

## Fractionation of memory in medial temporal lobe amnesia

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### Abstract

We report a comprehensive investigation of the anterograde memory functions of two patients with memory impairments (RH and JC). RH had neuroradiological evidence of apparently selective right-sided hippocampal damage and an intact cognitive profile apart from selective memory impairments. JC, had neuroradiological evidence of bilateral hippocampal damage following anoxia due to cardiac arrest. He had anomic and “executive” difficulties in addition to a global amnesia, suggesting atrophy extending beyond hippocampal regions. Their performance is compared with that of a previously reported hippocampal amnesic patient who showed preserved recollection and familiarity for faces in the context of severe verbal and topographical memory impairment [VC; Cipolotti, L., Bird, C., Good, T., Macmanus, D., Rudge, P., & Shallice, T. (2006). Recollection and familiarity in dense hippocampal amnesia: A case study. *Neuropsychologia*, 44, 489–506.] The patients were administered experimental tests using verbal (words) and two types of non-verbal materials (faces and buildings). Receiver operating characteristic analyses were used to estimate the contribution of recollection and familiarity to recognition performance on the experimental tests. RH had preserved verbal recognition memory. Interestingly, her face recognition memory was also spared, whilst topographical recognition memory was impaired. JC was impaired for all types of verbal and non-verbal materials. In both patients, deficits in recollection were invariably associated with deficits in familiarity. JC’s data demonstrate the need for a comprehensive cognitive investigation in patients with apparently selective hippocampal damage following anoxia. The data from RH suggest that the right hippocampus is necessary for recollection and familiarity for topographical materials, whilst the left hippocampus is sufficient to underpin these processes for at least some types of verbal materials. Face recognition memory may be adequately subserved by areas outside of the hippocampus.

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### 1. Introduction

Classical neuropsychological studies of patients with episodic memory deficits have documented selective verbal or visual memory deficits following left or right medial temporal lobe (MTL) lesions (Frisk & Milner, 1990; Smith & Milner, 1981; see for a review Cipolotti & Bird, 2006). Interestingly, striking dissociations have been reported within the domain of non-verbal memory functions. Memory for unknown human faces and memory for novel topographical memoranda has been shown to dissociate. For example, Cipolotti and colleagues

reported selective preservation of topographical memory for unknown buildings, landscapes and outdoor scenes despite impairment of memory for unknown human faces in patients with neurodevelopmental (autism and Gilles de la Tourette syndrome and autism) disorders (Blair, Frith, Smith, Abell, & Cipolotti, 2002; Cipolotti, Robinson, Blair, & Frith, 1999).

Patients with brain damage acquired later in life have also been described with selective impairment of, or selective sparing of, topographical memory. Two patients reported by Warrington and colleagues fall within the former class of patients (Whiteley & Warrington, 1978; Incisa della Rocchetta, Cipolotti, & Warrington, 1996). Both of these patients had a selective impairment in recognition of novel topographical stimuli (outdoor scenes, buildings and landscapes), whilst memory for other material, including unknown human faces, was normal. The latter patient was also unable to recognize familiar landmarks or

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recall familiar routes, suggesting that perception and/or semantic memory of topographical items may have been compromised. Unfortunately both patients are uninformative with respect to the anatomy of topographical memory since they had rather widespread cortical damage due to traumatic head injury and small vessel disease, respectively.

Patients with selective preservation of topographical memory are also on record. Two patients have been described with selective sparing of topographical recognition memory for unknown buildings, landscapes and outdoor scenes, despite severe impairment for unknown human faces and verbal memory (Cipolotti & Maguire, 2003; Maguire & Cipolotti, 1998). Both patients had semantic dementia (SD), with predominant temporal lobe atrophy, greater on the left than on the right. Interestingly, right-sided MTL structures such as the hippocampus were clearly better preserved.

Recently, Lee, Buckley, Gaffan, Emery, Hodges, and Graham (2006) reported a behavioural and anatomical double dissociation between topographical and face memory in Alzheimer's disease (AD) and SD patients. Patients with AD showed a greater deficit on an unfamiliar scenes recognition memory test, than an unfamiliar faces recognition memory test, whilst the SD patients were disproportionately impaired on the faces rather than the scenes task. The authors suggested that perceptual impairments may have underpinned these difficulties. The AD patients had predominant hippocampal atrophy, whilst the SD patients had greater damage to the perirhinal cortex.

A few patients with selective impairment/preservation of face memory have also been reported. Tippett, Miller, and Farah (2000) described a patient with traumatic brain injury who was unable to learn new faces despite preserved face perception, verbal memory and memory for abstract designs. Unfortunately, the authors did not investigate the patient's topographical memory functions. Carlesimo, Fadda, Turriziani, Tomaiuolo, & Caltagirone (2001) reported a patient with bilateral hippocampal damage due to carbon monoxide poisoning, who had a selective sparing of recognition memory for new faces in the context of an otherwise global amnesia encompassing a wide variety of verbal and non-verbal materials including topography.

Recently, Cipolotti et al. (2006) documented sparing of unknown face recognition memory in the densely amnesic patient, VC. The patient, despite intact general intelligence, language, semantic memory, perception and executive functions, had a severe and ungraded retrograde amnesia and profound anterograde amnesia. His anterograde amnesia affected recall and recognition for verbal memoranda. Similarly recall and recognition of non-verbal memoranda (topographical stimuli, abstract designs) was impaired. However, his performance on tests employing unknown human faces, whilst initially impaired (Kartsounis, Rudge, & Stevens, 1995), had come to be consistently within the normal range. The authors employed receiver operating characteristics (ROC) analyses to estimate the relative contribution of two putative memory processes – recollection and familiarity (Mandler, 1980; Tulving, 1985) – to VC's performance on novel experimental memory tests. These were recognition memory tests using words, topographical stimuli

(unknown buildings and landscapes) and unknown faces memoranda. Estimates of VC's recollection for verbal and topographical materials were at floor and his familiarity for these materials was also poor. In contrast, both his recollection and familiarity for faces were unimpaired.

