambiens is marked by a shallow sulcus (the intrarhinal sulcus). Caudally, the entorhinal cortex blends with the presubiculum and parasubiculum. Laterally, the entorhinal cortex extends to the medial bank of the collateral sulcus,

where it borders the perirhinal cortex. The posterior border of the entorhinal cortex is located at the posterior limit of the gyrus intralimbicus (Reber, Wong, & Buxton, 2002).

2.2.5. Hippocampal region

The posterior boundary of the hippocampus was the division of the lateral ventricles into the frontal and temporal horns. The hippocampus appears as grey matter surrounded by white matter, although sometimes the white matter of the alveus can be seen on the superior surface, in which case it was included as part of the hippocampus. The anterior boundary is distinguished from the posterior amygdala by a boundary between the two structures, provided by the alveus and a thin line of CSF. Moving further anterior, the hippocampus decreases in size until its anterior tip is no longer visible. Using these boundaries the volume measurement included the dentate gyrus, CA1–4, the fimbria, and the subicular cortices.

2.2.6. Amygdala

The posterior limit of the amygdala was the same as the anterior hippocampal boundary. At its anterior boundary, the amygdala merges with the white matter of the temporal pole; therefore the anterior limit was the last slice on which the boundary of the amygdala was distinguishable. The medial border of the amygdala is formed in part by CSF and part by the entorhinal cortex. Laterally, the amygdala is bordered by white matter of the temporal lobe and by the temporal horn of the lateral ventricles.

2.2.7. Temporal lobe

The posterior boundary was the first slice marking the anterior limit of the division of the lateral ventricles into their frontal and temporal horns. Posteriorly, CSF defines the inferior, medial and lateral borders of the temporal lobes. However, superiorly the temporal lobe is joined to the overlying hemisphere through the temporal stem, and the boundary used was where the temporal stem was narrowest. More an-

terior, the circumference of the temporal lobe is completely defined by CSF. The anterior boundary was the last slice on which the temporal lobes were visible.

2.2.8. Cerebral hemisphere

The posterior and anterior boundaries were the first and last slice on which the brain was visible. The cerebellum and brain stem from the superior extent of the pons were excluded.

2.2.9. Lateral ventricle

The cerebral ventricular system is well delineated as regions of very low signal intensity on T1-weighted images. Points that fell in the choroid plexus were included in the ventricular volume.

2.3. Neuropsychological status of KN

The performance of KN on a number of standard cognitive tests has been published (McKenna & Gerhand, 2002). When tested four months after his meningitis, KN achieved IQ scores on the WAIS-R (Wechsler, 1981) that were appreciably above average. These scores (WAIS-R, Verbal IQ = 136, Performance IQ = 116) were consistent with the nature of his previous job (research biochemist). The possible discrepancy between his Verbal and Performance IQ scores may, in part, reflect his visual impairments. His language and literacy skills appear intact, and when tested in 1993 on the Category Specific Names Test (McKenna, 1997) he scored 112 out of 120 (95th percentile). KN appeared to have no difficulty on the Behavioural Assessment of the Dysexecutive Syndrome (Wilson, Alderman, Burgess, Emslie, & Evans, 1996) except for those tasks that required long-term retention of the instructions (McKenna & Gerhand, 2002). Likewise his Word Fluency was not impaired (McKenna & Gerhand, 2002). In spite of his visual problems, when tested in 1994 (McKenna & Gerhand, 2002) with the Visual Object and Space Perception battery (VOSP, Warrington & James, 1991), KN performed at normal levels on most, but not all, subtests (Number Location 20/20; Incomplete Letters 17/20, 1–14th percentile; Progressive Silhouettes 10/20, 54th percentile; Silhouettes 20/30, 23rd percentile).

When tested in 1998 (McKenna & Gerhand, 2002) KN showed clear memory deficits for both verbal and visual material that were most evident when delays were placed between learning and recall. His WMS-R Index scores (Wechsler, 1987) were as follows; Attention/Concentration 123, Verbal Memory 90, Visual Memory 117, General Memory 88, Delayed Recall 50. His relatively high score on Visual Memory is surprising at first glance but the index is compiled from three scores, one of which is a test of visual recognition. In addition, the test that contributes the most to this index is Visual Reproduction I, which is a test of immediate memory. While he scored 40/41 on Visual Reproduction I, he could only score 1/41 on the delayed recall version (Visual Reproduction II). He also scored only 1/50 on the Logical Memory (prose recall) test.

2.4. Additional assessments of memory

2.4.1. Comparisons of recall and recognition

The WMS-III (Wechsler, 1997) was used to assess the persistence and severity of his memory problems. In addition, he was tested in the standard manner on the Recognition Memory Test (Warrington, 1984), which provides a forced-choice test of both face and word recognition. KN was also given the Camden Pictorial Recognition Memory Test (Warrington, 1996).

Two additional tests provided more direct comparisons between levels of recall and recognition. The Doors and People Test (Baddeley, Emslie, & Nimmo-Smith, 1994) was selected as its norms enable direct comparisons between free recall and forced-choice recognition. This task contains four tests, two of recall and two of recognition. The recall tests are for symbols and names, while the forced-choice recognition tests are for doors and for names (Baddeley et al., 1994). The Calev task (Calev, 1984) was designed so that the tests of word recall and word recognition (yes/no) should give equivalent scores for normal subjects, while avoiding ceiling effects. In the recall task subjects are read a list of 24 words for immediate recall, the words falling into six semantic groups. For the recognition test subjects are read 40 words and recognition is then tested immediately afterwards using a yes/no response. There are 40 distracter items in the task, and 20 of the target items are confusable with the distracters as they have similar meanings or rhymes. Of the 40 target words, 24 are designated as those to be used in order to match with recall levels (Calev, 1984).

