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Differential involvement of the hippocampus and temporal lobe cortices in rapid and slow learning of new semantic information

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Abstract

The present study examined the rapid and slow acquisition of new semantic information by two patients with differing brain pathology. A partial double dissociation was found between the patterns of new learning shown by these two patients. Rapid acquisition was impaired in a patient (YR) who had relatively selective hippocampal damage, but it was unimpaired in another patient (JL) who, according to structural MRI, had an intact hippocampus but damage to anterolateral temporal cortex accompanied by epileptic seizures. Slow acquisition was impaired in both patients, but was impaired to a much greater extent in JL. The dissociation suggests that the mechanisms underlying rapid and slow acquisition of new semantic information are at least partially separable. The findings indicate that rapid acquisition of semantic, as well as episodic information, is critically dependent on the hippocampus. However, they suggest that hippocampal processing is less important for the gradual acquisition of semantic information through repeated exposure, although it is probably necessary for normal levels of such learning to be achieved.

Keywords: Amnesia; Neocortex; Memory; Acquisition; Consolidation

1. Introduction

The focus of this paper is the nature of the neural processes that underlie the rapid and slow acquisition of semantic memory. The term ‘semantic memory’ has been used to refer to memories for factual information such as that comprising general knowledge and vocabulary and it has been distinguished from ‘episodic memory’ which has been used to refer to memories for personally experienced episodes or events [70]. One issue which has recently been debated [49,69,74] is whether different neural mechanisms mediate memory for episodic and semantic information. This debate was stimulated by the recent claim that hippocampal lesions disrupt the acquisition and development of episodic but not semantic memory [77].

Vargha-Khadem et al. [77] examined three young patients who had suffered selective hippocampal damage early in life. These patients had episodic memory deficits which impaired their ability to remember what they had done and what had happened to them in the recent past so that their everyday lives were disrupted. Despite these deficits, the young people all attended mainstream schools and acquired speech, language, literacy and factual knowledge to levels within the low-average to average range.

The findings of Vargha-Khadem et al. [77] are consistent with the influential view proposed by Tulving and coworkers that the acquisition of semantic memories is not dependent on the acquisition of episodic memories [71,72,74]. This view is based on the proposal that certain neural processes underlie the acquisition of factual memories which are common to semantic memory and many episodic memories, whereas further neural processes are required to create memories of the other information specific to episodes, such as context. This view predicts that: (1) the acquisition of episodic memories can be impaired when the acquisition of semantic memories is not; (2) impairments in the acquisition of semantic memories cannot occur without impairments in the acquisition of episodic memories. Vargha-Khadem et al.’s findings are consistent with the first prediction.

Vargha-Khadem et al.’s findings provide the strongest support for the view of Tulving and coworkers. Other evidence has come from studies of patients with global amnesia, and thus a severe episodic memory deficit. Although there have been no convincing claims that semantic memory

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acquisition is ever completely normal in global amnesia, it has sometimes been argued that the learning of new facts is less impaired than the learning of new episodic information [18,36,73,75,76,82]. If the case for this argument could be made convincingly, then it would provide weak support for the view of Tulving and coworkers. However, these studies of global amnesics and the study of the young patients with hippocampal damage [77] have suffered from a serious confound which prevents a clear interpretation from being made: memory for semantic information has been tested after repeated learning trials whereas memory for episodic information has been tested after a single learning trial, i.e. the experienced event. As the semantic/episodic memory distinction has been defined in terms of the type of information being remembered, and not the amount of exposure there has been to this information, this is a serious confound.

The view espoused by Tulving and coworkers has been challenged by Squire and Zola [69], who have argued that the acquisition of factual memories (semantic memory) depends on the acquisition of memories for the episodes of which they form part (episodic memory). This view predicts that an impairment in the acquisition of episodic memory cannot occur without an impairment in the acquisition of semantic memory.

Alvarez and Squire have argued that facts and episodes are initially put into memory by a rapid learning system that depends on synaptic changes in limbic structures such as the hippocampus, and also possibly in the medial temporal lobe (MTL) cortices such as the perirhinal cortex [4]. Following Milner [48], Alvarez and Squire proposed that plastic changes occur quickly in the connections within MTL and between MTL and neocortex both in learning and forgetting. This would enable the MTL to learn quickly but would also cause it to lose information quickly, giving it the characteristics of a temporary store. Alvarez and Squire argue that storage is slowly transferred to the neocortex as a result of gradual changes in the connections between neocortical regions. Changes in neocortical synapses do not occur rapidly, resulting in slow learning and slow forgetting of information [48]. Alvarez and Squires hypothesis proposes that neocortical learning is dependent on repeated reactivation of the neocortical representation by the MTL, i.e. rehearsal. It has been proposed that this longer-term neocortical storage system includes the anterolateral temporal lobes, close to the inferior temporal lobe gyrus and the temporal pole [32]. This view, therefore, predicts that damage to the MTL should impair the rapid acquisition of both factual and episodic information and its slow transfer to neocortical sites. In contrast, damage to neocortical storage sites, such as the anterolateral temporal lobe, will not impair the rapid acquisition of episodic and semantic information if sufficient input to the MTL is still available, but will impair the transfer of this information from MTL to neocortical storage. This neocortical damage would cause semantic and episodic memories to be lost pathologically fast over periods of weeks or months, and would cause older semantic and episodic memories to be grossly impaired.