Unlike previous reports of patients with material specific memory impairments, very detailed neuroanatomical data exists for VC. Five different neuroradiological investigations provided converging evidence of marked and selective bilateral hippocampal damage (qualitative MRIs, volumetric MRI, voxel-based morphometry, MR spectroscopy, functional MRI: Cipolotti et al., 2001, 2006; Kartsounis et al., 1995; Maguire, Frith, Rudge, & Cipolotti, 2005). One only of these investigations (volumetric MRI) just detected a mild and selective reduction in the volume of the left parahippocampal gyrus (between 2 and 3 standard deviations below controls). It has been argued that this slight volume loss was due to white matter shrinkage consequent to hippocampal damage (Cipolotti et al., 2001). In keeping with this, an fMRI study of autobiographical memory retrieval indicated that VC activated the left parahippocampal region (Maguire et al., 2005). In contrast, he was functionally ahippocampal, although able to activate normally an extensive left lateralized network of brain areas. These data suggest that the hippocampus plays a critical role in both recollection and familiarity for verbal and topographical materials, but not for faces.

The present study aimed to replicate and extend these results by investigating the memory abilities of two new patients. The first patient (RH) with right-sided hippocampal damage was tested on three experimental tasks previously used in VC employing words, unknown buildings and unknown faces (Cipolotti et al., 2006). On the basis of the results obtained in patient VC and the classical neuropsychological findings in patients with selective MTL lesions, we hypothesized that RH would show a selective impairment of topographical memory with preserved memory for unknown faces and verbal memoranda. The second patient (JC) was globally amnesic following anoxia which caused bilateral hippocampal damage. Such patients have been previously used in the literature, although not without controversy, as models of selective hippocampal damage (e.g. Chun and Phelps, 1999; Hannula, Tranel, & Cohen, 2006; Yonelinas et al., 2002). We were interested to compare JC's performance with that of RH and the previously reported VC on the three experimental tasks.

## 2. Case descriptions

### 2.1. RH

RH is a 58-year-old, female, housewife. In 1996, she developed sudden onset tingling and weakness in the left arm. Subsequent to this event, she noticed an impairment in remembering events, appointments and conversations. She also began to notice a difficulty with her sense of direction particularly when walking in unfamiliar places. However, she had no difficulty in remembering names and faces, nor in recognizing familiar places or landmarks. Neurological examination was entirely normal.

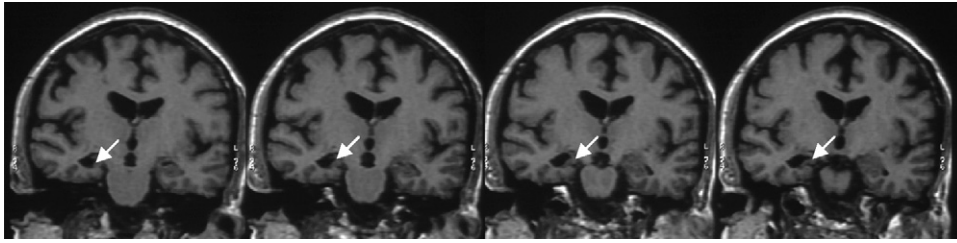


Fig. 1. Coronal T1-weighted images of RH's brain depicting selective right hippocampal atrophy (see arrows). The left hippocampus and left and right extrahippocampal areas appeared normal. Images are left/right reversed according to convention.

## 2.2. JC

JC is a 60-year-old, male, who worked as a safety advisor. In 2004 he sustained a prolonged ventricular fibrillation arrest and was resuscitated after six dc shocks. He remained in an intensive therapy unit for 3 days and upon reduction of sedation was noted to have cognitive problems, particularly in the memory domain. Neurological examination was unremarkable apart from brisk reflexes in the upper and lower limbs, which were symmetrical.

## 3. Neuroradiological findings

### 3.1. RH

#### 3.1.1. Qualitative investigation

Using a scanner operating at 1.0T (Signa 1.5T MRI system, GE Milwaukee), axial T2-weighted (TR=3320 ms; TE=108 ms) and coronal T1-weighted (TR=15.3 ms; TE=4.2 ms) scans covering the whole brain were obtained from RH. A qualitative review of the images was independently performed by three expert neuroradiologists blinded to the purposes of the present investigation. Few peri-ventricular non-specific white matter abnormalities were detected on T2-weighted scan. On T1-weighted images there was a selective atrophy of the right hippocampal formation. Consistent with such focal volume loss, there was an enlargement of the right lateral ventricle, prominently involving its temporal horn. No abnormalities were noted in the left hippocampus. Furthermore, the appearances of the left and right entorhinal cortex, parahippocampal gyrus, fusiform gyrus and other temporal lobe areas were normal (see Fig. 1).

#### 3.1.2. MRI volumetry

MRI volumetry was carried out by a very experienced rater, blind to the purposes of the investigation (JB—see acknowl-

edgements). Segmentations were performed on a 3.0 GHz Xeon Linux workstation. The software package MIDAS was used for all manual segmentation (Freeborough, Fox, & Kitney, 1997). The operator traced around the boundaries of the hippocampus with two orthogonal views available. The hippocampus was defined as including the hippocampus proper, the subiculum and the alveus (see Barnes et al., 2004). In addition, brain volume was derived using a previously described protocol (Freeborough, Fox & Kitney, 1997).

RH's brain volume was calculated to be 1,146,300 mm<sup>3</sup>, which is well within the normal range for such measurements, suggesting no evidence of widespread atrophy (e.g. Aggleton et al., 2005; Cipolotti et al., 2001). The volume of her left hippocampus was 2654 mm<sup>3</sup>, which is comparable to previous volumetric measurements for this structure reported for healthy adults (e.g. Aggleton et al., 2005; Cipolotti et al., 2001). In contrast, her right hippocampus was calculated to have a volume of 1100 mm<sup>3</sup>, which is markedly small. Thus, the volume of her right hippocampus was 58.6% smaller than her left hippocampus.