2.4.2. Tests to distinguish recollective- and familiarity-based recognition

Two different experimental methods were used to assess putative components within recognition memory, namely recollective and familiarity based recognition. The two tasks were the Remember/Know procedure (Tulving, 1985; Yonelinas & Jacoby, 1995) and the receiver operating characteristic (ROC) procedure (Yonelinas, 1994, 2002). Details of the specific test procedures have been reported previously (Yonelinas & Kroll, 1998; Yonelinas et al., 2002). For each procedure, estimates of recollection and familiarity were derived for patient KN and for seven age-matched biochemists/neurochemists.

2.4.2.1. Remember/Know procedure. This experiment took place over one session. Participants first heard 25 words and indicated how many syllables were in each word (i.e., the shallow encoding condition). They then heard 50 additional words and rated the pleasantness of each word using a six-point scale (i.e., the deep encoding condition). This was followed by another 25 words encoded under the shallow encoding instructions. A recognition test was given immediately afterwards in which subjects heard the 100 studied words intermixed with 50 novel foils. Participants were asked to indicate if each word was remembered (R), familiar but not

remembered (F), or new (N). Participants were told to make a remember response if they could recollect something specific about the moment they studied the word, such as what they thought about, what judgment they made about the word or their initial reaction to the word. They were told to make a familiar response if they thought the word was studied earlier but they could not recollect any specific details about the study event. They were told to make a new response if they thought the word was not studied earlier in the experiment. Participants were allowed to refer to a sheet of test instructions throughout the test period. For the first 20 test items and for several items throughout the rest of the test participants were required to explain why a particular response was made to ensure they understood the remember/familiar distinction. None of the participants appeared to have any difficulties understanding the instructions.

2.4.2.2. ROC procedure. In a second recognition experiment, participants rated the confidence of their recognition responses and these responses were used to plot ROCs. The test involved two parallel sessions completed approximately 2 weeks apart. In the first session, subjects heard 80 words and were required to indicate if each word was abstract or concrete (deep encoding), followed by another 80 words for which they indicated how many syllables were in each word (shallow encoding). Subjects were then given a recognition memory test in which they heard a mixture of 160 studied words and 80 new lures. For the recognition test, participants were asked to rate the confidence of their recognition responses on a six-point scale (6 = certain the word was studied, 1 = certain it was not studied). The second session was

the similar to the first, except that the order of the study conditions was reversed and a different set of words was used.

3. Results

3.1. Analysis of neuropathology in KN

Inspection of the 2003 MRI images for KN suggested a reduction in the volume of medial temporal lobe structures (Fig. 1). Table 1 provides the estimated volumes (cm^3) for the right and left cerebral hemispheres, lateral ventricles, temporal lobes, hippocampal region, entorhinal cortex, perirhinal cortex, and amygdala for KN and the 10 control subjects.

The volume estimates for grey matter were all within one standard deviation of those found for the control subjects with the exception of the left and right hippocampal region, the left and right amygdala, and the left entorhinal cortex, all of which were reduced in size (Table 1). It is noteworthy that there was no evidence of a change in the volume of the perirhinal cortex in KN (left and right both larger than controls by 6.4% and 1.1%, respectively), and that this region appeared normal.

In KN the hippocampal region appeared to show the largest, relative decrease among the various regions of interest. The estimated volumes for the left and right hippocampal region were 1.3 cm^3 and 1.4 cm^3 , respectively. These measurements reflect a volume reduction of 48.8% (left) and 46.2% (right) (2.88 S.D. and 2.86 S.D. below control means, respectively). This reduction in the volume of the hippocam-

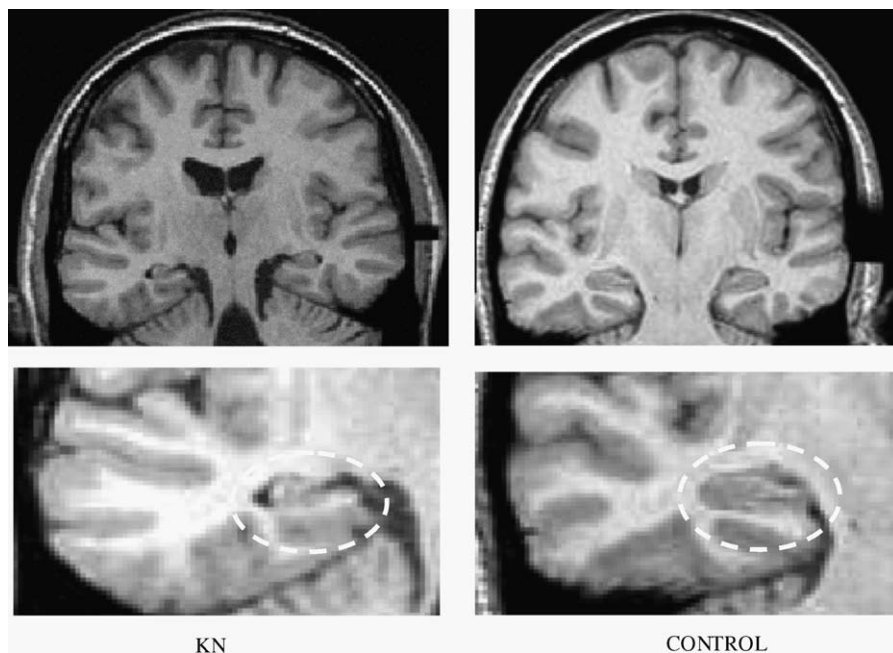


Fig. 1. Coronal MRI sections from case KN (left) and from one of the age matched controls (right). The MRI series were collected in 2003 and the enlarged sections of the medial temporal lobe show the markedly, shrunken hippocampal region in KN (within the dashed lines).