Other models have also made a similar distinction between fast MTL and slow neocortical learning mechanisms to that made by Alvarez and Squire [4]. These include the complementary learning systems framework (CLSF) [47] and the TraceLink model [52,53]. These models, which will not be considered in detail in the present paper, specify the hippocampus, rather than the entire MTL, as mediating rapid learning and view the perirhinal cortex as part of the slow neocortical learning system. The model proposed by Nadel and Moscovitch [54,55] also postulates a critical role for the hippocampus in the rapid acquisition of semantic and episodic memories and allows for slow neocortical learning of semantic information. However, according to this model, episodic memories remain dependent on the hippocampus for as long as they last.

It has been argued that it is computationally efficient to have both rapid and slow learning systems [47]. According to the CLSF [47] there is a small change in neocortical synapses each time a recent memory is reinstated. This gradual learning, interleaved with learning about other items, enables the neocortex to "discover the structure in ensembles of experiences" ([47], p. 419). In contrast, it is argued that the hippocampal system supports rapid learning of items without disrupting the structure of the neocortical memory representations and then "reinstatement of new memories interleaves them with others to integrate them into structured neocortical memory systems" ([47], p. 419). According to this model, therefore, the slow integration of memories of specific items into the neocortical memory systems enables commonalities between items to emerge. The implication of this is that some of our knowledge (generalities and category information) is not explicitly learned but emerges from the way in which, through slow learning, the representations of specific exemplars are organized in the cortex. The focus of our paper is not on the learning of generalizations but on the acquisition of specific facts from which such generalizations can be abstracted. A key question, therefore, is whether different brain systems are necessary for establishing memories for semantic and episodic information, or whether different brain systems underlie rapid acquisition and slow integration of new memories with established memories for both types of information.

In general, the evidence from global amnesia supports Squire's view that the acquisition of semantic and episodic memories depend on the same neural processes. There is strong evidence that large MTL or midline diencephalic lesions, which cause this disorder, disrupt both episodic and semantic memory (see [12,41,68] for reviews). As discussed earlier, although it has been argued by some that the acquisition of semantic memories is impaired less than the acquisition of episodic memories by global amnesia, this has not been convincingly demonstrated. Further evidence that semantic memory acquisition is not spared relative to episodic memory acquisition in global amnesia was provided by the

results of a quantitative comparison between memory for new facts and memory for new episodes [25]. This study showed that a group of patients who had lesions to either the MTL or diencephalon (Korsakoff's syndrome) were impaired at fact learning (learning three word sentences) and episodic memory (responding to questions about the experimental session) to a similar extent. When amnesic and control performance was matched on the episodic memory test, by testing the controls after a longer delay, semantic memory was also matched. In addition, one of the reported patients, EP, had no detectable episodic memory and correspondingly showed no learning on the fact learning task at all. In another study, Gabrieli et al. [17] showed that patient HM, who underwent a bilateral temporal lobectomy in 1953, and who has a severe episodic memory deficit, was not only impaired at rapidly learning new facts, but was also impaired at remembering facts to which he had been repeatedly exposed over a long period of time.

Further support for the view of Squire and coworkers has been found in studies of semantic dementia. In this disorder, pathology gradually spreads within and eventually beyond the anterolateral temporal lobe but, at least for a while, spares the hippocampus ([20,27,66] for a review see [21]). This results in a progressive loss of previously well-established semantic memories and more recent work suggests that it also causes a loss of autobiographical (i.e. episodic) memories that becomes more severe with older memories [20,67]. In other words, there is a retrograde amnesia the gradient of which is the reverse of that seen in global amnesia. However, other evidence indicates that patients with semantic dementia can learn new declarative information relatively normally if one allows for the fact that these patients have reduced semantic knowledge and so cannot encode much new information in the rich meaningful fashion that is known to enhance long-term memory. Normal acquisition both of new episodes and relatively normal acquisition of new facts has been demonstrated. For example, forced-choice recognition for visually presented objects has been shown to be relatively normal [23] and relearning of vocabulary has also been reported [16,22]. There is evidence, however, that retention declines pathologically fast over periods of weeks or longer [22]. Therefore, these patients show the pattern of intact and impaired memory which Alvarez and Squire's model predicts will follow damage to the neocortical sites mediating long-term storage. According to this model, new learning is possible, because it can be mediated by the intact hippocampus but these memories are lost at a pathologically fast rate because transfer to long-term neocortical storage is not possible.