### 3.2. JC

Using a scanner operating at 1.5T (Signa 1.5T MRI system, GE Milwaukee), axial T2-weighted (TR=6000 ms; TE=98.2 ms) and coronal fluid attenuated inversion recovery (FLAIR) (TR=9897; TE=161 ms; TI=2473 ms) scans covering the whole brain were obtained from JC. Similarly to RH, a qualitative review of the images was independently performed by three expert neuroradiologists blinded to the purposes of the present investigation. Increased signal return was observed in the hippocampus bilaterally (see Fig. 2). There was no evidence of abnormal signal return from any other part of the brain. In particular, no abnormalities were observed in the thalamus, temporal poles, anterior

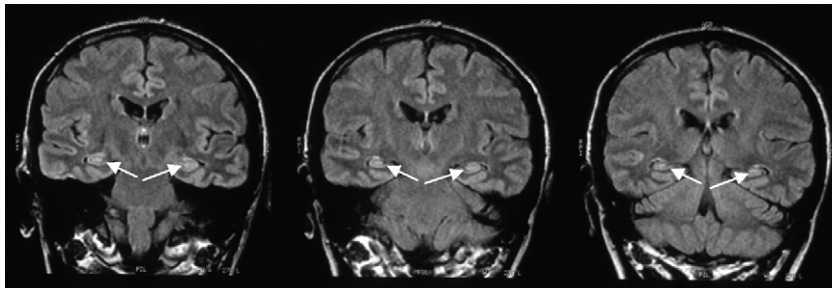


Fig. 2. Coronal FLAIR images of JC's brain showing abnormal signal return from the hippocampi bilaterally (see arrows). Images are left/right reversed according to convention.

middle temporal and anterior parahippocampal gyri of both sides.

#### 4. Performance on general cognitive tests

##### 4.1. RH

RH was assessed twice, 1 year apart. The experimental investigation that will be described took place around the time of the second assessment (see Table 1a). Overall the results demonstrated a static cognitive profile, across the two assessments.

RH obtained remarkably similar verbal and performance IQ scores across both assessments, as assessed using the WAIS-R (Wechsler, 1981). These were in keeping with premorbid estimates based on educational level and occupational background, but somewhat lower than the level predicted by her performance on the National Adult Reading Test (NART; 1991). Nominal skills as assessed by the Graded Naming Test were high average at both assessments (GNT: McKenna & Warrington, 1983). Similarly, visual and visuospatial perception as assessed by the Object Decision, Number Location and Cube Analysis subtests of the Visual Object and Space Perception Battery was normal (VOSP: Warrington & James, 1991). RH's performance on several tests of executive processing was also normal. Her interpretations of proverbs were normal and she provided good cognitive estimates (Shallice & Evans, 1978). She obtained promptly and efficiently all six categories on the modified Wisconsin card sorting test (Nelson, 1976). At the second assessment her verbal fluency (Lezak, 1995) was good and she obtained average scores on the Hayling and Brixton tests (Burgess & Shallice, 1997).

RH was also administered a comprehensive assessment of her semantic memory at the time of the experimental investigations (see Table 1b). Her performance was normal on four

Table 1b

Results of the semantic memory assessment for patient RH (March 2004)

Category specific naming test	
Animals	21/30
Fruit/vegetables	25/30
Small manipulable objects	26/30
Large objects	25/30
Famous buildings (visual naming)	12/12
Famous faces (visual naming)	9/12
Verbal fluency	
Birds	13
Dogs	10
Household items	20
Animals	19
Vehicles	10
Fruits	20
Tools	9
Boats	9
Letter "F"	21
Letter "A"	18
Concrete word synonym test	25/25
Abstract word synonym test	24/25
Cambridge category comprehension test	64/64
Camel and cactus test	
Living (words)	31/32
Manmade (words)	32/32
Living (pictures)	31/32
Manmade (pictures)	32/32

stringent tests of picture naming (Category Specific Names Test: McKenna, 1998). Importantly, she was able to name all photographs of famous landmarks, as well as 9/12 photographs of famous faces (she recognized the remaining three items). RH's category fluency was normal for eight semantic categories and

Table 1a

Results of the general cognitive assessment for both patients

	RH March 2003	RH March 2004	JC June 2004
Intellectual functioning			
Verbal IQ	109	110	100
Performance IQ	101	101	86
Nominal skills			
GNT	27/30 (>75 percentile)	25/30 (>75 percentile)	0/30 (<5 percentile)
Visual perception			
Fragmented letters	n.t.	n.t.	18/20 (>5% cut-off)
Object decision	18/20 (>5% cut-off)	19/20 (>5% cut-off)	16/20 (>5% cut-off)
Cube analysis	10/10 (>5% cut-off)	10/10 (>5% cut-off)	n.t.
Number location	8/10 (>5% cut-off)	9/10 (>5% cut-off)	n.t.
Executive function			
Proverbs	n.t.	Passed	Fail
Easy Stroop	n.t.	n.t.	Fail
Cognitive estimates	n.t.	Passed	n.t.
Modified WCST	6 categories	n.t.	n.t.
Verbal fluency <sup>a</sup>	18	25	2
Hayling test	n.t.	17 (average)	n.t.
Brixton test	n.t.	15 (average)	n.t.
Weigl	n.t.	n.t.	Passed

Scores are given as raw scores (percentile and cut-off scores in parentheses), GNT = graded naming test, WCST = Wisconsin card sorting test.

<sup>a</sup> Number of words beginning with the letter "s" in 1 min, n.t. = not tested.

three phonemic categories. Three tests of comprehension were administered; the Concrete and Abstract Word Synonyms Test; the Camel and Cactus Test; the Cambridge Category Comprehension Test (Warrington, McKenna, & Orpwood, 1998; Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000; Hodges & Patterson, 1995). She performed all three tests entirely satisfactorily.