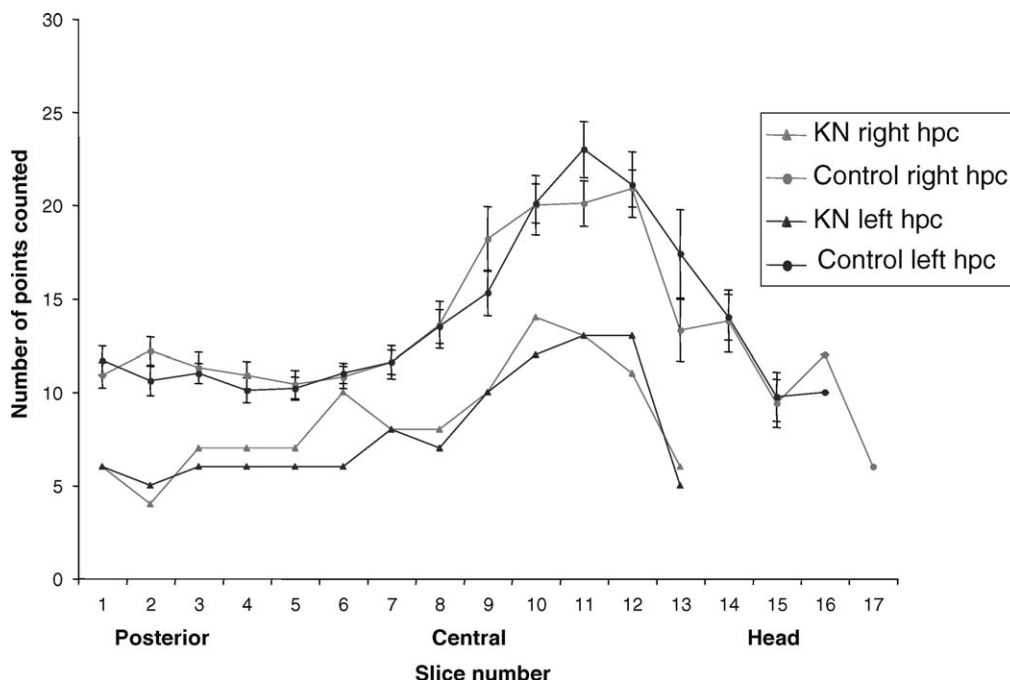


Fig. 2. Volume estimates at different AP levels along the longitudinal axis of the hippocampal region (including subicular cortices) for KN and 10 age-matched controls. Data for controls are given as mean \pm S.E. The volume is determined from number of 'points' counted (see text for details).

pal region was consistent along the anterior–posterior axis of the structure (Fig. 2). There is also evidence of a shortening along the anterior–posterior axis.

3.2. Cognitive status of KN: recall and recognition

KN's persistent difficulties in recalling new verbal and visual material are evident from his scores on the WMS-III (Wechsler, 1997) when tested in 2003 (raw scores Table 2). His percentile scores on the various Index measures from the WMS-III (Table 2) reveal extremely poor performance across an array of memory tasks with the exception of working memory, which is at normal levels. Although KN achieved a score in only the 9th percentile for the Auditory Recognition Index from the WMS-III this is not a standard test of recognition as participants are required to decide whether sentences include correct information from the stories in Logical Memory test, a task that inevitably taxes recall.

In contrast to his WMS-R and WMS-III scores, KN performed surprisingly well on the words subtest of the Recognition Memory Test (Warrington, 1984) with 48/50 (words, 75th percentile), though only 37/40 for Faces (5th percentile). He also scored 25/25 (90th percentile) for word recognition but only 18/25 (<5th percentile) for face recognition on the relatively easy Camden Pictorial Recognition Memory Test (Warrington, 1996).

More direct comparisons between levels of recall and recognition were provided by the Doors and People Test (Baddeley et al., 1994). KN's recognition of names (17) and doors (19) was only slightly below normal (25th and 25–50th percentiles, respectively). In contrast, his recall of people's

Table 2

KN's raw scores and index scores for the subtests on the WMS-III when tested in 2003

Sub-test	Scaled-score
Logical memory I	6
Logical memory II	1
Faces I	7
Faces II	8
Verbal paired associates I	6
Verbal paired associates II	3
Family pictures I	1
Family pictures II	1
Spatial span	13
Auditory recognition delayed	6
Letter number sequence	17
Logical memory II recognition	21/30
Verbal paired associates recognition	24/24

Sub-test	Index score	Percentile
Auditory immediate	77	6
Visual immediate	61	0.5
Immediate memory	63	1
Auditory delayed	52	0.1
Auditory recognition-delayed	80	9
General memory	57	0.2
Working memory index	131	98

names (12) and symbols (22) was very impaired (both 1st percentile). The difference between his recall and recognition performance is very evident when his performance is converted to *z* scores (Fig. 3A) using age-banded variance data from the controls originally used to validate the Doors and People Test (provided by I. Nimmo-Smith).

