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Relative Sparing of Item Recognition Memory in a Patient With Adult-Onset Damage Limited to the Hippocampus

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ABSTRACT: There is disagreement about whether selective hippocampal lesions in humans cause clear item recognition as well as recall deficits. Whereas Reed and Squire (Behav Neurosci 1997;111:667–775) found that patients with adult-onset relatively selective hippocampal lesions showed clear item recognition deficits, Vargha-Khadem et al. (Science 1997;277: 376–380, Soc Neurosci Abstr 1998;24:1523) found that 3 patients who suffered selective hippocampal damage in early childhood showed clear recall deficits, but had relatively normal item recognition. Manns and Squire (Hippocampus 1999;9:495–499) argued, however, that item recognition may have been spared in these patients because the early onset of their pathology allowed compensatory mechanisms to develop. Therefore, to determine whether early lesion onset is critical for the relative sparing of item recognition and to determine whether its occurrence is influenced by task factors, we extensively examined item recognition in patient Y.R., who has pathology of adult-onset restricted to the hippocampus. Like the developmental cases, she showed clear free recall deficits on 34 tests, but her item recognition on 43 tests was relatively spared, and markedly less disrupted than her recall. Her item recognition performance relative to that of her controls was not significantly influenced by whether tests tapped visual or verbal materials, had a yes/no or forced-choice format, contained few or many items, had one or several foils per target item, used short or very long delays, or were difficult or easy for normal subjects. Interestingly, YR's bilateral hippocampal destruction was greater than at least 2 of the 3 patients of Manns and Squire (Hippocampus 1999;9:495–499). The possible reasons why item recognition differs across patients with relatively selective hippocampal damage of adult-onset and how the reasons that are truly critical can be best identified are discussed. *Hippocampus 2002;12:325–340.*

INTRODUCTION

There is currently considerable debate about the role of the hippocampus in item recognition memory. There are two main views, both of which assume that familiarity as well as recollection contribute to item recognition memory (Mandler, 1980; Jacoby, 1991). One view is that the hippocampus is critical for recollection, but is only necessary for item recognition when this cannot be based on item familiarity (Aggleton and Shaw, 1996; Aggleton and Brown, 1999; Baddeley et al., 2001; Holdstock et al., 2000b; Mayes et al., 2001; Murray and Mishkin, 1998; Vargha-Khadem et al., 1997). Item familiarity depends critically on the integrity of the perirhinal cortex as well as other extrahippocampal structures, such as the dorsomedial thalamus (see Aggleton and Brown, 1999). An alternative view is that the hippocampus is always important not only for recall, but also for item recognition, regardless of the extent to which item recognition is based on either recollection or item familiarity (Haist et al., 1992; Reed and Squire, 1997; Squire and Zola, 1998; Suzuki, 1999; Zola and Squire, 1999; Zola et al., 2000).

The first view predicts that hippocampal damage will at most cause mild item recognition deficits and that recognition may often appear to be normal; the alternative view predicts that item recognition should be clearly impaired regardless of how much it depends on recollection. Also, as recollection is a recall process, the first view predicts that hippocampal damage should disrupt free recall clearly more than it affects item recognition. In contrast, the alternative view predicts that recall and item recognition should both be clearly impaired to approximately equivalent degrees.

Aggleton and Shaw (1996) argued that the first view was supported by the results of a meta-analysis that they had conducted. This meta-analysis examined the performance of a large number of amnesics with lesions of varying extents and locations on the Recognition Memory Test (RMT; Warrington, 1984), which measures forced-choice item recognition, and the Wechsler Memory Scale-Revised (WMS-R), which primarily measures free and cued recall. Seven patients in whom damage was limited to the hippocampus, fornix, or mammillary bod-

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ies showed a level of performance on the RMT that was only slightly below the mean level of normal subjects. A *t*-test comparison of the group's recognition z-scores against zero showed that the trend towards impairment on these recognition tests did not reach significance ($t = 2.170$, $P = 0.073$ for words; $t = 0.806$, $P = 0.451$ for faces). Although the failure to show a significant item recognition deficit may simply have arisen because both the deficit and the group's size were small, the group did show significantly better recognition than the amnesic patients in whom damage was more widespread and who showed clear item recognition deficits. The more selectively lesioned patients showed good RMT performance, even though they were not significantly less impaired than the more severely damaged global amnesics on the WMS-R verbal and visual memory quotients (which primarily tap recall). A real difference may have been concealed, however, because the global amnesic patients were performing at floor levels.

Furthermore, the three hippocampally lesioned patients whom Aggleton and Shaw (1996) included in their meta-analysis were subsequently shown to be clearly impaired on a wide range of other item recognition memory tests (Reed and Squire, 1997). Two further patients, R.B. and G.D., shown by neurohistological analysis to have damage mainly confined to the CA1 field of the hippocampus, also showed item recognition deficits on other tests. R.B. was clearly impaired on a test which contained forced-choice and yes/no word recognition components (Zola et al., 1986), and G.D. was clearly impaired on a word yes/no recognition task with five study-test presentations and a modification of the RMT which used a 1-day delay between study and test rather than no delay. These findings suggest that even if some patients with selective hippocampal lesions perform relatively normally on the RMT, they may be clearly impaired on other tests of item recognition. It is important, therefore, to determine the extent to which any differences found between patients reflect the use of different item recognition tests, and which test factors may influence the degree to which performance is normal. If test-related factors are not as important as the above results suggest, then differences presumably arise because of variation across patients in factors such as lesion extent and location.

Some support for the view that the hippocampus is not critical for item recognition memory where test-related factors seemed less likely to be critical was provided by Vargha-Khadem et al. (1997). These researchers found that item recognition was apparently normal in 3 young patients who had suffered relatively selective hippocampal damage early in life. The patients' recall of episodic information was impaired, but they performed normally not only on the RMT, but also on *several* other tests of item recognition. One of these patients, Jon, was assessed on the Doors and People Test (Baddeley et al., 1994), a battery which taps recall and forced-choice recognition of visual and verbal items using tests equated for difficulty. Jon was found to score at the 50th percentile for item recognition, but at below the first percentile for recall (Baddeley et al., 2001). These data were interpreted as showing that the hippocampus is not necessary for some kinds of item recognition memory, even when these tests are as difficult as free recall tests for which it is necessary.

However, Manns and Squire (1999) reported that 3 patients (A.B., who was included in the analysis of Reed and Squire (1997), P.H., and L.J.) with adult-onset pathology apparently restricted to the hippocampus were clearly impaired on both recall and item recognition subtests of the Doors and People Test. The difference in item recognition performance on the Doors and People Test between Jon and A.B., P.H., and L.J. cannot be attributed to differences between tests. Instead of this, it must be due to differences between Jon and the other patients. Indeed, Manns and Squire (1999) explained these findings by arguing that the hippocampus *is* necessary for normal item recognition except in cases, such as Jon, in whom very early hippocampal damage allows compensatory mechanisms to develop. These mechanisms are able to mediate normal levels of item recognition memory on the Doors and People Test and other similar tasks.

Our primary aim was to determine whether early-onset hippocampal lesions are critical for the relative preservation of item recognition memory, and to identify what, if any, test factors influence the degree of preservation shown. To achieve this, we extensively tested a patient, Y.R., who has selective adult-onset bilateral pathology of the hippocampus. We report a summary of her performance on a battery of 43 item recognition tests. These tests varied in a number of ways, including: whether the test had a forced-choice or yes/no format, whether the stimuli were verbal or nonverbal, the length of retention interval, the number of test choices, length of the study list, and difficulty of the test for control subjects.

In addition to the RMT, the battery included the recognition subtests of the Doors and People Test. Y.R.'s performance on the Doors and People Test is described in detail because it allows a comparison between her recall and item recognition memory on tests matched for difficulty for the normative sample. In addition, it allows us to make a comparison between the recall and item recognition of Y.R., Jon (Vargha-Khadem et al., 1998), and the patients described by Manns and Squire (1999) on identical memory tests. Her performance closely resembles that of Jon, whose early-onset selective hippocampal damage was of similar severity.

Finally, in order to check that Y.R.'s recall was clearly more impaired than her item recognition as indicated by her performance on the Doors and People Test, and that her performance on the recall tests of this battery generalized to other recall tests, we compared her performance on a further 32 tests of free recall with the performance of her matched control subjects.

METHODS

Subjects

Patient Y.R. has had a memory impairment since 1986, when, aged 49 years, she was given an opiate drug to relieve severe back pain, which may have caused an ischemic infarct. Her memory impairment immediately followed this incident and has persisted until the present time.

A magnetic resonance imaging (MRI) scan was obtained for patient Y.R., using a three-dimensional (3D) T1-weighted radiofrequency spoiled gradient echo (SPGR) sequence (TE = 9 ms, TR = 34 ms, flip angle = 45°, matrix size = 256 × 192, 2 NEX, field of view = 20 cm, acquisition time = 27 min and 52 s) available on a 1.5T SIGNA whole-body magnetic imaging system (General Electric, Milwaukee, WI). Volumetric analysis using the Cavalieri method of modern design stereology (Gunderson and Jensen, 1987) revealed bilateral damage to the hippocampus throughout its entire length. Hippocampal volume measures were calculated using the boundaries defined by Mackay et al. (1998). In percentage terms, Y.R.'s hippocampus, corrected for intracranial volume, was reduced by 45% on the right and 47% on the left relative to her gender, age, and IQ-matched control group's mean. The amygdala was small but showed no sign of pathology, and there were no visible abnormalities of the medial temporal lobe cortices. Volumetric measures, corrected for intracranial volume, were also obtained for the parahippocampal gyrus, frontal lobes, and parietal lobes. The parahippocampal gyrus measure included the entorhinal, perirhinal, and parahippocampal cortices as well as white matter. Y.R.'s parahippocampal gyrus was slightly larger than the mean level of her control group. The volumes of both the frontal and the parietal lobes were within two standard deviations of the control group's mean volume bilaterally. Y.R.'s left frontal lobe was marginally (less than 10%) larger and her right frontal lobe was marginally smaller than the mean levels for her control group. Y.R.'s left parietal lobe was 14% smaller and her right parietal lobe was 13% smaller than the mean level of her control subjects (for a more detailed report of the volumetric analysis of Y.R.'s scan, see Holdstock et al., 2000a).