In sum, RH presented with an intact performance on general intelligence, focal language, perception and executive tasks, which remained static over a 1.5-year period. This indicated that there was no progressive cognitive decline. Interestingly, her performance on an extensive semantic memory battery was also entirely normal.

#### 4.2. JC

JC underwent a neuropsychological assessment in 2004, at the time of the present experimental investigation (see Table 1a). When assessed on the WAIS-R, JC's verbal IQ was in the average range, whilst performance IQ was in the low average range. Of note, JC obtained average scores on stringent subtests requiring sustained attention and concentration, such as arithmetic and block design and his digit span was high average. His premorbid IQ was assessed to be average in terms of educational level, occupational level, and reading performance (on the NART). These scores therefore, reflect a mild and selective underfunctioning in performance IQ. Nominal skills for common nouns were profoundly impaired. Thus, he failed to name any items on the GNT, and he only named 13 of the 30 items in the easy Oldfield Picture Naming Test (Oldfield & Wingfield, 1965). In contrast, naming of proper nouns was relatively spared. For example, he achieved an average score on a stringent naming test of proper nouns (McKenna & Warrington, 1980). JC's visual perception was normal (Object Decision and Fragmented Letters subtests of the VOSP). In contrast, JC was impaired on 3/4 tests of executive functioning. He provided concrete interpretations of proverbs. He failed the ink-colour naming conflict condition of a simplified version of the Stroop test. Similarly, his phonemic fluency

was severely reduced. However, he was able to provide both solutions on the Weigl Test (Weigl, 1941). His performance on a test of speed and attention was within the normal range (cancelling 0's, Willison & Warrington, 1992). These results, together with his average/high average performance on the digit span and arithmetic subtests of the WAIS-R, suggest that his attentional processes are preserved.

In sum, JC presented with a selective common noun anomia, some executive difficulties and a mild selective intellectual underfunctioning on the non-verbal part of the WAIS-R. However, his performance on verbal tests of abstract reasoning, his word retrieval skills for proper nouns and his perceptual processes were normal.

### 5. Performance on episodic memory tests

#### 5.1. RH

RH's performance on a range of recall and recognition memory tests from both neuropsychological assessments is shown in Table 2. RH's performance on story recall tests was rather weak (Coughlan & Hollows, 1985). At first assessment, for both immediate and delayed recall she obtained scores around the 10th percentile. At second assessment her immediate recall was somewhat better, but her delayed recall was impaired. Her performance on the Paired Associate Learning test was within the lower end of the normal range at the first assessment, but at the upper end of the average range at the second (from the Camden memory tests: Warrington, 1996). Interestingly, her visual recall as tested by the Rey–Osterrieth complex figure, was clearly impaired (Osterrieth, 1944). RH's spatial span was normal (five blocks), but she was unable to learn a supraspan sequence (of seven blocks) after 25 attempts (De Renzi, Faglioni, & Previdi, 1977). Her performance on both subtests of the Recognition Memory Test (RMT: Warrington, 1984) was normal, suggesting preserved recognition memory for verbal material and unfamiliar human faces. In striking contrast, her performance on the Topographical Recognition Memory Test, which comprises pic-

Table 2  
Results of the anterograde memory assessment for both patients

	RH March 2003	RH March 2004	JC June 2004
Story recall			
Immediate	15 (10 percentile)	18 (10–25 percentile)	7 (<10 percentile)
Delay	14 (5–10 percentile)	9 (<5 percentile)	0
Paired associate learning			
Time 1	11/24 (10–25 percentile)	16/24 (25–50 percentile)	n.t.
Time 2	19/24 (10–25 percentile)	24/24 (>75 percentile)	n.t.
Rey figure			
Copy	n.t.	33/36 (>75 percentile)	35/36 (>75 percentile)
Recall	n.t.	8/36 (<10 percentile)	0/36 (<5 percentile)
Spatial span	5	n.t.	n.t.
Spatial supraspan	Fail (25 attempts)	n.t.	n.t.
RMT (words)	44/50 (50–75 percentile)	50/50 (>75 percentile)	28/50 (<5 percentile)
RMT (faces)	41/50 (25–50 percentile)	39/50 (25 percentile)	34/50 (<5 percentile)
Topographical memory test	16/30 (5 percentile)	18/30 (10 percentile)	14/30 (<5 percentile)

Scores are given as raw scores (percentile scores in parentheses), RMT = Recognition Memory Test, n.t. = not tested.

tures of outdoor urban scenes was poor at both assessments (from the Camden memory tests: Warrington, 1996).

In sum, RH performed in the normal range on several verbal recall and recognition memory tests, although her performance on tests of story recall was poor. Her recognition memory for human faces was intact. By contrast, her recall of an abstract design and her recognition memory for topographical material was poor.

## 5.2. JC

The results of recall and recognition memory tests are shown in Table 2. Verbal recall was gravely impaired, as measured by a test of story recall. Similarly, visual recall was also very impaired. Indeed, for both recall tests, JC was unable to remember having been administered the tests after a short delay. JC's recognition memory was also severely impaired. Thus, his performance on both the words and the faces subtests of the RMT as well as the topographical recognition memory test was below the 5th percentile.

In sum, JC has a marked global amnesia affecting both recall and recognition tests for verbal and non-verbal stimuli.

## 6. Performance on the Doors and People Test (DPT)

This test comprises four subtests matched for difficulty, two tapping verbal and visual recall memory and two tapping verbal and visual recognition memory. The recognition memory subtests use a four-alternative forced-choice format. All subtests were administered according to the published manual (Baddeley, Emslie, & Nimmo-Smith, 1994). The results are shown in Table 3.

### 6.1. RH

RH showed a very interesting pattern of performance. Her verbal immediate recall was clearly intact whereas her visual recall was strikingly impaired. It should be noted however, that her delayed recall of the verbal information was poor. On the verbal recognition subtest RH obtained a score well above the

75th percentile whilst her performance on the visual subtest was at the 25th percentile. Thus, RH had relatively intact verbal recall and recognition memory. In contrast, her visual recall was clearly impaired. Her visual recognition was in the normal range, albeit considerably lower than her verbal recognition.