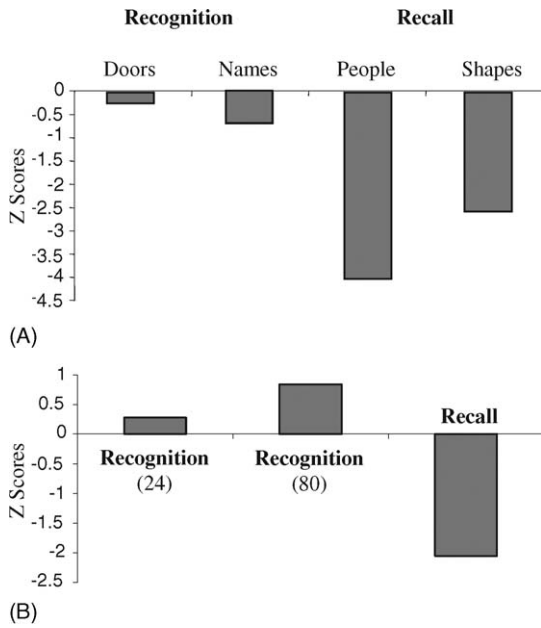


Fig. 3. (A) Doors and People Test: the performance of KN is shown as *z* scores against the age matched control subjects. KN shows very severe impairments on the two recall tests (People, Shapes), but near normal performance on two recognition tests (Doors, Names). (B) Performance of KN on the Calev Test, with scores for recall and recognition converted to *z* scores using seven age-matched Biochemist controls. Recognition *z* scores are shown for the 24 ‘target’ items and for all 80 test items.

An even clearer recall/recognition dissociation was found for the Calev task (Calev, 1984). Initial comparisons were made with the published control data (Calev, 1984), taken from 35 men (firemen) with a mean IQ of 105. KN achieved only 7/24 for word recall compared to 15.1/24 for the Calev controls. In contrast, KN achieved an above average recognition score of 20 (Calev control mean 15.6) for the 24 items used to match recognition against levels of recall. KN’s performance corresponds to *z* scores of -2.48 for recall but $+1.05$ for recognition. Of all the 40 target items KN correctly recognised 35, this represents a *z* score of $+1.13$ from the published control mean (Calev, 1984). A further set of comparisons was made with the seven age-matched Cardiff controls. These controls achieved a mean of 16.0/24 for recognition and 13.9/24 for recall. For all 80 items the mean correct score for the controls was $66.4 (\pm 5.68 \text{ S.D.})$, while KN had a score of 68/80. In Fig. 3B these results are converted to *z* scores, which again highlight the relative sparing that KN shows on some recognition tests. Finally, the performance of KN over all 80 test items was similar to that of the seven controls when compared using the signal detection measure d' (KN = 2.09, control mean = 2.25, S.D. 0.34).

3.3. Cognitive status of KN’s memory: divisions within recognition memory

3.3.1. Remember/Know procedure

Table 3 presents the numbers of remember, familiar, and new responses in each experimental condition, plus d' scores

Table 3

Remember/Know task

Encoding	Remember	Familiar	New	d'
Deep				
KN	26	17	7	1.92
Controls	44.7 ± 2.36	3.9 ± 1.57	1.4 ± 1.4	3.01
Shallow				
KN	15	15	20	1.09
Control	23.0 ± 12.9	15.3 ± 8.52	11.7 ± 7.61	1.88
New				
KN	2	8	40	
Controls	1.9 ± 3.34	6.1 ± 2.79	42 ± 5.35	

Frequency of each response for the two encoding conditions for patient KN and seven controls. For controls the scores are mean \pm standard error. The d' scores are also given for both the deep and shallow encoding conditions. Two control subjects had a hit rate of 1 and so their ‘new’ responses were changed from 0/50 to 0.5/50 in order to calculate d' .

for both encoding conditions. Fig. 4A presents the derived estimates for recollection and familiarity. Recollection was estimated as the probability of responding ‘remember’ to an old item minus the probability of responding ‘remember’ to a new item. Because the pattern of results was similar across the deep and shallow encoding conditions, even though the raw scores differed, the data were collapsed across the two encoding conditions. Familiarity was estimated as the probability of a familiar response given that the item was not recollected (i.e., $F/(1 - R)$). Familiarity was estimated in the same way for old and new items then the new item familiarity estimate was subtracted from that of the old items to account for potential differences in false alarm rates.