Y.R.'s performance on psychometric tests was reported previously (Holdstock et al., 2000a,b; Mayes et al., 2001). It revealed that Y.R. had a full-scale IQ, assessed by the WAIS-R, of 102. She showed no indication of executive impairment tested by verbal fluency (FAS; Benton, 1968), cognitive estimates (CET; Shallice and Evans, 1978), and the Wisconsin Card Sorting Test (WCST; Heaton, 1981). Her performance on the FAS was 0.1 SD below her control group's mean, and on the CET was 0.69 SD below her control group's mean. On the WCST, having rapidly identified the three simple sorting rules, she attempted to use other more complex rules for the remaining categorizations and so only achieved three correct categories (6th–10th percentiles). However, consistent with this complex strategy, she had a minimal tendency to make perseverative errors (88th percentile). Y.R.'s performance on the WCST, therefore, provided no evidence that she perseverated or that she was unable to switch hypotheses, two hallmarks of executive dysfunction caused by frontal lobe damage (see Lezak, 1995).

On the Wechsler Memory Scale-Revised, which mainly taps recall, Y.R. was impaired. Her general memory index fell at the 1st percentile, whereas her delayed memory index fell at the 4th percentile. On the Adult Memory and Information Processing Battery (Coughlan, 1985), Y.R. was impaired at learning a list of words, recalling a story (immediately and after a delay), and recalling a figure (immediately and after a delay). She also performed at less than the 10th percentile at design learning. In contrast, on the RMT, she correctly recognized 45 out of 50 words (75th percentile) and 48 out of 50 faces (above the 95th percentile). For each of the item recognition and free recall tests to be reported here, Y.R.'s performance was compared with a group of female control subjects matched for age and IQ. The size of the group varied from 8–12 subjects. Control groups for each task overlapped, but were not identical. Subjects for each group were drawn from a limited pool of 20 well-matched individuals.

Materials and Procedure

Y.R. and control subjects were tested on 43 item recognition tests. The details of these tests are summarized in Table 1. The tests varied with respect to whether they tapped memory for verbal (n = 19) or visual (n = 24) items, whether they were of the forced-choice (n = 27) or yes/no (n = 16) format, the ratio of number of test items to number of targets at test, the study-test delay used, study list length, and how difficult normal subjects found the tasks. Four of the tasks were from standardised memory tests: the RMT and the Doors and People Test. Three tests used materials from the Camden Memory Tests (Warrington, 1996), but tested memory after longer delays than the published test. The other tasks were constructed either in our laboratory or by collaborators. These specially constructed tests used words, nonfamous names, definitions, facts from previously presented stories, faces, abstract patterns, line-drawn object pictures, photographs of scenes, and photographs of animals as stimuli. Subsets of these tests are reported in more detail by Holdstock et al. (2000b, in press a,b), and Mayes et al. (2001), and are indicated as such in Table 1. In all tests, subjects studied a list of items. Recognition of items was then examined after a delay. In some tests, recognition was examined with a forced choice procedure and in other tests with a yes/no procedure.

Y.R.'s performance on the Doors and People Test is also reported in detail. The test comprises four subtests: a visual and a verbal recall test, and a visual and a verbal recognition test (for a description see Manns and Squire, 1999). The test was administered to Y.R. according to the instructions in the published manual (Baddeley et al., 1994).

Y.R. and her control subjects were also given 32 further free recall tests. Only tests in which Y.R. and her control subjects were treated in exactly the same way were included. No standardized indices, which combine several different recall tests, were included. All tests differed from the others selected in some significant respect, e.g., delay. No test was included where performance could largely be mediated by working memory, which may happen when one or two simple stimuli are presented only once and then tested immediately. The tests assessed free recall of various kinds of verbal information (e.g., words, stories, or word meanings) and various kinds of visual information (e.g., line drawings and visuospatial information). The tests differed with respect to list length, number of presentations at study, and length of delay. These features of the 32 tests and the two free recall tests of the Doors and People Test are summarized in Table 4.

Y.R.'s performance on each item recognition and each free recall test was converted to a z-score, i.e., expressed as the number of standard deviations (SDs) above (+) or below (−) the control

TABLE 1.

Main Features of Forty Three Item Recognition Tests Together With Y.R.'s Performance Relative to That of Her Control Subjects on These Tests[a]

Test description	Stimulus type	Paradigm type	Delay	Test choices	Difficulty	List length	Y.R.'s performance
RMT word recognition (S)	Verbal	FC	0 s	2	86.0	50	−0.67
Single word recognition	Verbal	FC	0 s	2	58.8	60	−0.4
D&P name recognition (S)	Verbal	FC	0 s	4	69.3	12	1.04
Single word recognition accompanied by confidence judgment	Verbal	FC	20 s	3	68.7	60	−2.8[b]
Recognition of facts from a short story read to the subject at study	Verbal	FC	20 s	4	62.7	12	−0.9
Selecting studied (previously unfamiliar) definitions from among similar definitions (1)	Verbal	FC	20 s	4	64.7	9	−0.4
Single word recognition (2)	Verbal	FC	15 s	5	90.0	10	−1.1
Single word recognition	Verbal	FC	60 s	2	68.6	12	−0.2
Recognition of facts from a short story read to the subject at study	Verbal	FC	10 min	4	54.7	12	−0.9
Recognition of facts from a short story read to the subject at study	Verbal	FC	60 min	4	46.7	12	−0.6
Selecting studied (previously unfamiliar) definitions from among similar definitions (1)	Verbal	FC	24 hr	4	51.2	9	−0.77
Selecting studied (previously unfamiliar) definitions from among similar definitions (1)	Verbal	FC	21 days	4	62.9	9	−1.1
Selecting studied (previously unfamiliar) definitions from among similar definitions (1)	Verbal	FC	30 days	4	73.3	10	−1.0
Single word recognition	Verbal	YN	0 s	2	75.0	60	−0.66
Recognition of unfamiliar names with a remember/know judgment	Verbal	YN	0 s	2	44.0	50	1.93
Recognition of unfamiliar names with a remember/know judgment	Verbal	YN	0 s	2	45.0	50	0.9
Recognition of unfamiliar names with a remember/know judgment	Verbal	YN	0 s	2	44.0	50	0.71
Recognition of words with a remember/know judgment	Verbal	YN	0 s	2	71.2	25	−2.6[b]
Single word recognition (2)	Verbal	YN	15 s	5	72.0	10	−2.0[b]
RMT face recognition (S)	Nonverbal	FC	0 s	2	80.0	50	1.3
Recognizing visual scenes (digitized photographs presented on computer)	Nonverbal	FC	0 s	2	91.6	150	−1.5
D&P recognition of pictures of doors (S)	Nonverbal	FC	0 s	4	82.7	12	−0.91
Delayed match to sample task using abstract patterns as stimuli (3)	Nonverbal	FC	10 s	14	84.1	1	−0.94
Selection of studied wallpaper patterns from among similar wallpaper patterns (2)	Nonverbal	FC	15 s	5	82.5	10	0.3
Delayed match to sample task using abstract patterns as stimuli (3)	Nonverbal	FC	20 s	14	69.8	1	0.32
Delayed match to sample task using abstract patterns as stimuli (3)	Nonverbal	FC	30 s	14	74.2	1	−1.1
Recognition of line-drawn pictures of natural and manmade objects (4)	Nonverbal	FC	40 s	4	55.6	12	0.53

TABLE 1. (Continued)

Test description	Stimulus type	Paradigm type	Delay	Test choices	Difficulty	List length	Y.R.'s performance
Recognition of line-drawn pictures of natural and manmade objects (4)	Nonverbal	FC	30 min	4	66.4	12	0.83
Recognizing visual scenes (digitized photographs presented on computer)	Nonverbal	FC	24 hrs	2	67.6	150	0.03
Recognizing visual scenes (digitized photographs presented on computer)	Nonverbal	FC	21 days	2	35.2	150	−0.4
Scene recognition using materials from the topographical subtest of the CMT (S)	Nonverbal	FC	24 hrs	3	59.5	30	−0.2
Scene recognition using materials from the picture subtest of the CMT (S)	Nonverbal	FC	30 days	3	42.5	30	−1.3
Scene recognition using materials from the topographical subtest of the CMT (S)	Nonverbal	FC	30 days	3	36.5	30	−1.1
Recognition of black and white pictures of unfamiliar faces created using Photo-Fit software; computer presentation	Nonverbal	YN	0 s	2	53.0	12	0.4
Recognition of unfamiliar faces with remember/know judgment	Nonverbal	YN	0 s	2	43.0	50	−0.46
Recognition of unfamiliar faces with remember/know judgment	Nonverbal	YN	0 s	2	40.0	50	0.4
Recognition of unfamiliar faces with remember/know judgment	Nonverbal	YN	0 s	2	43.0	50	0.47
Selection of studied wallpaper patterns from among similar wallpaper patterns (2)	Nonverbal	YN	15 s	5	54.2	10	−0.4
Selecting studied photographs of animals from among unstudied photographs of the same animals	Nonverbal	YN	20 s	2	60.5	36	−0.23
Selecting studied faces from among unstudied faces; digitized photographs; hair masked	Nonverbal	YN	20 s	2	51.4	8	0.65
Recognition of abstract patterns (5) with remember/know judgment	Nonverbal	YN	40 s	2	78.5	20	−1.45
Recognition of line-drawn pictures of natural and manmade objects (4)	Nonverbal	YN	40 s	4	62.0	12	−2.7[b]
Selecting studied faces from among unstudied faces; digitized photographs; hair masked	Nonverbal	YN	40 min	2	43.9	8	−0.54

[a]Standardized published tests are indicated by (S). All other tasks were tests developed in our laboratory or the laboratories of collaborators. Tasks described in more detail in other papers are indicated by a number in parentheses. These numbers refer, respectively, to: 1, Holdstock et al., in press b; 2, Mayes et al., in press; 3, Holdstock et al., Cortex, 2000; 4, Holdstock et al. in press, a; 5, Holdstock et al., 1995 (stimuli taken from the hard version of the pattern recognition task described in experiment 2). RMT, Recognition Memory Test (Warrington, 1984); D&P, Doors and People Test (Baddeley et al., 1994); CMT, Camden Memory Tests (Warrington, 1996). YN, yes/no recognition paradigm; FC, forced-choice recognition paradigm; Delay, delay from end of presentation of study list to start of test. Test choices, number of choices at test per studied item, e.g., in a forced choice test where three foils are presented with the studied item at test, the number of test choices is four; in a yes/no test where 20 items are studied and 40 test items are presented (20 studied and 20 new), the number of test choices is two. Difficulty, a percentage score indicating where between chance and a perfect score the control subjects' mean score fell. List length, length of the study list. Y.R.'s performance, Y.R.'s performance expressed as z-scores (i.e., number of standard deviations that her performance fell above (+) or below (−) the control mean).
[b]Indicates tests on which YR performed more than 1.96 SDs worse than the control mean.

mean. Two forms of statistical analysis were performed on her z-scores. First, on the assumption that a set of tests (e.g., recall or item recognition) was reasonably functionally homogeneous, one-sample *t*-tests were used to compare Y.R.'s z-scores against the control mean of zero. This allowed us to determine whether her memory performance was significantly below the mean level of her control subjects. However, a considerable proportion of the normal population also scores below the control group mean. So finding that performance is significantly below the control mean is in itself not sufficient to determine whether a patient is impaired. The standard criterion for making such an inference is that the subject's score falls in the bottom 2.5% of the normal population, which corresponds to a z-score of less than −1.96. Such a criterion reduces the risk of wrongly inferring that brain damage has caused the below-average performance to a probability of 0.05. Second, therefore, Y.R.'s z-scores on individual tests or her mean z-scores on sets of reasonably functionally homogeneous tests were compared against this standard criterion to determine whether we were entitled to infer that she did have a clear memory impairment.