### 6.2. JC

JC's performance on the DPT is consistent with his global and severe memory impairment. His performance was impaired on all subtests. Thus, his memory impairment impacted upon recall and recognition for both verbal and visual material to a similar extent.

## 7. Three new verbal and non-verbal recognition memory tests

The results from the previous tests indicated that RH has a rather selective memory impairment, greater for non-verbal materials. Conversely, JC presented with a global anterograde memory impairments affecting both verbal and visual recall and recognition memory. We used three of the five experimental tasks developed by Cipolotti et al. (2006) to investigate the relative contribution of recollection and familiarity to the patients' residual verbal and non-verbal recognition memory skills. There was one test using verbal material (words), one test using topographical material (buildings) and one using unknown human faces. Following previous studies we adopted a receiver operating characteristics (ROC) analysis of recognition memory.

### 7.1. Controls

Sixteen healthy adults (12 female), matched in age to RH and JC, took part in the present study. Their mean age was 63.1 years old ( $SD = 5.6$ , range = 55–73) and their NART estimated IQ was 101.2 ( $SD = 7.7$ , range = 95–109). All controls were neurologically intact. Not all controls were administered all three of the memory tests. However, it was ensured that the subsample that served as controls for each test were representative of the larger "pool". The number of controls for each test is presented together with the results.

### 7.2. Materials

The stimuli have been previously described by Cipolotti et al. (2006) so will only be briefly described here. For the verbal test, 160 words from the Toronto word pool were used, comprising both concrete and abstract words. For the buildings test, 160 black and white photographs of outdoor scenes, containing buildings were used (see for examples, supplementary online materials). The scenes did not contain people. Verbal cues (e.g. house numbers, street names) were digitally removed. For the faces test, 160 black and white photographs of male Caucasian faces with no obvious distinguishing features were used (similar to those used in the faces subtest of the RMT). For each test the 160 stimulus items were split to form a set of 80 study items and 80 unstudied "lure" items.

Table 3  
Results of the Door and People Test for both patients

	RH March 2004	JC June 2004
<i>Verbal subtests</i>		
Immediate recall	30/36 (75 percentile)	1/36 (<5 percentile)
Delayed recall	7/12 (5 percentile)	0/12 (N/A)
Recognition	21/24 (>75 percentile)	11/24 (<5 percentile)
<i>Visual subtests</i>		
Immediate recall	10/36 (<1 percentile)	8/36 (<1 percentile)
Delayed recall	6/12 (75 percentile) <sup>a</sup>	0/12 (N/A)
Recognition	17/24 (25 percentile)	12/24 (<5 percentile)

Scores are given as raw scores (percentile scores in parentheses), N/A = not applicable since the material was not retained at immediate recall.

<sup>a</sup> RH only learnt a small amount of visual information in the immediate recall trials, although she retained this information over a delay. However, given her overall low level of performance, her delayed recall percentile score should not be taken as evidence of good delayed visual recall since she only had a small amount of information to forget.

### 7.3. Procedure

For each test there was a study phase and a test phase. The study phase required the subjects to decide whether (1) the word was “concrete” or “abstract” (words test); (2) the architecture was “pleasant” or “unpleasant” (buildings test), or; (3) the face was “pleasant” or “unpleasant” (faces test). These intentional encoding instructions were adopted since they were similar to those used in previous studies, make the task more engaging for the participants and focus attention on each word/picture. Study items were presented individually for approximately 3 s each.

In the test phase the study items and lure items were randomly intermixed and presented sequentially. Subjects made recognition judgements after each item. Judgements were made according to a 6-point confidence scale. “1” corresponded to the most confident judgement that the item was “new” (previously unstudied) and “6” corresponded to the most confident judgement that the stimulus was “old” (previously studied). It was stressed that participants had to make full use of the 6-point scale by spreading their responses across all the possible confidence ratings.

### 7.4. Design

For the words test, the 80 study items were presented in one block, immediately followed by the 160 items used in the tests phase (80 studied and 80 unstudied lure items). In order to equate the visual tests with the verbal test for difficulty, we presented the stimuli in two blocks separated by a short break (no less than 10 min). In each block we presented 40 study items and 80 test items. In our subsequent analyses we sum across the results obtained in the two blocks for each visual memory test. Despite the relatively large number of study items, there was no indication that any of the patients or controls suffered from a lack of attention or motivation during the tasks.

### 7.5. Analysis 1

The first analysis aimed to investigate overall levels of performance on the tests. The ratings from the confidence levels 4–6 were collapsed to provide a measure of the total number of “yes” responses (“the item was previously seen”). Similarly, the ratings from confidence levels 1–3 were collapsed to provide a measure of the total number of “no” responses (“the item was not previously seen”). Accuracy for each participant was measured as the sensitivity ( $d'$ ), which was calculated using standard signal detection theory methodology (Macmillan & Creelman,

2003). This is based upon the proportion of “yes” responses to old items (hits) minus the proportion of yes responses to new items (false alarms) (see also supplementary material online for an analysis of the data simply in terms of hits–false alarms).

We first checked that the controls did not alter their pattern of responding during the second blocks of the buildings and faces tests. This did not appear to be the case, either when inspecting the distribution of responses for each participant, and a paired t-test comparing the performance on the first and second blocks was not significant. We therefore, combined the responses from both blocks for all further analyses. We used the procedure of Crawford and Garthwaite (2002), for testing the abnormality of the patients’ scores with reference to the modestly sized control groups. This procedure is more resistant to departures from normality than procedures that use z-scores and is a more conservative measure of the abnormality of a patient’s score.