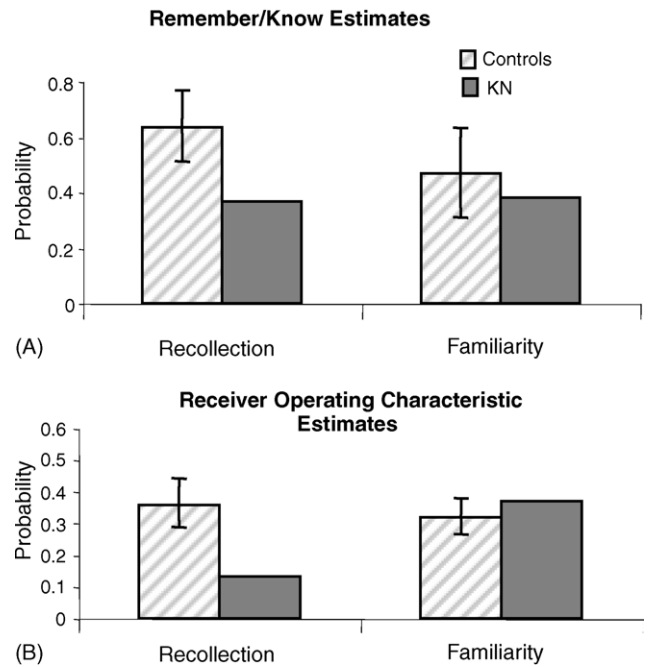


Fig. 4. Probability estimates of recollection and familiarity for KN and controls (mean \pm SE) from (A) the Remember/Know experiment and (B) ROC experiment.

Table 4

Number of recognition responses in each confidence category for old and new items in the ROC experiment (controls mean \pm standard error)

Encoding	Not confident			Very confident		
	1	2	3	4	5	6
New						
KN	50	55	27	14	10	4
Controls	82.6 \pm 11.8	46.7 \pm 7.0	11.0 \pm 3.5	10.1 \pm 2.8	7.3 \pm 1.4	2.3 \pm 0.9
Deep						
KN	8	13	21	23	35	60
Controls	14.0 \pm 3.7	17.7 \pm 3.7	7.1 \pm 1.9	13.3 \pm 2.5	25.4 \pm 4.5	83.4 \pm 8.8
Shallow						
KN	10	27	29	25	33	36
Controls	24.3 \pm 6.1	34.7 \pm 5.3	11.3 \pm 2.7	19 \pm 2.5	25.4 \pm 3.8	45.3 \pm 7.7

All rows sum to 160.

KN's overall word recognition performance was close to that of the controls (hit rate $z = -1.62$; false alarm $z = 0.37$). Likewise, the d' scores across conditions and subjects was 2.10 for the controls and 1.46 for KN. Nevertheless, Fig. 4A shows that KN's estimates of recollection were abnormally low ($z = -2.07$) while his overall estimate of familiarity was comparable to that of the controls ($z = -0.54$).

3.3.2. ROC procedure

ROC curves were plotted from the confidence ratings for the recognition responses for two tests of yes/no recognition, one using a deep encoding orienting task the other using a shallow encoding task (Table 4). The average ROCs for the age-matched control group along with the ROCs for KN are presented in Fig. 5. The proportion of new items accepted as old and the proportion of old items accepted as old are plotted on the x - and y -axes, respectively. The left most point on each function represent the proportion of items receiving the most confident old responses (i.e., a six response), and each consecutive point includes items receiving the next most confident old response (e.g., the second point includes items receiving five or six responses).

An examination of Fig. 5C shows that KN's ROC intersected that of the control subjects, indicating that his recognition performance was not generally lower than that of the control subjects. However, the shapes of the ROCs were quite different (Fig. 5A and B). That is, for the high confidence recognition responses (i.e., the left most points in the ROCs) KN's ROC fell below that of the controls, and overall, his ROC was more symmetrical along the diagonal than the controls' ROC. These results are consistent with the claim that KN exhibited a selective recollection deficit because recollection generally leads to high confidence recognition responses and leads the ROC to be more asymmetrical by pushing the function up and towards the left. These observations were further assessed by quantifying the observed ROCs.

The average ROC for each participant was quantified by fitting a nonlinear equation to the observed ROCs using a sum of squares search algorithm (Yonelinas & Kroll, 1998). The equation (i.e., $P(\text{"old"}|\text{old}) = P(\text{"old"}|\text{new}) + R + (1 - R)$

$\Phi(d'/2 - c_i) - \Phi(-d'/2 - c_i)$) assumes that recognition reflects the contribution of recollection (R) and an independent familiarity process (d' reflects the distance between two equal-variance Gaussian strength distributions; c_i reflects the response criterion at point i ; and Φ reflects the cumulative normal response function). To facilitate comparison to recollection, which was measured as a probability, each d' value was converted to the probability of a hit given the average false alarm rate (i.e., 0.11, which was the proportion of new items receiving a response of 4, 5 or 6). Familiarity accuracy was then measured by subtracting the average false alarm rate from the calculated hit rate.

Parameter estimates for recollection and familiarity were derived for each subject and are presented in Fig. 4B. As in the Remember/Know experiment, performance was collapsed across the deep and shallow encoding conditions. An examination of Fig. 4B indicates that KN's estimate of recollection was lower than the controls ($z = -1.14$), whereas his estimate of familiarity was comparable to that of the controls ($z = 0.34$). Note that although the patient's recollection score was reduced by more than 60% compared to the controls, the corresponding z score indicated that this was just over one standard deviation below normal. This very likely underestimates the patient's true deficit because it reflects the fact that one of the control participants performed extremely poorly on the recognition test and produced a recollection estimate that was $z = -3.13$ below the mean of the other controls. Why this participant performed so poorly in this test is unclear because he performed normally in the Remember/Know experiment. In any case, if that outlier is excluded, KN's recollection deficit in the ROC experiment appears to be similar to that observed in the Remember/Know experiment ($z = -2.16$).