RESULTS

Item Recognition Tests

Y.R.'s mean item recognition z-score, calculated from all 43 tests, was just −0.5. Although the difference between Y.R.'s performance and the control mean was only slight, it was statistically significant ($t = 2.87$, df = 42, $P < 0.05$), indicating that Y.R.'s item recognition was consistently below average. However, her mean z-score of −0.5 fell well above the standard criterion for impairment of −1.96. Therefore, we cannot reject the possibility that her below-average performance reflects normal variability around the population mean. There were only 4 of the 43 tests on which she obtained a z-score of less than −1.96. Furthermore, her performance was either at or above her control group's mean on about a third of the tests (see Table 1).

Y.R.'s mean performance on visual (n = 24) and verbal (n = 19) item recognition tests did not differ significantly ($t = 0.853$, df = 41, $P > 0.05$). Her mean z-score was −0.3 on visual item recognition tests and −0.6 on verbal item recognition tests. Y.R.'s performance was also comparable on forced-choice (n = 27) and yes/no (n = 16) tests, where her mean z-scores were −0.5 and −0.4, respectively ($t = 0.507$, df = 41, $P > 0.05$).

The effects of study list length, delay, difficulty, and ratio of number of test items per target item were also investigated. There was no significant difference between Y.R.'s item recognition when study lists of between 1–20 items long (n = 24), between 2–50 items long (n = 13), and more than 50 items (n = 6) were compared (F = 1.75, df = 2, 40, $P > 0.05$). Y.R.'s mean z-scores were −0.5, −0.1, and −1.0 for list lengths of 1–20, 21–50, and greater than 50 items, respectively. The power of this analysis may be limited by the small group size of the latter two categories of test. However, we also found no significant difference in item recognition performance when study list lengths of less than (n = 24) or greater than (n = 19) 20 items were compared ($t = 0.6$, df = 41, $P > 0.05$).

A one-way ANOVA comparing Y.R.'s performance at delays of less than or equal to 1 min (n = 31, mean z-score = −0.4), of between 1 min and 1 h (n = 4, mean z-score = −0.3), and of greater than 1 h (n = 8, mean z-score = −0.8) found no significant effect of delay (F = 0.35, dfs = 2, 40, $P > 0.05$). Due to the small number of tests for some delays, a *t*-test comparing Y.R.'s performance for delays of up to 1 min (n = 31) and of greater than 1 min (n = 12) was also performed and again found no significant delay effect ($t = 0.52$, df = 41, $P > 0.05$).

Difficulty was measured as a percentage score indicating where between chance and a perfect score the control subjects' mean performance fell, so that a higher score corresponded to an easier test. Tests were categorized as easy (above 75), moderately difficult (between 50–75), or hard (below 50). Y.R.'s mean item recognition test z-scores were −0.6, −0.6, and 0 on easy (n = 8), moderately difficult (n = 24), or hard (n = 11) tests, respectively. A one-way ANOVA showed that Y.R.'s z-scores did not significantly differ from each other as a function of difficulty (F = 1.45, df = 2, 40, $P > 0.05$). Post hoc Tukey test comparisons of Y.R.'s item recognition scores for the ANOVAs, used to investigate the effect of list length, delay, and difficulty, failed to reveal any significant differences.

There was also no significant difference ($t = 0.94$, df = 41, $P > 0.05$) between Y.R.'s mean item recognition z-scores on tests with two or three test items per target (n = 24) and more than three test items per target (n = 19), which were respectively −0.3 and −0.6.

Pearson correlations were performed between z-scores and ratio of number of test items to number of targets, delay, study list length, and difficulty. These factors were selected because they showed an appreciable spread of values across tests. Correlations were performed with the logarithms of delay and list length because the distribution of values of these factors was heavily skewed. None of these correlations reached statistical significance at the 0.05 level. Correlation coefficients and significance levels are shown in Table 2.

In summary, Y.R.'s item recognition performance across 43 tests was significantly below average but was not clearly impaired (i.e., more than 1.96 SD below her control group's mean level). In addition, none of the factors, such as delay and difficulty, which differed between tests, significantly influenced the relative normality of Y.R.'s item recognition performance, as shown both by *t*-test and ANOVA comparisons and, where appropriate, by correlational analysis.

Doors and People Test

Using the Doors and People Test norms (Table 15 of the test manual), Y.R. was found to have obtained midpercentile scores of 2.3 for the verbal recall test (raw score = 9/36) and 4.8 for the visual recall test (raw score = 22/36). In contrast, she obtained a midpercentile score of 97.7 for verbal recognition (raw score = 22/24) and 36.9 for visual recognition (raw score = 18/24). Midpercentile scores for overall recall and overall recognition were calculated by totaling visual and verbal age-scaled scores for recall

TABLE 2.

Pearson Correlation Coefficients and P Value Obtained When Investigating Whether There Was a Relationship Between Y.R.'s Performance and the Following Independent Variables: Ratio of Test Items to Number of Targets (2–3 and more than 3), Log of the Study to Test Delay in Minutes, Log of List Length, and Difficulty (Measured as a Percentage Score Indicating Where Between Chance and a Perfect Score the Control Subject's Mean Performance Fell)

Variables	Pearson correlation	*P*
Y.R. performance + ratio of test items to targets	−0.113	0.472
Y.R. performance + log delay	−0.220	0.156
Y.R. performance + log list length	0.088	0.575
Y.R. performance + difficulty	−0.288	0.061

and recognition separately, and then Tables 9 and 10 from the manual were used to obtain combined recall and combined recognition age-scaled scores, respectively. Midpercentile scores were derived from these age-scaled scores, using Table 15 of the manual. Y.R. obtained a midpercentile score of 1 for recall but a midpercentile score of 84.1 for recognition.

In patients with midpercentile scores on overall recall and/or recognition of 1, the norms of the Doors and People Test do not allow sensitive comparisons of the relative severity of recall and recognition deficits to be made because of floor effects (the same problem applies to the use of age-scaled scores). It was possible to make a more sensitive comparison of the relative severity of Y.R.'s overall recall and recognition deficits, however, by comparing her performance with a group of 10 female control subjects matched for age and IQ (mean age = 60.1, SD = 3.67; predicted full-scale IQ from the NART-R = 105.6, SD = 7.44). The percentage-correct overall recall and recognition scores were calculated for Y.R. and her control group from their raw scores. Y.R.'s z-score for overall recall was −4.1, whereas her z-score for overall recognition was only −0.2. This and the equivalent measures for the individual visual and verbal recall and recognition subtests are illustrated in Table 3.

Free Recall Tests

Y.R.'s performance on the 34 free recall tests, which is shown in Table 4, was significantly below the mean level of her control subjects ($t = 12.02$, df = 33, $P < 0.0001$). Furthermore, her mean z-score for recall was −3.6 and was therefore clearly below the standard criterion for impairment (z of −1.96). Strikingly, there were only two of the 34 free recall tests for which her z-score fell above −1.96.

Her performance (measured as a z-score) on the 34 recall tests and the 43 item recognition tests differed significantly ($t = 9.79$, df = 75, $P < 0.0001$). This indicates that Y.R.'s mean recall-recognition discrepancy differed significantly from the mean discrepancy level of normal people. By itself, the significant result does not indicate that her discrepancy resulted from her hippocampal damage, because many normal people may show an equivalent or greater discrepancy. However, the difference between her free recall z-score (−3.6) and her item recognition z-score (−0.5) was 3.1 SD, which is much greater than the standard criterion for impairment of 1.96 SD below her control group's mean difference score. It is, therefore, justifiable to infer that, relative to her item recognition, Y.R.'s recall was clearly impaired. Her mean recall-recognition discrepancy on the 34 recall tests was also broadly comparable to the discrepancies of 3.9 SD between her recall and recognition scores on the Doors and People Test.

Just as Y.R.'s verbal and visual item recognition z-scores did not differ significantly, Y.R.'s recall of verbal and visual materials was similarly impaired ($t = 1.41$, df = 32, $P > 0.05$). Her mean visual recall-recognition discrepancy differed significantly from the mean discrepancy level of normal people ($t = 6.80$, df = 34, $P < 0.0001$), and the same applied to her verbal recall-recognition discrepancy ($t = 7.30$, df = 39, $P < 0.0001$). Furthermore, in both cases, Y.R.'s recall was clearly more impaired than her item recognition by 3.8 and 2.7 SD, respectively.

Further analyses of the possible influence on the severity of Y.R.'s clear recall deficit of factors such as delay or difficulty were not attempted in detail. Unlike with item recognition, such analyses were not the focus of this paper because Y.R. was clearly impaired on all but 2 of the 34 recall tests used. We also have direct evidence that the use of controlled manipulations may be more sensitive to possible effects of variables such as delay on the severity of free recall deficits. A comparison of Y.R.'s performance on the 34 recall tests at delays of 0 s (n = 12), between 1–60 s (n = 7), and

TABLE 3.