### 7.6. Results of analysis 1

The results of analysis 1 are shown in Table 4a. The data indicated that in the control group, the memory tests were matched for difficulty. Striking differential results were obtained according to the types of material used for RH, with right-sided hippocampal damage. Thus, RH’s memory for topographical material was impaired. However, her memory for words was preserved, as was her memory for faces. No material specific effects were observed in JC’s performance on the three tests. In fact, he was clearly impaired for faces, topography and words. In the second analysis we wished to extend these findings by analyzing separately the contribution of recollection and familiarity to the patients’ performance on these tests.

### 7.7. Analysis 2

The purpose of analysis 2 was to estimate the contribution of recollective and familiarity-based processes to performance on the three tests. Following several previous studies we used a ROC analysis of the confidence judgements made for old and new stimuli to (e.g. Aggleton et al., 2005; Cipolotti et al., 2006; Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998). The ROC is a function that relates the proportion of correct recognitions (i.e. the hit rate) to the proportion of incorrect recognitions (i.e. the false alarm rate). Yonelinas and colleagues (e.g. Yonelinas et al., 1998) have developed a procedure for fitting ROC data, which makes the assumption that performance on the recognition tasks is underpinned by two independent

Table 4a  
Three new verbal and non-verbal recognition memory tests: analysis 1

	RH			JC			Controls		
	$d'$	$t$	$P$	$d'$	$t$	$P$	Mean $d'$	S.D.	Number
Overall performance									
Words	2.10	+0.29	0.61	0.64	−2.40	0.02	1.94	0.51	8
Scenes	0.92	−2.23	0.03	0.23	−3.90	<0.01	1.85	0.39	8
Faces	1.49	−0.74	0.24	0.79	−2.03	0.04	1.89	0.51	8

$d'$  = sensitivity measured as  $d$ -prime;  $t$  = standardized score from the  $t$ -distribution;  $P$  = probability; S.D. = standard deviation.

Table 4b  
Three new verbal and non-verbal recognition memory tests: analysis 2

	RH			JC			Controls	
	Value	<i>t</i>	<i>P</i>	Value	<i>t</i>	<i>P</i>	Mean value	S.D.
<b>Recollection</b>								
Words	0.46	−0.22	0.42	0.00	−4.59	<0.01	0.49	0.10
Scenes	0.15	−3.02	0.01	0.00	−4.51	<0.01	0.45	0.10
Faces	0.43	+0.64	0.27	0.03	−2.49	0.02	0.34	0.12
<b>Familiarity</b>								
Words	1.60	+1.16	0.14	0.31	−2.73	0.01	1.21	0.31
Scenes	0.74	−1.68	0.07	0.31	−3.52	<0.01	1.36	0.28
Faces	1.05	−0.69	0.26	0.61	−1.74	0.06	1.34	0.39

Value = performance in terms of probability (for recollection) and *d*-prime (for familiarity); *t* = standardized score from the *t*-distribution; *P* = probability; S.D. = standard deviation.

processes (recollection and familiarity). Recollection is held to be a threshold retrieval process whilst familiarity is described by a standard equal-variance signal detection model. Based on these assumptions, it is possible to estimate the relative contributions of recollection and familiarity to performance on the memory tests both for the patients and the controls.

In this study, as in our previous study (Cipolotti et al., 2006) we needed to modify the original procedure of Yonelinas. This was because some of the controls obtained high overall levels of performance on the tests, whilst at the same time, were rather cautious in their use of the most conservative confidence level. As a result of this, the ROC curve fitted to the points tended towards an asymptote with the *y*-axis and sometimes resulted in impossibly low (because in some cases they were negative) estimates of recollection. This pattern of performance was observed in both older and younger adult controls. Thus, it does not appear to be a direct consequence of age related drops in recollection in the older adults. This received further support from one of our pilot studies indicating that even within a young adult group (adults in their 20s and 30s), there were individuals producing negative estimates of recollection. A procedure was therefore adopted for estimating recollection using the hit and false alarm rates for the most conservative criterion adopted by a subject. This adopted estimate effectively assumes that after correcting for guessing, all “6” responses reflect recollection. Familiarity estimates were then obtained by constraining the intercept with the *y*-axis according to the probability that an item was recollected (see above) and then fitting the points of the ROC curve using a standard equal-variance model. This was carried out using a least-square method with the solver in Excel, using the program kindly provided by A.P. Yonelinas. Importantly, this modified procedure preserves the basic assumptions of the dual process theory.

We used the procedure of Crawford and Garthwaite (2002) to test whether the patients' estimates of recollection and familiarity differed from those of the healthy controls.

### 7.8. Results of analysis 2

The results of this analysis are shown in Table 4b. Again, performance in the controls was matched between tests with respect

to both estimates of recollection and familiarity. It is clear that the same material specific effects that were observed in analysis 1 for the overall performance of RH, are present in analysis 2. Interestingly, the same patterns of performance were observed for both the patients' estimates of recollection and familiarity. RH's recollection was normal on both the words and faces tests. However, her recollection estimates on the topographical test was significantly impaired. JC's recollection estimates were at floor for all three tests, i.e. for verbal, topographical and faces materials.

RH's familiarity estimates followed the same pattern as her recollection estimates. Thus, her familiarity for verbal and faces materials was well within the normal range. In contrast, her familiarity for topographical materials was weak, with the difference between RH and the controls being marginally significant ( $P < 0.1$ ). JC continued to show no clear evidence of spared memory processes for any material. His familiarity estimates were markedly low on all three tests; they were impaired on the verbal and topographical memory tests and borderline impaired for the faces memory test ( $P < 0.1$ ).

Overall, the second analysis produced a number of interesting results. First, the material specific effects found for RH, with right hippocampal damage, were in evidence both for recollection and familiarity estimates. Thus, RH showed normal recollection and familiarity for human faces, but very poor recollection and familiarity for topographical material. Patient JC, with more extensive cortical damage showed no clear evidence of sparing of either recollection or familiarity for both visual materials. RH's estimates of recollection for verbal materials were similar, and in the case of familiarity, better, than the controls'. In contrast, JC's estimates of recollection and familiarity for verbal materials were grossly impaired.