To provide an average index of KN's recollection and familiarity abilities, estimates were collapsed across the Remember/Know and ROC experiments for all participants. This analysis indicated that KN's estimate of recollection was below that of the controls ($z = -2.45$), whereas his estimate of familiarity was in the normal range ($z = -0.30$).

The ROC and RK analyses just described were based on the assumptions of a dual-process theory of recognition.

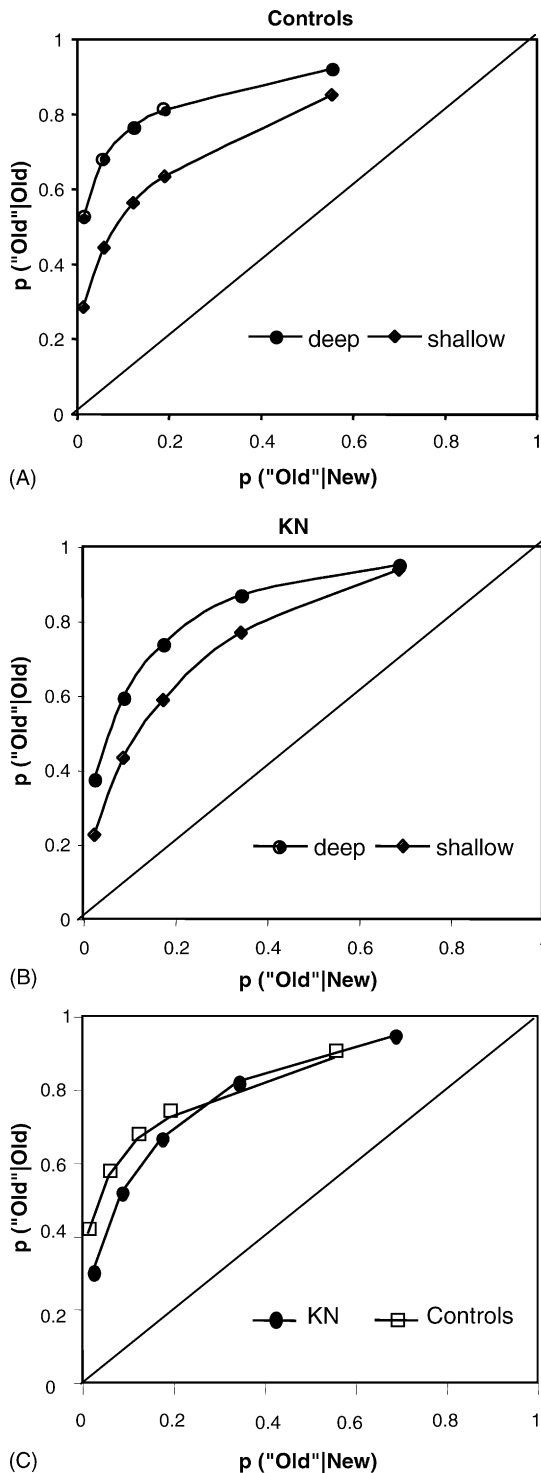


Fig. 5. ROCs for KN and the Controls with least squares model fits for the deep and shallow encoding conditions (A and B). The most confidently recognised items are at the left (and so are typically associated with recollection), and each consecutive point includes the next most confidently recognised items. The graphs become increasingly symmetrical as recognition is more reliant on familiarity. Part (C) shows the combined performance across the two conditions, and the intersection shows that the recognition performance of KN was not generally lower than that of the control subjects.

However, one can ask what the conclusions would be if one adopted the assumptions underlying a pure signal detection model. To account for recognition memory signal detection theory requires two independent memory components; a sensitivity parameter (i.e., d') to capture the difference in the familiarity strength values of the old and new items, and a variance ratio parameter to account the fact that there is more variance in the strength of the old items than that of the new items. This latter parameter is necessary to account for the fact that the ROCs are asymmetrical along the diagonal (for reviews see [Glanzer, Kim, Hilford, & Adams, 1999](#); [Ratcliff, Sheu, & Gronland, 1992](#); [Yonelinas, 1994, 2001](#)). To assess the signal detection model, the average ROCs were plotted in z -space in order to estimate slope and intercept values. The slope of the z -ROC, which measures the asymmetry of the ROC, was higher for KN than for the controls (0.87 versus 0.62), indicating that the variance ratio was greater for the controls than for KN. In contrast, the intercept was slightly greater for KN than the controls (1.21 versus 1.12). Based on these parameters one can estimate sensitivity (i.e., how much more familiar the old items are compared to the new items (i.e., [Macmillan & Creelman, 2003](#)), and one finds that sensitivity was almost identical for KN and controls ($da = 1.29$, and 1.35, respectively).

Thus, signal detection theory indicates that memory strength (i.e., familiarity) was not disrupted by hippocampal damage, but that the variance ratio was affected. Although signal detection theory in itself does not provide insight into what the mechanism is that controls the variance ratio, one possibility is that it reflects a recollection-like process. That is, the increased variance associated with old items is due the fact that recollection contributes to performance, and it is this process that is selectively disrupted by hippocampal damage. In any case, both dual process theory and signal detection theory converge in showing that familiarity strength is not disrupted in KN, whereas, the other recognition memory component (i.e., recollection or variance ratio) is disrupted.