Percentage Correct Scores for Y.R. and the Mean Percentage-Correct Scores for a Group of 10 Female Controls Matched for Age and IQ (SDs in Parentheses) for the Four Subtests of the Doors and People Test*

	Control mean	Y.R.	Number of SD from control mean
Verbal recall	76.7 (15.9)	25	−3.3*
Visual recall	92.2 (8.5)	61	−3.7*
Verbal recognition	81.7 (11.3)	92	+0.9
Visual recognition	87.9 (11.0)	75	−1.2
Combined recall	84.4 (10.0)	43	−4.1*
Combined recognition	84.8 (8.2)	83	−0.2

As the maximum raw scores for the recall and recognition subtests were unequal (36 and 24, respectively), these were converted to percent-correct scores to allow an unbiased comparison of recall and recognition scores. Also shown are percentage correct scores for combined visual and verbal recall and combined visual and verbal recognition. The number of standard deviations that Y.R.'s performance fell above (+) or below (−) the control mean is also given.

*Performance falling more than 1.96 SD below the control mean.

TABLE 4.

Main Features of Thirty Four Recall Tests Together With Y.R.'s Performance Relative to That of Her Control Subjects on These Tests[a]

Task	Stimulus type	Delay	List length	Y.R.'s z-score
AMIPB Complex Figure immediate (S)	Nonverbal	0 s	1	−3.0[b]
AMIPB Design Learning total a1–a5 (S)	Nonverbal	0 s	1	−2.7[b]
Doors and People—Shapes Subtest (S)	Nonverbal	0 s	4	−3.7[b]
Object recall (1)	Nonverbal	40 s	12	−4.4[b]
Object-location recall (1)	Nonverbal	40 s	12	−10.5[b]
Allocentric recall of locations (2)	Nonverbal	60 s	1	−3.5[b]
Egocentric recall of locations (2)	Nonverbal	60 s	1	−1.4
AMIPB Complex Figure delayed (S)	Nonverbal	30 min	1	−3.0[b]
Visual reproduction II from WMS-R (S)	Nonverbal	30 min	1	−2.2[b]
Object-location recall (1)	Nonverbal	30 min	12	−6.8[b]
Object recall (1)	Nonverbal	30 min	12	−3.4[b]
Recall of temporal order in which patterns were presented at study (3) (measured using a correlation)	Nonverbal	20 s	8	−5.0[b]
WMS-R Logical Memory I (S)	Verbal	0 s	1	−3.4[b]
Doors and People—People Subtest (S)	Verbal	0 s	4	−3.3[b]
Verbal paired associates I from WMS-R (S)	Verbal	0 s	8	−2.7[b]
AB AC paired associate learning				
AB (after third learning trial)	Verbal	0 s	12	−4.2[b]
AC (after third learning trial)	Verbal	0 s	12	−4.5[b]
AMIPB List Learning total a1–a5 (S)	Verbal	0 s	15	−3.6[b]
New definitions (after 5 learning trials) (4)	Verbal	0 s	10	−2.7[b]
New definitions (after 10 learning trials) (4)	Verbal	0 s	10	−4.7[b]
Calev free recall	Verbal	0 s	24	−2.8[b]
Name-occupation PA learning (after 5 learning trials)	Verbal	5 s	6	−3.5[b]
Recall of temporal order in which words were presented at study (3) (measured as a correlation)	Verbal	20 s	8	−0.4[b]
WMS-R Logical Memory II (S)	Verbal	30 min	1	−3.2[b]
Name-occupation PA learning (after 5 learning trials)	Verbal	30 min	6	−2.8[b]
Verbal paired associates II from WMS-R (S)	Verbal	30 min	8	−6.9[b]
New definitions (after 5 learning trials) (4)	Verbal	30 min	10	−2.2[b]
New definitions (after 5 learning trials) (4)	Verbal	24 h	10	−2.5[b]
New definitions (after 10 learning trials) (4)	Verbal	4 weeks	10	−2.6[b]
Remote Postmorbid Memory				
Recalling year of peak fame for people who became famous in postmorbid period (4)	Verbal	0–10 years	N/A	−4.0[b]
Recalling the year of famous public events which occurred in the postmorbid period (4)	Verbal	0–10 years	N/A	−2.1[b]
Recalling as much information as possible about people who had become famous since 1986 (4)	Verbal	0–10 years	N/A	−1.9
Recalling as much information as possible about public events which had occurred since 1986 (4)	Verbal	0–10 years	N/A	−2.3[b]
Giving definitions of terms which had entered the English language since 1986 (4)	Verbal	0–10 years	N/A	−2.0[b]

[a]Standardized published tests are indicated by an (S) in the table. All other tasks were tests developed in our laboratory or the laboratories of collaborators. Tasks described in more detail in other papers are indicated by a number in parentheses. These numbers refer to: 1, Holdstock et al., in press a; 2, Holdstock et al., 2000; 3, Mayes et al., 2001; 4, Holdstock et al., in press b. AMIPB, Adult Memory and Information Processing Battery (Coughlan, 1985); Doors and People, Doors and People Test (Baddeley et al., 1994); WMS-R, Wechsler Memory Scale—Revised. Delay, delay from end of presentation of study list to start of test; List length, length of the study list. Y.R.'s z-score, Y.R.'s performance expressed as z-scores (i.e., number of standard deviations that her performance fell above (+) or below (−) the control mean).

[b]Indicates that Y.R.'s performance was more than 1.96 below that of healthy controls.

longer than 1 min (n = 15) with a one-way ANOVA failed to show any significant effect of delay ($F = 1.730$, $df = 2, 31$, $P = 0.194$), and post hoc Tukey tests failed to show differences in the extent of Y.R.'s deficit between any of these delays. However, in unpublished work, we showed that Y.R. lost her ability to free-recall studied stories over filled delays of between 20 s and 10 min pathologically fast. As we used the procedure of Isaac and Mayes (1999a,b), which involved Y.R. receiving five study presentations of each story relative to her control subjects' single presentations in order to match recall at the 15-s delay, the recall test was not included in the battery of 34 recall tests shown in Table 4. Despite recalling the story slightly better than her controls at the 15-s delay (z-score = 0.8), Y.R.'s recall dropped to nearly chance at the 10-min delay (z-score = −3.3). Interestingly, although the controlled procedure showed that Y.R. lost the ability to recall stories abnormally fast in the first few minutes after studying them, when trained and tested under identical conditions to her control subjects, she lost the ability to recognize story features at an entirely normal rate over the same time period (see Table 1).

DISCUSSION

Following extensive testing, Y.R.'s item recognition memory was found to be 0.5 SD below the mean level of her control subjects. This difference was significant, which means that Y.R.'s item recognition level lay significantly below the mean level of normal women of her age and intelligence. However, without being able to assess Y.R.'s premorbid item recognition, it is impossible to be sure whether her item recognition had always been slightly below average or whether it had declined slightly but significantly following her hippocampal injury in 1986. This is because she performed only 0.5 SD below the mean level of her control subjects, which is much less than the standard criterion of impairment of 1.96 SD below the control mean (on a two -tailed test). In contrast, not only was Y.R.'s recall performance on 34 tests significantly worse than that of her control subjects, its mean level fell 3.6 SD below that of the control group's mean. Her recall performance was therefore clearly impaired. Similarly, Y.R.'s mean free recall-item recognition discrepancy of 3.1 SD indicates that her free recall was clearly more impaired than her item recognition. This relative impairment was likely to have been caused by her hippocampal damage.

Y.R. only showed recall that was not clearly impaired (less than 1.96 SD below her control subjects' mean score) on 2 of the 34 recall tests. One of these tests tapped free recall of egocentric spatial information a minute following study. Performance on it may have failed to show a clear impairment not only because hippocampal lesions possibly disrupt egocentric spatial memory less than allocentric spatial memory, but also because the recall test was recognition-like in that target positions were visible to subjects during retrieval (see Holdstock et al., 2000a). The other test tapped recall of information about famous faces to which there had been repeated exposure for periods up to years in length. There is evidence that recall of information that is acquired slowly through repeated exposure and rehearsal is less impaired after hippocampal lesions than is recall of information more rapidly acquired after fewer exposures (Holdstock et al., in press b; Vargha-Khadem et al., 1997).

The relative normality of Y.R.'s item recognition memory was not significantly affected by factors such as the visual or verbal nature of the stimuli, whether the test was of forced-choice or yes/no format, list length, number of test choices per target, delay, and difficulty. Furthermore, there was no effect of delay even though some of the tests used very long delays of 24 h, 3 weeks, and 4 weeks.

Although too much weight should not be placed on these null findings, they are compatible with performance on the 43 item recognition tests, each depending on common processes, which at most were only mildly impaired in Y.R.. However, as indicated above, Y.R.'s performance on 4 of the 43 item recognition tests did fall more than 1.96 SD below her control group's mean score. As she was given over 40 tests, some of these 4 exceptions could have been type 1 errors. Alternatively, they may indicate that her performance on some types of item recognition test was clearly impaired because these tests depend critically on processes impaired by Y.R.'s hippocampal damage. If this was the case, one would expect these tests to differ in specific ways from the tests on which Y.R. scored close to the mean level of her control subjects. This was not the case for the first 2 exceptions. The first of these was a test of forced-choice recognition which also required Y.R. to indicate how confident she was about each response. The second exception was a yes/no recognition task, which used unrelated and dissimilar targets and lures and required a remember/know decision for each "yes" response. Y.R.'s performance was not significantly impaired, however, on any of the other 7 yes/no tests using the remember/know procedure. Indeed, she performed above the control group mean on 5 of these tests. It seems probable, therefore, that Y.R. had no specific problem with recognition tasks which require extra judgments to be made, and this conclusion is likely to apply to forced-choice as much as yes/no tasks. Therefore, task-related processing differences cannot plausibly explain Y.R.'s poor performance on these 2 exceptional item recognition tests because she performed well on other similar item recognition tests. It is more likely that the apparently clear deficits on these 2 exceptional cases were type 1 errors.