## 8. Discussion

The present study focused on the role of the MTL in verbal and non-verbal memory for human faces and topography. We explored this issue in two patients with memory impairments following MTL damage.

The global amnesic patient JC, had bilateral hippocampal damage following anoxia caused by cardiac arrest. This type of



pathology has been considered in some studies as a model for selective hippocampal damage (Chun & Phelps, 1999; Hannula, Tranel, & Cohen, 2006; Yonelinas et al., 2002). However, this assumption is controversial: it has been argued that anoxia can cause additional cortical damage (e.g. Grubb et al., 2000; Markowitsch et al., 1997). Thus, detailed cognitive testing is crucial to ascertain whether the damage is really limited to the hippocampus (see also, Wixted & Squire, 2004). JC not only had a global amnesia, but also showed a mild underfunctioning on performance IQ, anomia for common nouns and a degree of executive dysfunction. This suggests that despite the lack of neuroradiological evidence, he had dysfunction in cortical areas other than the hippocampus. Perhaps unsurprisingly, JC's performance on the three experimental tasks was different from patient VC, who had a global amnesia, but an otherwise intact cognitive profile. JC was impaired on tasks employing verbal, topography and faces memoranda. These results demonstrate that dense amnesia following anoxia is not always associated with sparing of face recognition memory for unfamiliar faces, but also suggests that this is because damage extends beyond the hippocampus.

According to expert radiographers blind to the hypotheses of this study, the second patient, RH, had clear evidence of selective right-sided hippocampal damage. The appearance of her left hippocampus was normal. Similarly, her entorhinal cortex, parahippocampal gyrus, fusiform gyrus and other temporal lobe structures appeared normal in both hemispheres. Her cognitive profile revealed intact and static performance on tests tapping intelligence, language, perception and executive functions as well as completely preserved semantic memory. Detailed investigation of her anterograde memory revealed an interesting pattern of performance. On verbal memory tests her performance was generally good, as assessed by paired-associate learning, word and name recognition. Her recall of prose and her delayed recall of names was somewhat poorer. On non-verbal recall memory tests her performance was impaired. Performance on recognition memory tests for faces and doors was within the normal range. However, her performance on the topographical recognition test, which involves pictures of outdoor urban scenes, was consistently poor. On the basis of the sudden onset of her memory problems, her static cognitive profile and the neuroradiological evidence, RH's hippocampal damage is presumed to be ischaemic in origin.

RH's performance on the three experimental tests was striking. She obtained normal scores on the tests using verbal and faces memoranda. In stark contrast, she was impaired on the test using topographical memoranda. Interestingly, estimates of recollection and familiarity followed the same pattern. Thus, recollection and familiarity estimates for verbal and faces memoranda were in the normal range. However, recollection for topographical material was impaired and familiarity was markedly weak. These results replicated and extended those of the previously reported patient VC (Cipolotti et al., 2006). Like VC, RH showed impaired topographical memory in the context of spared memory for unknown faces. However, unlike VC, verbal memory was also largely spared.

### 8.1. *The hippocampus and verbal memory*

Patient RH, with selective right hippocampal damage, performed well on several verbal memory tests and her estimates of recollection and familiarity for words were normal. The bilateral hippocampal amnesic, VC, showed a profound verbal memory impairment. These findings suggest that the left hippocampus is sufficient to subserve both recollection and familiarity for at least some types of verbal memoranda. This is consistent with classic studies reporting selective verbal memory impairments in left-sided MTL patients (Frisk & Milner, 1990; Milner, 1971). However, RH's performance on standard tests of prose recall and a test of delayed recall for names was poor. It may be that the ability to form some types of robust associative verbal memories, particularly those involving complex narrative, requires both the left and right hippocampus. It has been reported that right-sided MTL patients were impaired in a test of verbal memory, when visual strategies could be used to aid performance in healthy adults (Jones-Gotman & Milner, 1978). Therefore, it may be that the right hippocampus plays a role in providing a visuospatial framework for the encoding of complex verbal memoranda.

### 8.2. *The hippocampus and unknown face memory*

RH performed normally on tests employing human faces memoranda. In fact, this is not an uncommon finding in patients with hippocampal lesions. The memory profiles of hippocampal amnesics vary widely in terms of their performance on recognition memory tests for different materials, but face recognition memory is often preserved (Carlesimo et al., 2001; patients LM, PH, LJ, AB and WH, Reed & Squire, 1997; patient BE, Kapur, Thompson, Kartsounis, & Abbott, 1999). An analysis of the performance of a very well-documented hippocampal amnesic, YR, showed that her performance on recognition memory tests using faces was superior to her performance on similar tests using words and visual scenes (Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002).<sup>1</sup> In keeping with this, patients with predominant hippocampal damage recently reported by Lee et al. (2005a, 2005b, 2006) performed well on the faces subtest of the RMT.

We are aware of two patients with impaired face recognition in the context of selective hippocampal damage (patient GD: Reed & Squire, 1997; patient PS: Verfaellie, Koseff, & Alexander, 2000). However, interpretation of these cases is problematic. GD was described as being "uncooperative, depressed, and uninterested in testing" and "his frequent low motivation during testing sessions made it difficult to interpret low scores" (Rempel-Clower, Zola, Squire, & Amaral, 1996, p. 5293). The

<sup>1</sup> YR's recognition performance on seven tasks using faces, six tasks using visual scenes and eight tasks using words is reported (Table 1, Mayes et al., 2002). Her mean performance in terms of *z*-scores was +0.32, -0.75 and -1.3 for the respective materials. The difference in means is significant, even when covarying for overall difficulty of the separate tests ( $P < 0.01$ ). Post-hoc comparisons confirmed the superiority of face recognition over words ( $P < 0.01$ ) with the difference between faces and visual scenes being marginally significant ( $P < 0.1$ ).

pathology in patient PS may extend beyond the hippocampus as her MRI scan is reported to show “mild generalized cortical atrophy” and “ventricular enlargement for her age may be present” (Verfaellie et al., 2000, p. 487).