4. Discussion

The present findings have direct implications for two related debates. The first debate concerns the relationship between recall and recognition, and the extent to which these aspects of memory can be dissociated after brain damage. The data from KN reveal a single dissociation between recall and recognition that is most consistent for verbal material. For example, his word recognition score on the Recognition Memory Test ([Warrington, 1984](#)) was in the 75th percentile, but his delayed word recall from the WMS-III was at the 0.1 percentile. Likewise for the Calev task (1984), word recognition was slightly superior to that of the controls while word recall was severely impaired. Furthermore, within recognition memory KN appears to show a sparing of familiarity-based recognition but a loss of recollective-based recognition. There have been other single case reports of amnesics who were able

to perform disproportionately well on tests of item recognition (Baddeley et al., 2001; Hanley & Davies, 1997; Mayes et al., 2002; Parkin, Dunn, Lee, O'Hara, & Nussbaum, 1993, 1994; Parkin & Hunkin, 1993). Some of these cases are a result of frontal/diencephalic damage (Hanley & Davies, 1997; Parkin & Hunkin, 1993; Parkin et al., 1993, 1994) while others arise from hippocampal-based pathology (Baddeley et al., 2001; Mayes et al., 2002). In some of these examples Remember/Know biases during recognition also indicated a relative sparing of familiarity (Holdstock et al., 2002; Parkin et al., 1993), but this is not always the case (Hanley et al., 2001). An important feature of the present study was, therefore, the ability of KN to show consistent evidence from more than one task that helps to discriminate between these different, putative components of recognition memory.

The second debate concerns the importance of the hippocampus for recognition, and whether its importance for recognition is comparable to that for recall. Based on MRI evidence KN has bilateral shrinkage of his hippocampal region while most of the adjacent cortices (including the perirhinal cortex) are of normal volume. The present results, therefore, indicate that the hippocampus is vital for recall but not for recognition as familiarity-based recognition can be spared. In this regard KN is similar to another subject YR (Holdstock et al., 2002; Mayes et al., 2002) who also appears to show selective hippocampal pathology within the temporal lobe, and also shows a relative sparing of recognition. These cases can be compared with the patient VC (Cipolotti et al., 2001) who again suffered bilateral shrinkage of the hippocampus but was impaired on both recall and recognition. Unlike KN and YR, volumetric analysis of the MRIs from VC showed shrinkage in the parahippocampal gyrus, in addition to the hippocampus (Cipolotti et al., 2001). This additional damage may be critical given the considerable evidence implicating the perirhinal cortex in recognition and, in particular, for familiarity judgements (Brown & Aggleton, 2001).

Before considering the implications of the present study, it is useful to discuss some of its potential limitations. One issue is that KN's pathology is bilateral and symmetrical, and yet he appears to show a clearer dissociation between recall and recognition for verbal than facial stimuli. There are several factors to be considered. The first factor is that KN has visual problems, including a complete loss of the lower visual fields. While it is difficult to gauge how these problems might affect tests of visual recognition, it is the case that tests like the Doors and People (Baddeley et al., 1994) deliberately use foils that are highly similar to avoid ceiling effects. This may pose an additional challenge for KN, yet he was able to perform at normal levels on the Door recognition test. The second factor is that KN has probably suffered bilateral amygdala damage, and one frequent consequence of bilateral damage to this region is poorer performance on face recognition than word recognition when measured with the Warrington RMT (Aggleton, 1992; Aggleton & Shaw, 1986). This difference could arise from the impact of amygdala damage on the way that some facial expressions are

judged (Adolphs et al., 2005). Other evidence that memory for faces might be dissociated from memory for other forms of information following temporal lobe damage (Carlesimo, Fadda, Turriziani, & Caltagirone, 2001; Tippett, Miller, & Farah, 2000) suggests that it might be profitable to test this distinction more formally.

A second issue is the problem that can arise when tests of recognition are easier than tests of recall and so prone to ceiling effects. In the present study the recognition tests in the Calev task (Calev, 1984) and the Doors and People Test (Baddeley et al., 1994) were selected as they help to avoid this problem. A third issue concerns the two tasks (R/K procedure and ROC analyses) used to measure different aspects of recognition memory. In order to derive measures of recollection and familiarity it is necessary to make assumptions about how they interact to support recognition. One consequence is that there are no direct, assumption-free measures of these putative components of recognition, although support for their independence comes from cognitive studies (Yonelinas, 2002), structural equation modelling (Quamme et al., 2004), and brain imaging techniques (Davachi, Mitchell, & Wagner, 2003; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Ranganath et al., 2003; Rugg & Yonelinas, 2003). The need to make assumptions about the underlying nature of the memory processes means, however, that strong conclusions can only be reached when there is a convergent pattern of results. A further issue arises from the fact that KN not only performed more accurately on the deep encoding conditions but also showed more recollective responses (Fig. 5; Table 3). At first sight this finding might appear to run counter to the notion of a selective loss of recollection versus familiarity. In fact, KN did not have a zero recollective score for the shallow conditions, and so an increase in recollective scores with the deeper encoding tasks is only to be expected. At the same time, as KN started at a much lower level of recollective responses than the control subjects it is not meaningful to compare relative increases in recollective scores across the shallow and deep conditions. A final, related issue is that KN suffered a loss of approximately half of his hippocampal region, and we have not determined the functional status of the remaining tissue. It is, however, noteworthy that the hippocampal damage appears to have occurred along the entire length of the structure, and so there is no selective sparing of rostral or caudal regions that might have different cognitive contributions (Colombo, Fernandez, Nakamura, & Gross, 1998; Gabrieli, Brewer, & Poldrack, 1998; Moser & Moser, 1998). It must finally be remembered that the description of KN's pathology is based on MRI evidence and not post-mortem findings.