The other 2 exceptions both involved recognition tests which had yes/no formats and may have been relatively difficult because each target was either semantically or perceptually very similar to a subset of foils (Mayes et al., 2001; Holdstock et al., in press a). Y.R.'s performance on both these exceptional tests was over 1.96 SD more below the mean performance level of her control subjects than was her mean performance on the remaining 41 recognition tests. This is consistent with her performance on these two tests critically depending on a process that was disrupted by hippocampal lesions to a much greater extent than were any processes critical for good performance on the remaining 41 tests. One of the two tests examined yes/no recognition memory for target words, for each of which there were four semantically similar foils (see Mayes et al., 2001). Although the foils in this test were selected so as to be semantically similar to their respective targets, there was no exper-

imental confirmation that the relative difficulty of making discriminations without the need to use episodic memory was greater for this test than for the other yes/no recognition tests, which Y.R. had performed relatively normally. However, the relative difficulty of discriminating between targets and foils was confirmed for the other test, which examined recognition memory for line drawings of natural and manmade objects, for each of which there were three perceptually similar foils. A perceptual discrimination task was used to show that target-foil discriminations were harder for this yes/no object recognition task than for the other visual yes/no item recognition tests which Y.R. had performed relatively normally. In contrast to Y.R.'s clearly impaired performance on the object yes/no recognition test, her forced-choice recognition of line-drawn objects in a closely equivalent test was unimpaired (see Holdstock et al., in press a and Table 1).

Mayes et al. (in press) and Holdstock et al. (in press a) interpreted this pattern of findings by arguing that when targets and foils are very similar and difficult to discriminate, familiarity is unable to support performance on yes/no item recognition tests successfully, so that recollection becomes critically important. In contrast, familiarity is sufficient to support good performance on forced-choice item recognition tests, even when target-foil discriminations are difficult. This is consistent with the view put forward by the Complementary Learning Systems model of recognition (Norman and O'Reilly, in preparation; Norman et al., 2000; Norman, 2000; for more background on the complementary learning systems idea, see McClelland et al., 1995; O'Reilly and Rudy, 2001) and is discussed in detail by Holdstock et al. (in press a). In concrete terms, the relative familiarity of even very similar targets and foils appearing together should typically be discriminable. In contrast, when they appear one at a time, discrimination will be very unreliable because foils corresponding to some targets will be more familiar than other targets. In such a case, good performance is only possible if subjects can recall (recollect) details of items from the study session that are either identical to features of the test items or differ slightly from them.

Y.R.'s results, therefore, suggest that item recognition can be relatively or completely spared in a way that is little, if at all, influenced by factors such as delay or task difficulty, whereas recall can be clearly more impaired in patients with adult-onset damage to the hippocampus. An exception to this relative sparing occurred when recognition was tested using a yes/no format and very similar targets and foils. In this exceptional case, it can be plausibly argued that good item recognition memory cannot be mediated by familiarity and depends critically on recollection. If this interpretation is correct, then Y.R.'s item recognition results are consistent with the view of Aggleton and Brown (1999) that hippocampal damage impairs recollection, but not familiarity. Further support for this view is provided by Y.R.'s clearly impaired recall, which implies that her recollection was impaired, and her completely normal level of know responding on eight versions of the remember/know procedure (see Holdstock et al., in press a and Table 1), which implies that her familiarity memory was normal.

Two comments on this conclusion are warranted. First, if both recollection and familiarity normally contribute to item recognition and are stochastically independent of one another, then a recollection impairment should mean that item recognition will not be completely normal. This conclusion would apply unless 1) whenever items were recollected, they were also found to be familiar; 2) normal subjects were effectively at floor level on recollection; or 3) even though their recollection was not at floor levels, normal subjects did not use it to guide their recognition decisions. If one or more of these conditions hold, then item recognition might be completely normal. However, even if none of them hold, an impairment in the ability to recollect studied items is likely to disrupt recognition only *very slightly* as long as familiarity provides an effective basis for recognition judgments. So, item recognition is likely to be only very slightly impaired except when tested by a yes/no format with very similar targets and foils. It is unknown whether one or more of these conditions holds and item recognition should be expected to be unimpaired, or whether none of them apply and a subtle deficit should be expected. However, confidently identifying a subtle item recognition deficit in a single patient such as Y.R. cannot be done. Y.R.'s item recognition may be anything from completely unimpaired to moderately impaired, depending on whether her premorbid memory level was at, above, or below her control group's mean. A group study would be required to identify confidently a subtle impairment because it is reasonable to assume that the mean premorbid item recognition in a group of patients would be very close to its control group's mean. This cannot be assumed about the premorbid item recognition of a single case. Identifying that a group is functionally homogeneous and that all patients have sufficiently focal hippocampal lesions is, however, extremely hard.

Second, in preliminary work, Y.R. was found to be impaired when memory for faces was tested using the visual paired-comparison task at delays of 5 and 10 s (Pascalis et al., 2000). If paired-comparison task performance depends mainly on familiarity, then Y.R.'s clear impairment would be inconsistent with the view that her familiarity memory is preserved. However, this argument is currently unconvincing. On seven different face recognition tests (see Table 1), which involved longer delays and many more faces than the paired-comparison task, Y.R. performed above the mean level of her control group. In other words, as far as can be determined, her face recognition memory is completely normal. There is far stronger evidence that item recognition performance depends on familiarity than does paired-comparison task performance, so it is implausible to suggest that Y.R.'s face familiarity memory as well as her face recollection was impaired. Relevant to this point, Baxter and Murray (2001a) found that a hierarchical linear regression analysis using data from Zola et al. (2000) revealed a significant interaction between memory measures (object recognition and visual paired-comparison) and extent of hippocampal damage in monkeys. Whereas there was a weak negative correlation between extent of hippocampal damage and severity of object recognition impairment, there was a weak positive correlation between extent of hippocampal damage and degree of paired-comparison performance impairment. Although this dissociation needs replicating, if reliable, it clearly implies that these two kinds of memory test tap partially different memory processes. It may be, therefore, that Y.R.'s face recognition was perfect under the same conditions in which her visual paired-comparison performance was at chance

(see Pascalis et al., 2000), because she was impaired at memory processes that are not required for familiarity memory and good item recognition, but which block the automatic tendency to foveate and process recently studied faces.

The view that Y.R.'s pattern of item recognition performance is broadly consistent with the framework of Aggleton and Brown (1999) is further supported by examination of her performance on the Doors and People Test. Scores on this test battery have also been reported for Jon (Vargha-Khadem et al., 1998), P.H., L.J., and A.B. (Manns and Squire, 1999). Y.R.'s pattern of performance is like that of the developmental case, Jon (Vargha-Khadem et al., 1998), but unlike that of patients P.H., L.J., and A.B. (Manns and Squire, 1999), who have lesions of adult onset. For this test battery as for the whole sample of recall and recognition tests reported, Y.R.'s free recall was markedly more impaired than her relatively normal item recognition.

Overall, Y.R.'s item recognition memory was good, like Jon's, and clearly better than that of P.H., L.J., and A.B. (Manns and Squire, 1999) as well as R.B. (Zola et al., 1986) and G.D. (Rempel-Clower et al., 1996), who all showed clear impairment of item recognition. This difference is almost certainly not caused by differences in the tests used with the two groups of patients, but must relate to differences in patient characteristics.

One possible difference between Y.R. and Jon and the patients of Manns and Squire (1999) is severity of amnesia. Thus, it might be argued that Y.R.'s item recognition was relatively normal simply because her amnesia was milder than that of L.J., P.H., and A.B. The function relating recall and recognition across the full range of severity of amnesia that has been caused by medial temporal lobe or midline diencephalic lesions has not been fully characterized. It is possible, therefore, that as recall deficits become milder, item recognition reaches normal (or near normal) levels sooner than might be expected from examination of patients with more severe amnesia. Such a relationship between recall and recognition deficits would be consistent with the view that the functions disrupted by amnesia mediate item recognition as well as recall, but that good recall typically needs more of this functional resource than does good item recognition. In other words, Y.R. and Jon, unlike L.J., P.H., and A.B., showed relatively preserved item recognition despite showing impaired recall because their hippocampal damage has only very mildly impaired a functional resource, more of which is needed for good recall than for good item recognition. There is some evidence that Y.R.'s and Jon's recall is less impaired than that of L.J., P.H., and A.B. Thus, on the Doors and People Test, L.J., P.H., and A.B. obtained lower recall scores on the verbal and visual tests (1 and 5, 0 and 3, and 3 and 11, respectively) than Y.R. (9 and 22). Jon's recall performance was at a level comparable to Y.R.'s. The "'milder amnesia" possibility, therefore, needs to be seriously considered.

There are two reasons why this "milder amnesia" explanation is unlikely to explain why Y.R.'s and Jon's item recognition is relatively well-preserved. First, it is difficult to explain why recall should be more impaired than item recognition if both types of memory are critically dependent on the same memory processes, unless item recognition is easier. This is because one might expect a mild amnesia, which only partially disrupts a common recall-recognition functional resource, to leave performance on easier tests relatively spared because good performance on these needs less of the functional resource than does good performance on more difficult tests. However, as shown by the correlational analysis of Y.R.'s recognition results, her performance was not significantly more impaired on item recognition tests that control subjects found more difficult. In addition, Y.R. was found to be clearly impaired on recall tests, but to perform relatively normally on item recognition tests that control subjects found to be of comparable difficulty (the Doors and People Test described here, and Holdstock et al., in press a). So, although Y.R.'s recall impairment may be less severe than that of L.J., P.H., and A.B., it is difficult to see how this can explain her relative preservation of item recognition.

The second, and perhaps strongest, reason why the "milder amnesia" explanation for the differences found between Y.R. and Jon and the patients of Manns and Squire (1999) is unconvincing is that there is evidence for the existence of independent recognition and recall factors. Hunkin et al. (2000) analyzed the scores on several standardized tests of recall and recognition of 50 memory impaired patients with mixed etiologies and lesion locations. Factor analysis showed that there were several independent factors that loaded particularly strongly on recall and recognition scores, respectively. This strongly suggests that amnesia is a syndrome comprising several independent memory deficits, each caused by a partially distinct set of lesions. If correct, severity of recall deficits is an unreliable guide for severity of item recognition deficits. Strong support for this conclusion was provided by examination of the scores of the patients on the Doors and People Test (one of the tests used in this study). A rough estimate of how impaired the overall recall and recognition scores of these patients were was obtained by comparing them with Y.R.'s control group. Nine patients had a comparable overall recall deficit on this test to Y.R. Their mean performance was 4.0 SD (range, 3.6–4.5 SD) below the mean performance of Y.R.'s controls, which was nearly identical to Y.R.'s performance (4.1 SD below her control group's mean). In contrast to Y.R.'s overall recognition performance (0.2 SD below her control group's mean), however, these 9 patients had a mean recognition performance which was 3.5 SD (range, 1.7–5.5 SD) below the mean of Y.R.'s controls. MRI scans were available on 4 of these patients. There was no evidence of frontal lobe damage in any of these patients, whose amnesia appeared to have resulted from either medial temporal lobe or thalamic lesions. This shows that amnesics with milder recall deficits than L.J., P.H., and A.B., which have been caused by relatively selective medial temporal lobe or thalamic lesions, do not necessarily show relatively preserved item recognition. It, therefore, seems unlikely that Y.R.'s and Jon's relatively preserved item recognition memory is a simple consequence of their being only mildly amnesic.