Our findings of preserved recognition memory for unknown faces following hippocampal damage in patients VC and RH support the view that this type of memory is not critically dependent on the hippocampus, and may depend on other structures. Areas implicated in face processing such as the fusiform gyrus and perhaps the anterior temporal lobe may be sufficient to subserve face recognition memory (e.g. Kim et al., 1999; Lee et al., 2006; Maguire, Frith, & Cipolotti, 2001). Face recognition represents an interesting challenge, because we meet people in all manner of different contexts (places, times of the day, social situations, etc.). In fact, the formation of relatively context-free memories of faces might actually be useful in our daily life. In contrast, some dominant theories of hippocampal function, stress its role in the formation of configural associations between otherwise independent elements (Rudy & Sutherland, 1995), or of flexible relations between discontinuous stimuli (Eichenbaum & Cohen, 2001). It is plausible therefore, that perceptual and mnemonic circuits may have become specialized for face recognition.

### 8.3. *The right hippocampus and other non-verbal memory*

Patient RH performed poorly on recognition memory tests using topographical but not faces memoranda. However, RH's non-verbal memory deficit extended beyond topographical memory. She was impaired in recalling abstract designs and in learning a supraspan block tapping sequence. Similarly, other hippocampal patients in the literature have been impaired on these types of memoranda (see Spiers, Maguire, & Burgess, 2001). Thus, the hippocampus, particularly on the right, clearly plays a mnemonic role for materials other than topography. Nevertheless, RH was able to perform in the normal range on a recognition memory test using doors as stimuli. It may be that her recognition memory for other materials not tested here (e.g. objects, patterns) is intact. There are on record patients who have shown spared recognition memory for non-verbal memoranda other than faces, following hippocampal and more extensive MTL damage (Mayes et al., 2002; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Barbeau et al., 2005). Future research will be necessary to establish which aspects of non-verbal memory can be mediated successfully by areas outside the hippocampus.

### 8.4. *The right hippocampus and topographical memory*

RH was impaired on clinical and experimental tests employing topographical memoranda, showing buildings in the context of a large-scale space. In her daily life, RH got disorientated in unfamiliar places. However, she had no difficulty recognizing familiar landmarks, suggesting that her topographical perception was largely intact. Outside of the laboratory, topographical stimuli such as buildings are generally encountered in a specific geographical location. It may be therefore, that they are

encoded in terms of a spatial framework, used to aid navigation. Therefore, one can speculate that recognition tests employing topographical materials may be underpinned by the same areas known to subserve navigation in healthy adults (see Maguire & Cipolotti, 1998; for a similar argument). There is a considerable body of evidence that the right hippocampus plays a critical role in navigation, both from the animal literature and from neuroimaging in healthy adults (Burgess, Maguire, & O'Keefe, 2002; Hartley, Maguire, Spiers, & Burgess, 2003).

The evidence collected from patient VC suggested that the hippocampus was necessary for topographical memory. However, it was not clear whether the left, right or both hippocampi were critical. RH's data suggest the right hippocampus is necessary to subserve this ability.<sup>2</sup> This is in keeping with other neuropsychological studies that have demonstrated a greater role for the right hippocampus over the left, in spatial memory (Nunn, Graydon, Polkey, & Morris, 1999; Stepankova, Fenton, Pastalkova, Kalina, & Bohbot, 2004). A recent study demonstrated a selective topographical memory failure in a group of patients with hippocampal lesions that included both RH and VC (Hartley et al., *in press*). All the hippocampal patients showed impairment in retaining flexible allocentric spatial representations of the positions of landmarks in visual scenes, even over a few seconds. Interestingly, these patients were unimpaired at retaining non-spatial visual information about the scenes.

### 8.5. *The role of the hippocampus in recollection and familiarity*

The issue of whether the hippocampus plays a critical role in both recollection and familiarity-based recognition processes is highly contentious (for reviews, see Aggleton & Brown, 1999; Rugg & Yonelinas, 2003; Squire, Stark, & Clark, 2004). Some researchers have proposed that extrahippocampal areas such as the perirhinal cortex may be sufficient to subserve familiarity-based recognition processes (Aggleton & Brown, 1999; Mayes et al., 2002; Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997; Rugg & Yonelinas, 2003). Indeed, there are several neuropsychological studies that support this position (see for a review, Cipolotti & Bird, 2006). For example, Mayes and colleagues have reported three single case studies of patients with lesions involving the hippocampus, which have shown relative sparing of familiarity-based over recollective-based memory processes (Aggleton et al., 2005; Bastin et al., 2004; Holdstock et al., 2002; Mayes et al., 2004).

In the present study, deficits in recollection were always associated with deficits in familiarity. The ROC analyses revealed that RH's familiarity for topographical materials was markedly weak and was not sufficient to support normal recognition memory. Together with the previous results from VC, these data appear to support the position held by Squire and colleagues;

<sup>2</sup> There are on record at least three hippocampal amnesics with normal performance on static tests of topographical recognition memory (Barbeau et al., 2005; Mayes et al., 2002; Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001). Differences in the test format, number of items and test stimuli may partially account for these inconsistent findings.

namely, that the hippocampus plays a role in both recollection and familiarity (Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Wais, Wixted, Hopkins, & Squire, 2006). However, we were only able to characterize RH's lesion on the basis of a qualitative MRI investigation. Thus, caution is necessary before drawing strong conclusions from these data about the neuroanatomy of recollection and familiarity.

## 9. Conclusions

We have previously suggested that the hippocampus is necessary for recollection and familiarity for verbal and topographical materials, but not for unfamiliar faces (Cipolotti et al., 2006). The present findings support this proposal and suggest that specifically the right hippocampus is necessary for recollection and familiarity for topographical materials. The left hippocampus appears to be sufficient to subservise at least some aspects of both recollection and familiarity for verbal memoranda.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2006.10.011.

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