It might be felt that a single case study cannot have as much weight as a group study but, as has been pointed out, the most relevant group studies all concern the consequences of anoxia, and their findings appear inconsistent. Thus, evidence has been published that anoxics with seemingly selective hippocampal pathology can have marked deficits in both recall and recognition (Manns & Squire, 1999; Manns

et al., 2003; Reed et al., 1997; Stark & Squire, 2001). In contrast, other groups report that some anoxic cases can show a relative sparing of item recognition even though recall is impaired (Bastin et al., 2004; Turriziana et al., 2004; Volpe & Hirst 1983; Volpe, Holtzmann, & Hirst, 1986; Yonelinas et al., 2002), and that this sparing may reflect an ability to use familiarity information (Bastin et al., 2004; Quamme et al., 2004; Turriziana et al., 2004; Yonelinas et al., 2002). Debates about the cognitive consequences of hypoxia or anoxia need, however, to bear in mind that the associated pathology is variable. One comprehensive review, for example, concluded that the cerebral cortex and basal ganglia are more frequently damaged than the hippocampus, and that evidence for selective hippocampal damage was found in only the minority (18%) of cases (Caine & Watson, 2000). The difficulty of interpreting these cases is exacerbated by the possible presence of ‘cryptic’ pathology following anoxia (Bachevalier & Meunier, 1996; Markowitsch, Weber-Luxemburger, Ewald, Kessler, & Heiss, 1997). Furthermore, the memory impairments after hypoxia may correlate better with changes in total brain volume rather than hippocampal volume (Grubb et al., 2000), again suggesting a frequent contribution from more diffuse pathology in this condition.

There are some striking similarities between KN and another amnesic patient, YR. Like KN, case YR has suffered bilateral hippocampal shrinkage of between 40% and 50% total volume and shows a clear anterograde amnesia (Holdstock et al., 2002; Mayes et al., 2002). The aetiology of her hippocampal pathology is, however, different and thought to be the result of an opiate drug. YR shows consistent deficits for the recall of verbal and nonverbal material, which are in striking contrast to her performance on tests of item recognition, where she typically performs at or close to normal levels. Evidence from the Remember/Know task points to a sparing of familiarity in YR (Holdstock et al., 2002). Although findings from the ROC task have not been reported, YR’s contrasting performance on associative recognition tests accords with a reliance on familiarity (Mayes et al., 2004). Likewise, YR’s performance on yes/no recognition when the foils are very similar to the target (Holdstock et al., 2002) has also been interpreted as reflecting a selective sparing of familiarity. These patterns of deficits shown by KN and YR fit the predictions of a number of models of episodic memory that have assumed different contributions from the hippocampus and the adjacent cortices (Aggleton & Brown, 1999; Mishkin et al., 1997; Norman & O’Reilly, 2003). The fact that in both KN and YR the parahippocampal and perirhinal cortices appear to be intact may be crucial as the perirhinal cortex is thought by many to provide familiarity information (Brown & Aggleton, 2001).

An unresolved issue is the cause of the apparent discrepancy between cases KN and YR, and the cases with hypoxic-induced hippocampal damage in the study by Manns et al. (2003) who showed equally severe ‘remember’ and ‘know’ deficits. While a definitive answer cannot be given, a number of factors should be considered. The first concerns the

difficulty that some amnesics may have in subjectively appreciating the difference between ‘remember’ and ‘know’ (Baddeley et al., 2001), associated with the problem of maintaining this difference over a test session. It is also noteworthy that the decrease of hippocampal volume by approximately 45% in KN was as great as the largest volume decrease in any of the hypoxic cases studied by Manns et al. (2003). This suggests that the recall/recognition dissociation in KN is not simply due to partial hippocampal damage. At the same time, MRI measurements indicate that the volume of the perirhinal cortex is normal in both KN and YR. Whether the same is true in the cases examined by Manns et al. (2003) is not clear as selective, volumetric measures for the perirhinal cortex have not been provided for these hypoxic cases. While it is reported that the parahippocampal gyrus is within normal limits (Manns et al., 2003), this region contains considerably more tissue than just the perirhinal cortex and so does not confirm the status of this key area.

In conclusion, KN provides striking evidence not only for a dissociation between the neural substrates for word recall and word recognition, but also for different components within recognition. These findings complement recent fMRI and ERP studies that point to similar dissociations (Davachi et al., 2003; Eldridge et al., 2000; Ranganath et al., 2003; Rugg & Yonelinas, 2003). Although KN is not the first amnesic to show evidence of a relative sparing of recognition to recall, he is one of the first in which it has been possible to show a consistent dissociation within recognition across more than one task. These tests have been combined with detailed volumetric analyses of temporal lobe volume, revealing selective hippocampal region atrophy. Multiple assessments of recollection-based and familiarity-based recognition have up to now been confined to studies of anoxic patients (Yonelinas et al., 2002) and the patient YR (Holdstock et al., 2002; Mayes et al., 2002, 2004). The present findings not only strongly support the prediction that the severe recognition impairment normally found in anterograde amnesia reflects the loss of at least two distinct cognitive processes (Aggleton & Brown, 1999), but also highlight the care needed when testing animal models of amnesia as it is not sufficient to rely on recognition tests that can be solved by familiarity.

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