A rough estimate of how impaired L.J., P.H., and A.B.'s overall recall and recognition scores were can also be made by comparing their percentage-correct overall recall and recognition scores with the mean scores of Y.R.'s control group. Unlike Y.R. (4.1 and 0.2 SD, respectively, below her control group's mean), A.B. showed more severe and nearly equivalent overall recall and recognition deficits (6.5 and 5.5 SD, respectively, below Y.R."s control group's mean). This suggests that his memory may have differed from

Y.R.'s not only in severity, but also qualitatively. In contrast, although L.J. and P.H. showed more severe deficits than Y.R., they, like her, showed more severely impaired recall than recognition (for L.J., overall recall and recognition fell 7.6 and 4.5 SD, respectively, below the mean score of Y.R.'s control subjects; for P.H., overall recall and recognition fell 8.0 and 3.5 SD, respectively, below the mean score of Y.R.'s control group).

Some caution should be observed in accepting this conclusion, however, because it is uncertain how closely the control subjects were matched to L.J. and P.H., and relative levels and variability of recall and recognition may vary in different kinds of normal subjects. Also, one cannot assume that recall and recognition measurement scales are linear across the entire range of normal and abnormal scores (see Haist et al., 1992), so further caution is necessary before concluding that P.H. and L.J., like Y.R., showed recall deficits that were more severe than their recognition deficits. Alternative matching procedures have been used to avoid these possible scaling problems, but these have yielded conflicting results and are also liable to methodological artefacts (see Isaac and Mayes, 1999a,b). Nevertheless, not only A.B., but also the 9 patients of Hunkin et al. (2000), who had equivalent overall recall deficits to Y.R., showed overall recall and recognition deficits of similar severity. This was unlike P.H. and L.J., whose overall recall deficits were relatively more severe than their overall recognition deficits. The issue is complex, but although it seems likely that the qualitative nature as well as the severity of A.B.'s memory disorder differs from that of Y.R. and Jon, it is less clear that L.J.'s and P.H.'s memory deficits differ qualitatively as well as quantitatively from those of Y.R. and Jon. Four further possible differences between Y.R. and the patients of Manns and Squire (1999) that could explain the differences in their recall and recognition deficits are considered below.

The first two possible differences between the patients relate to compensatory changes following hippocampal damage. Manns and Squire (1999) suggested that Jon's spared item recognition could be dependent on one or both of two kinds of compensation that may have occurred during development following his early injury. One of these kinds of compensation results from functional reorganisation of the brain regions adjacent to the hippocampus, and the other results from the use of learned strategies that particularly facilitate item recognition memory (e.g., by increasing awareness of and hence sensitivity to familiarity signals). By extension, it might also be proposed that similar compensatory processes explain why Jon's recall is less impaired than that of L.J., P.H., and A.B. Compensation can be investigated using functional MRI. There is preliminary functional MRI evidence that when Jon succeeds in retrieving autobiographical incidents, he shows a slightly different pattern of increased connectivity between brain structures than do normal subjects (Maguire, 2001). If reliable, this may indicate that one or both kinds of compensatory changes have occurred in Jon. However, neither of these kinds of compensation is more likely to account for Y.R.'s pattern of performance than that of the patients of Manns and Squire (1999). This is so because hippocampal damage did not occur until all these patients were well into their adult years.

The third possible reason why patient item recognition differences occur is that the residual hippocampus may, to some degree, still be able to mediate familiarity as well as recollection, and may do so more effectively in patients with relatively normal item recognition. It is unclear that functional MRI is able yet to indicate the level of functionally effective residual hippocampal activity although, on the basis of her study, Maguire (2001) claimed that Jon's residual hippocampi are functional. She found that he showed a bilateral activation in the medial temporal lobe region, which appeared to be located in the hippocampus, for the rare events that he could successfully recollect. However, given the current limits to signal sensitivity and accuracy of spatial resolution in the medial temporal lobe region, it is uncertain that activation can be confidently located in a pathological hippocampus of about half normal size rather than in closely neighboring medial temporal cortex regions, even if special precautions are taken (see Mayes and Montaldi, 1999). The difference is theoretically critical, because if the true activation lies in the medial temporal cortices (e.g., the perirhinal cortex), then there would be no evidence that residual hippocampal activity is occurring. Nevertheless, likely developments in the near future mean that functional MRI should become a good direct method of measuring level of functioning of residual hippocampus.

In the absence of such direct evidence, likely levels of residual function can only be estimated through knowledge of the extent and precise location of hippocampal lesions. At present, however, the location of hippocampal damage can only be reliably determined postmortem, and the relationship between damage location and level of likely residual functioning is also imperfectly understood, so we will focus on the extent of hippocampal damage. If residual functioning declines as extent of damage increases and the hippocampus is critical for all types of item recognition, then item recognition sparing should be greater when there is less hippocampal destruction. As it is very widely agreed that hippocampal damage compromises recall and spatial memory, these forms of memory may also be less severely impaired when there is less hippocampal damage.

There is minimal evidence from human studies about the relationship between different degrees of hippocampal damage and levels of memory deficit although, as will be discussed, the animal literature is more extensive (see Baxter and Murray, 2001a,b; Zola and Squire, 2001). There is, however, little direct evidence that Y.R.'s item recognition is only relatively preserved because she has suffered only minor hippocampal damage. Y.R.'s hippocampal volume, corrected for intracranial volume, was reduced by 45% on the right and 47% on the left relative to a group of age-matched female controls. This is very comparable to the extent of Jon's reduction in hippocampal volume, which Manns and Squire (1999) estimated to be reduced by 46%. Item recognition memory was also closely comparable in these 2 patients, despite the fact that Jon's lesion was of childhood onset, whereas Y.R.'s was of adult onset. This suggests that Jon's preserved item recognition need not have arisen from the kinds of compensatory mechanisms proposed by Manns and Squire (1999). Interestingly, the two patients of Manns and Squire (1999) for whom hippocampal volume estimates are available had numerically less hippocampal damage than

Y.R. and Jon (L.J., 34% reduction; PH, 22% reduction to hippocampal region). This is important because if sparing of item recognition depends on the contribution of a residual hippocampus, it is more probable that L.J. and P.H. should perform better on item recognition than do Y.R. and Jon, but this is the reverse of what has been found. The same point applies to recall, at which L.J. and P.H. also seemed more impaired than Y.R. or Jon when given the Doors and People Test. As there is no evidence that the residual hippocampus in L.J. and P.H. comprised different subregions than in Y.R. and Jon and/or was more structurally deranged, there is no direct reason to believe that the greater sparing of item recognition (and recall) shown by Y.R. and Jon was due to superior residual hippocampal functioning.

Further evidence consistent with this view includes the pattern of item recognition memory performance of another patient, D.F., who has adult-onset hippocampal damage (Henke et al., 1999). D.F. has a comparable amount of right hippocampal damage to L.J. and P.H. and yet showed relatively normal visual item recognition. Furthermore, this patient showed equivalent and relatively normal verbal item recognition, even though his left hippocampus was more damaged than his right (to a level equivalent to that shown by Y.R. and Jon).

There is, therefore, no evidence that relative sparing of item recognition in patients Y.R., Jon, and D.F., and the milder recall deficits in Y.R. and Jon, are attributable to their having more residual hippocampus than do patients L.J. and P.H., whose item recognition memory was clearly impaired. Indeed Y.R., Jon, and D.F. appear to have less residual hippocampus than L.J. and P.H. Relative preservation of item recognition when a substantial amount of the hippocampus has been destroyed is difficult to explain if good item recognition memory depends critically on the hippocampus.

Relevant to the scant human literature is evidence from nonhuman primate research that lesser extents of hippocampal damage are associated with more impaired item recognition in nonhuman primates. Baxter and Murray (2001a) argued that a meta-analysis of studies by Zola et al. (2000) and Beason-Held et al. (1999), as well as Murray and Mishkin (1998), provides support for the view that as extent of hippocampal damage increases, the severity of recognition memory deficits decreases. Overall, the monkeys showed a slight but significant object recognition deficit, although individual recognition levels ranged from normal in Murray and Mishkin (1998) to moderately impaired in the other two studies. Zola and Squire (2001) pointed out that differences between the studies, such as in training and lesioning techniques, may have confounded the results of the simple correlation analysis used by Baxter and Murray (2001a). The multiple regression analysis by Zola and Squire (2001) of the same data, which corrected for study differences, found no significant negative relationship between lesion and recognition deficit extents. On balance, however, the nonhuman primate literature provides no evidence that there is a positive correlation between extent of hippocampal damage and extent of item recognition deficits. Indeed, the data are suggestive of a negative relationship between hippocampal lesion extent and recognition deficit extent, because 1) all the studies and analyses show weak negative relationships, and the data of Murray and Mishkin (1998) on their own show a significant negative correlation unconfounded by study differences; and 2) Baxter and Murray (2001b) showed that a Spearman correlation which partialled out study differences was still negative and significant. Nevertheless, further work is important to confirm the reliability of this relationship by controlling for the confounding factors, highlighted by Zola and Squire (2001), and by systematically varying lesion extent.

If rhinal cortex lesions do impair object recognition more than hippocampal lesions, and the extent of the two kinds of damage is respectively positively and negatively correlated with the extent of object recognition deficits (as the meta-analysis of Baxter and Murray (2001a) suggests), then it is likely that rhinal cortex and hippocampal lesions affect item recognition in different ways. One possibility is that the rhinal cortex is critical for familiarity as well as recollection, whereas the hippocampus is only critical for recollection. Positive correlations between extent of damage and severity of a memory deficit are more likely to occur if the damaged structure is critical for memory function, so that lesions of that structure cause clear deficits. If this is correct, then positive correlations are more likely to be found between extent of hippocampal damage and size of deficits for memory functions that include spatial memory, recall, and recollection (which is either equivalent to recall or a subvariety of it), because these functions are widely agreed to depend critically on the hippocampus. This would explain why larger hippocampal lesions have been found to impair spatial memory more than small lesions in rats (Moser et al., 1993, 1995). It is almost universally believed that hippocampal damage causes clear impairments of spatial memory and, consistent with this belief, Y.R.'s extensive hippocampal damage has severely impaired her ability to recognize as well as recall locations encoded within an allocentric spatial framework (Holdstock et al., 2000a) and to recognize as well as recall the locations occupied by specific objects (Holdstock et al., in press a,b).

In contrast, negative correlations are more likely to be found when good memory test performance does not depend on the hippocampus. One plausible explanation of the negative hippocampal damage-recognition deficit correlation which is consistent with this view is that any residual hippocampus tends to be malfunctioning, and that the degree of disruption of connected structures is positively related to the amount of residual hippocampus. It is the connected structures, such as the perirhinal cortex, that play a key role in item recognition. If correct, this would mean that clear item recognition deficits in patients with relatively small hippocampal lesions arise because possibly intact structures, such as the perirhinal cortex, which play a critical role in recognition, have been functionally disrupted by high levels of abnormal hippocampal inputs. The explanation implies that such patients should show familiarity as well as recollection deficits.

Another interesting explanation of the negative correlation is that smaller hippocampal lesions disrupt item recognition more because, although the ability to recollect studied items declines progressively as hippocampal lesion size increases, false recollection of unstudied items increases at first, but then peaks and declines as lesion size increases. As discussed above, relatively good recognition can be produced by familiarity memory, even when the ability

to recollect studied items is impaired. However, when the tendency to produce false recollections of unstudied items increases, item recognition will be progressively impaired. Norman and O'Reilly (2001) recently showed that progressively "damaging" the hippocampus in their Complementary Learning Systems neural network model of recognition (in which the hippocampus mediates recollection through the operations of pattern separation and pattern completion, but does not mediate item familiarity; see also Norman et al., 2000; Norman, 2000) accurately simulates the above pattern of results and reveals a negative correlation between extent of hippocampal damage and item recognition impairment (as well as a positive correlation between extent of perirhinal damage and item recognition impairment). Unlike the first explanation, this explanation does not predict that even small hippocampal lesions will disrupt familiarity. However, both explanations could be true, and, if only one is, it should be possible to identify which one by determining whether familiarity is intact in patients with small hippocampal lesions and clearly impaired item recognition.

As already noted, recall, which it is agreed depends critically on hippocampal integrity, seemed to be more impaired in P.H. and L.J. than it was in Y.R. and Jon, in whom hippocampal volume loss was greater. This was a similar pattern to the one found for these patients' item recognition memory, which may depend minimally if at all on the hippocampus, but critically on other structures, such as the perirhinal cortex, to which the hippocampus is connected. Two main factors that work in different directions may determine the effect of increasing amounts of hippocampal damage on extent of recall (and, by implication, recollection) impairment. First, even if a residual hippocampus is working suboptimally, greater damage should reduce the ability of this structure to mediate recall. Second, greater damage may also reduce the amount of abnormal hippocampal activity that is propagated to extrahippocampal structures, such as the perirhinal cortex. As these structures provide key input to the hippocampus, which is critical for the mediation of recollection (e.g., Aggleton and Brown, 1999), greater disruption of the processes that they mediate should disrupt hippocampal processing and recollection further. The extent to which hippocampally dependent forms of memory, such as spatial memory and recall, are disrupted by increasing extents of hippocampal damage may depend on where the balance of these factors lies. The conditions under which a residual hippocampus has beneficial or disruptive effects on different kinds of memory clearly requires further investigation. If higher levels of abnormal activity in structures such as the perirhinal and parahippocampal cortices are more often associated with smaller hippocampal lesions, then a negative rather than a positive correlation between extent of hippocampal damage and level of impairment in hippocampally dependent functions, such as recall and spatial memory, becomes more likely.

In humans, one way of examining whether hippocampal lesions are causing abnormal activity in other structures that mediate item recognition would be to use emission tomography or recently developed functional MRI procedures (e.g., Small et al., 2000) to determine whether there are blood flow, metabolic, or blood oxygenation changes in these other structures. Such changes have been shown to occur not only in the acute phase following anoxia-ischemia (see Markowitsch et al., 1997), but also in the more chronic phase (see Kopelman and Stanhope, 1998). However, it is unclear whether these changes are occurring in intact structures that are receiving abnormal inputs from a structurally damaged hippocampus, or whether they are occurring because there is subtle damage in the structures where the changes are found. Whichever possibility applies, conventional MRI and even volumetric procedures have typically failed to detect subtle damage in structures such as the perirhinal cortex.

We have argued that the relative preservation of item recognition (and the relative mildness of the recall deficit) in Y.R. is not convincingly explained in terms of the mildness of her overall amnesia, the compensatory changes following brain damage, or the incompleteness of her hippocampal lesion. Although these possibilities cannot be excluded, the current evidence in their favor is not strong. It is even possible that Y.R.'s item recognition was less impaired than that of some other patients because the destruction of her hippocampus was relatively greater. A fourth possibility, which is that the difference in item recognition (and recall) memory between Y.R. and those patients with clear item recognition deficits is related to the extent of undetected extrahippocampal damage, therefore, also needs to be seriously considered.

Although conventional structural MRI does not indicate that L.J. and P.H. have more extrahippocampal damage than do Y.R., Jon, and D.F., it probably fails to reveal the full extent of brain dysfunction. Overall, A.B.'s recall and recognition were about as impaired as those of L.J. and P.H., although, at least on the Doors and People Test, the relative severity of these two deficits seemed to be more equal than was the case for L.J. and P.H. The extent of A.B.'s pathology is, however, even more uncertain because he was unable to undergo MRI. A.B. suffered anoxia, and this etiology was presumed to have caused selective hippocampal damage, but this assumption is questionable because anoxia commonly results in widespread brain damage (Caine and Watson, 2000).

Supportive of the possibility that undetected extrahippocampal damage has caused the pattern of L.J.'s and P.H.'s performance on the Doors and People Test is a study by Holdstock et al. (1999), which reported the performance on this test of 2 patients, R.S. and N.M. Their performance was similar to that of L.J. and P.H. with respect not only to overall severity, but also relative severity of their recall and recognition deficits. R.S.'s overall recall was 6.9 SD, and his recognition was 2.4 SD worse than the mean performance of Y.R.'s control group; N.M.'s overall recall was 7.4 SD and his recognition was 4.5 SD below this control group's mean performance levels. In both patients, analysis of their MRI scans showed that hippocampal volume had been reduced bilaterally by slightly over 50% (similar to the extent of hippocampal damage in Y.R. and Jon), but the scans also showed some damage to the medial temporal cortex, which extended into the perirhinal cortex bilaterally, in both patients.

It is well-known that perirhinal cortex lesions typically cause severe item recognition deficits (see Aggleton and Brown, 1999), and because R.S. and N.M. also have hippocampal damage that seems at least as severe as that of L.J. and P.H., there is a tension between the two sets of data. This tension is even more striking with patient V.C., who shows a particularly sharp contrast between

the severity of his memory impairments and, like L.J. and P.H., the absence of structural MRI evidence of extrahippocampal damage that could plausibly cause these impairments. V.C. not only had severe deficits of postmorbid item recognition and recall, but also a severe, extensive, and ungraded retrograde amnesia (Cipolotti et al., 2001). Detailed analysis of his MRI scans showed bilateral hippocampal volume reduction of comparable extent to R.S., N.M., and Y.R. But Cipolotti et al. (2001) argued that V.C.'s brain otherwise appeared to be relatively normal. Although the volume of his parahippocampal gyrus was significantly reduced, the medial temporal cortices, but not the white matter within this region, appeared relatively normal. As the white matter loss probably reflected loss of connections to the damaged hippocampus, it was not implausible to argue that the memory deficits may have been caused primarily by hippocampal damage. If extrahippocampal structural damage *does* explain why V.C.'s amnesia was worse overall than that of either Y.R. and Jon, or of the patients of Manns and Squire (1999), one has to concede that structural MRI techniques have so far failed to identify such damage with confidence.

However, even detailed neurohistological examination at postmortem may fail to identify significant extrahippocampal structural damage (if it exists) as the possible cause of clear item recognition deficits. Such an examination was performed on the brains of R.B. and G.D., who in life had had clearly impaired item recognition (Zola et al., 1986; Rempel-Clower et al., 1996). Only minimal extrahippocampal structural damage was found. Although rarely possible, such an examination must be the method of choice over structural MRI because its superior spatial resolution can enable it to provide more detailed information about specific tissues. Nevertheless, it is unknown what structural measures may reveal that a region is likely to function suboptimally. For example, as well as having small foci of cell loss throughout the cortex, R.B. also showed minor pathology in the left internal medullary lamina of the thalamus, whereas G.D. showed multiple small white matter lesions that extended into the temporal pole and temporal stem regions. Is it safe to assume that these lesions have no functional effects on item recognition? Small reductions in neuronal density may also have been missed in a number of extrahippocampal regions in these patients, because density was assessed qualitatively. Similarly, neuronal synaptic density in these sites is currently not measured. It may also be important to assess the status of neurons using nucleolus measures (see Mayes et al., 1988) and to measure activity of different neurotransmitters and the density of different receptors using positron emission tomography procedures.

If the relative preservation of item recognition performance in patients such as Y.R., Jon, and D.F. and the clearly impaired item recognition performance in patients such as P.H. and L.J. are to be explained and the mnemonic role of the hippocampus better understood, then several things need to be done. First, more patients with apparently selective hippocampal lesions urgently need to be identified and given extensive hypothesis-driven neuropsychological assessments. Second, the range of measures used in the few brains that come to postmortem analysis needs to be extended so as to tap a greater number of possible structural causes of item recognition dysfunction. Third, improved imaging methods need to be used with patients in whom conventional MRI indicates there is selective hippocampal damage. As indicated above, this should include neurotransmitter and receptor measures that can be made using emission tomography. It should also include further MRI procedures, such as T2 relaxometry and diffusion tensor imaging, which are sensitive to various grey and white matter structural anomalies. Such emission tomography and MRI procedures may tap structural features that may not have been measured even in previous postmortem, let alone conventional MRI, studies. If the critical factors underlying memory differences between patients with relatively selective hippocampal lesions can be identified using all these procedures, then we may finally be able to resolve with confidence exactly what the hippocampus contributes to memory.

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REFERENCES

Aggleton JP, Brown M. 1999. Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. Behav Brain Sci 22:425–489.

Aggleton JP, Shaw C. 1996. Amnesia and recognition memory: a reanalysis of psychometric data. Neuropsychologia 34:51–62.

Baddeley A, Emslie H, Nimmo-Smith I. 1994. Doors and people. Thames Valley Test Co. Bury St. Edmunds, UK.

Baddeley A, Vargha-Khadem F, Mishkin M. 2001. Preserved recognition in a case of developmental amnesia: implications for the acquisition of semantic memory? J Cogn Neurosci 13:357–369.

Baxter MG, Murray EA. 2001a. Opposite relationship of hippocampal and rhinal cortex damage to delayed nonmatching-to-sample deficits in monkeys. Hippocampus 11:61–71.

Baxter MG, Murray EA. 2001b. Effects of hippocampal lesions on delayed nonmatching-to-sample in monkeys: a reply to Zola and Squire. Hippocampus 11:201–203.

Beason-Held LL, Rosene DL, Killian RJ, Moss MB. 1999. Hippocampal formation lesions produce memory impairments in the rhesus monkey. Hippocampus 9:562–574.

Benton AL. 1968. Differential behavioural effects in frontal lobe disease. Neuropsychologia 6:53–60.

Caine D, Watson JDG. 2000. Neuropsychological and neuropathological sequelae of cerebral anoxia: a critical review. J Int Neuropsychol Soc 6:86–99.

Cipolotti L, Shallice T, Chan D, Fox N, Scahill R, Harrison G, Stevens J, Rudge P. 2001. Long-term retrograde amnesia. . . the crucial role of the hippocampus. Neuropsychologia 39:151–172.

Coughlan AK. 1985. Adult memory and information processing battery. Leeds: St. James University Hospital.

Gunderson HJG, Jensen EB. 1987. The efficiency of systematic sampling in stereology and its prediction. J Microsci 147:229–263.

Haist F, Shimamura AP, Squire LR. 1992. On the relationship between recall and recognition memory. J Exp Psychol [Learn Mem Cogn] 18:691–702.

Heaton RK. 1981. Wisconsin card sorting test manual. Odessa, FL: Psychological Assessment Resources, Inc.

Henke K, Kroll NE, Behniea H, Amaral DG, Miller MB, Rafal R, Gazzaniga MS. 1999. Memory lost and regained following bilateral hippocampal damage. J Cogn Neurosci 11:682–697.

Holdstock JL, Mayes AR, Cezayirli E, Aggleton JP, Roberts N. 1999. A comparison of egocentric and allocentric spatial memory in medial temporal lobe and Korsakoff amnesics. Cortex 35:479–501.

Holdstock JS, Mayes AR, Cezayirli E, Isaac CL, Aggleton JP, Roberts N. 2000a. A comparison of egocentric and allocentric spatial memory in a patient with selective hippocampal damage. Neuropsychologia 38:410–425.

Holdstock JS, Gutnikov SA, Gaffan D, Mayes AR. 2000b. Perceptual and mnemonic matching-to-sample in humans: contributions of the hippocampus, perirhinal and other medial temporal lobe cortices. Cortex 36:301–322.

Holdstock JS, Mayes AR, Isaac CL, Roberts N, O'Reilly R, Norman K. In press a. Under what conditions is recognition spared relative to recall following selective hippocampal damage in humans? Hippocampus.

Holdstock JS, Mayes AR, Roberts N, Isaac CL. In press b. Differential involvement of the hippocampus and temporal cortices in rapid and slow learning of new semantic information. Neuropsychologia.

Hunkin NM, Stone JV, Isaac CL, Holdstock JS, Butterfield R, Wallis LI, Mayes AR. 2000. Factor analysis of three standardized tests of memory in a clinical population. Br J Clin Psychol 39:169–180.

Isaac CL, Mayes AR. 1999a. Rate of forgetting in amnesia I: recall and recognition of prose. J Exp Psychol [Learn Mem Cogn] 25:942–962.

Isaac CL. Mayes AR. 1999b. Rate of forgetting in amnesia II: Recall and recognition of word lists at different levels of organization. J Exp Psychol [Learn Mem Cogn] 25:963–977.

Jacoby LL. 1991. A process dissociation framework: separating automatic from intentional uses of memory. J Mem Lang 30:513–541.

Kopelman MD, Stanhope N. 1998. Recall and recognition memory in patients with focal frontal, temporal lobe and diencephalic lesions. Neuropsychologia 36:785–796.

Lezak MD. 1995. Neuropsychological assessment. Third edition. New York: Oxford University Press.

Mackay CE, Roberts N, Mayes AR, Downes JJ, Foster JK, Mann D. 1998. An exploratory study of the relationship between face recognition memory and the volume of medial temporal lobe structures in healthy young males. Behav Neurol 11:3–20.

Maguire EA. 2001. Neuroimaging studies of autobiographical event memory. Philos Trans R Soc Lond [Biol] 356:1441–1451.

Mandler G. 1980. Recognizing: the judgement of previous occurrence. Psychol Rev 87:252–271.

Manns JR, Squire LR. 1999. Impaired recognition memory on the Doors and People Test after damage limited to the hippocampal region. Hippocampus 9:495–499.

Markowitsch HJ, Weber-Luxemburger G, Ewald K, Kessler J, Heiss W-D. 1997. Patients with heart attacks are not valid models for medial temporal lobe amnesia. A neuropsychogical and FDG-PET study with consequences for memory research. Eur J Neurol 4:178–184.

Mayes AR, Meudell PR, Pickering A, Mann D. 1988. Locations of lesions in Korsakoff's syndrome: neuropsychological and neuropathological data on two patients. Cortex 24:1–22.

Mayes AR, Montaldi D. 1999. The neuroimaging of long-term memory encoding processes. Memory 7:613–659.

Mayes AR, Isaac CL. Downes JJ, Holdstock JS, Hunkin NM, Montaldi D, MacDonald C, Cezayirli E, Roberts JN. 2001. Memory for single items, word pairs, and temporal order in a patient with selective hippocampal lesions. Cogn Neuropsychol 18:97–123.

McClelland JL, McNaughton BL, O'Reilly RC. 1995. Why there are complementary learning systems in the hippocampus and neocortex—insights from the successes and failures of connectionist models of learning and memory. Psychol Rev 102:419–457.

Moser E, Moser MB, Andersen P. 1993. Spatial-learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. J Neurosci 13:3916–3925.

Moser MB, Moser EI, Forrest E, Andersen P, Morris RGM. 1995. Spatial learning with a minislab in the dorsal hippocampus. Proc Natl Acad Sci USA, 92:9697–9701.

Murray EA, Mishkin M. 1998. Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. J Neurosci 18:6568–6582.

Norman KA. 2000. Differential effects of list strength on recall and familiarity. Poster presented at the annual meeting of the Psychonomic Society, New Orleans, LA.

Norman KA, O'Reilly RC. 2001. Modeling hippocampal and neocortical contributions to recognition memory: a complementary learning systems approach. (ICS Technical Report 01-12). Boulder, CO: University of Colorado, Institute of Cognitive Science.

Norman KA, O'Reilly RC, Huber DE. 2000. Modeling hippocampal and neocortical contributions to recognition memory. Poster presented at the annual meeting of the Cognitive Neuroscience Society, San Francisco, CA.

O'Reilly RC, Rudy JW. 2001. Conjunctive representations in learning and memory: principles of cortical and hippocampal function. Psychological Review, 108:311–345.

Pascalis O, Hunkin NM, Holdstock JS, Isaac CL, Mayes AR. 2000. Differential performance on recognition memory tests and the visual paired comparison task in a patient with a selective hippocampal lesion. Soc Neurosci Abstr 26:1241.

Reed JM, Squire LR. 1997. Impaired recognition memory in patients with lesions limited to the hippocampal formation. Behav Neurosci 111: 667–675.

Rempel-Clower NL, Zola SM, Squire LR, Amaral DG. 1996. Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. J Neurosci 16:5233–5255.

Shallice T, Evans ME. 1978. The involvement of the frontal lobes in cognitive estimations. Cortex 14:294–303.

Small SA, Wu EX, Bartsch D, Perera GM, Lacefield CO, DeLaPaz R, Mayeux R, Stern Y, Kandel ER. 2000. Imaging physiologic dysfunction of individual hippocampal subregions in humans and genetically modified mice. Neuron 28:653–664.

Squire LR, Zola SM. 1998. Episodic memory, semantic memory, and amnesia. Hippocampus 8:205–211.

Suzuki W. 1999. The long and the short of it: memory signals in the medial temporal lobe. Neuron 24:295–298.

Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M. 1997. Differential effects of early hippocampal pathology on episodic and semantic memory. Science 277:376–380.

Vargha-Khadem F, Watkins KE, Baddeley AD, Mishkin M. 1998. Dissociation between recognition and recall after early hippocampal damage. Soc Neurosci Abstr 24:1523.

Warrington EK. 1984. Recognition memory test. Windsor, UK: NFER-Nelson Publishing Co.

Warrington EK. 1996. The Camden memory tests. Hove, UK: Psychology Press.

Zola SM, Squire LR. 1999. Remembering the hippocampus. Behav Brain Sci 22:469–470.

Zola SM, Squire LR. 2001. Relationship between magnitude of damage to the hippocampus and impaired recognition memory in monkeys. Hippocampus 11:92–98.

Zola SM, Squire LR, Amaral DG. 1986. Human amnesia and the medial temporal lobe region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci 6:2950–2967.

Zola SM, Squire LR, Teng E, Stefanacci L, Buffalo E, Clark RE. 2000. Impaired recognition memory in monkeys after damage limited to the hippocampal region. J Neurosci 20:451–463.