The findings reported by Vargha-Khadem et al. [77], however, have presented a challenge to Squire's view as the three young patients with hippocampal damage reported in that study acquired semantic memory levels within the normal range, whilst having a very impaired episodic memory. According to Squire's view, the acquisition of both of these types of information should depend on the MTL. In reply to Vargha-Khadem et al.'s paper, Squire and Zola [69] argue that the young patients did have some residual episodic memory and this may have been sufficient to support the acquisition of some semantic information. More recently, Manns and Squire [39] have argued that the pattern of intact and impaired memory performance shown by these young patients may be related to the early age at which hippocampal pathology occurred.

The three young patients were also reported to show other kinds of intact memory not found in global amnesics. They retained intact the ability to recognize, not only recently studied verbal and visual items, but also recently studied associations between items of the same kind (such as pairs of words or pairs of faces). In contrast, the three subjects were seriously impaired at recalling recently studied verbal and visual materials, and also showed impaired recognition for associations between different kinds of information that included associations between faces and voices, and between objects and locations. Squire and coworkers have been unable to replicate the dissociation between intact item recognition and impaired recall in their patients with adult-onset hippocampal damage [39,60] leading them to conclude that the sparing of some aspects of memory shown by Vargha-Khadem et al.'s young patients are, most likely, due to some form of re-organization of function [39].

In contrast to Squire, we have replicated the pattern of spared item recognition and impaired recall in our patient with adult-onset relatively selective hippocampal damage, YR, whose new semantic learning is reported in the present paper [29,43,45]. Our results suggest that compensatory strategies need not underlie the preserved memory performance of Vargha-Khadem et al.'s patients on, at least, tests of item recognition. Whether the acquisition of new semantic information is spared following adult-onset hippocampal damage is therefore of great importance and is an issue addressed in the present paper.

One thing which has been particularly striking in considering the literature concerning the acquisition of semantic and episodic memories is the importance of repeated learning trials in enabling patients with MTL damage to obtain above chance performance on tests of new semantic memories. Even the young patients reported by Vargha-Khadem et al. [77] were impaired at rapidly acquiring new semantic information. One of the materials for which the three young subjects showed a recall deficit was a short story. This is non-personal factual information just like the descriptions of historical events which make up our general knowledge (tested in Section 4 of the present paper). In contrast to their deficit in rapidly learning factual information, the young patients acquired normal levels of memory for facts to which there would have been considerable exposure over a period of years. This may be unexpected on Squire's view which stresses the critical contribution of the MTL to slow learning through rehearsal. However, it can be explained if slow neocortical learning can occur independently of input from the MTL or hippocampus. Alvarez

and Squire [4] do not exclude this possibility stating that "the neocortical representation is reactivated, usually with the help of the MTL" ([4], p. 7042). If hippocampal damage does not impair the slow learning system, then multiple repetitions of factual information over a period of years may allow semantic memory to develop relatively normally. Like hippocampal-dependent rehearsal, repetition of information would repeatedly reactivate the neocortical representation, slowly producing long-term changes.

This proposal is consistent with the findings and the view of Kapur [32]. Kapur reported a double dissociation between the performance of two patients on memory tests for factual information. A patient with damage to the mammillary bodies was impaired at rapidly acquiring name-occupation paired associates but was unimpaired at recalling information about personalities who had come to public attention since the onset of his pathology. A patient with bilateral non-MTL pathology showed the reverse dissociation. This led Kapur to propose that there are two learning systems through which factual information can be acquired: a rapid learning system dependent on limbic structures such as the mammillary bodies and hippocampus and an incremental learning system dependent on association cortices.

As we have discussed earlier, semantic and episodic memory have been defined in terms of the type of information being remembered and not the amount of exposure to that information. As we have seen, evidence from global amnesia and from patients with focal lesions to the hippocampus which has been presented as supporting a distinction between the neural mechanisms underlying semantic and episodic memory is weak and can be reinterpreted as suggesting a dissociation between rapid and slow acquisition of information. In the present paper we present data consistent with this reinterpretation of the literature. We investigate the view that the neural mechanisms underlying rapid and slow acquisition of information differ [32]. We hold category of information (episodic/semantic) constant and investigate the rapid and slow acquisition of non-personal factual information.

Drawing on the proposals of Kapur [32] and Alvarez and Squire [4] and the evidence from the patients described by Vargha-Khadem et al. [77], we suggest that rapid acquisition of semantic, like episodic, information depends on the hippocampus. Our view is that the hippocampus is critical for the rapid acquisition of non-personal factual information as well as personally experienced episodes and events which include contextual information. In addition, memory for both semantic and episodic information can be acquired slowly, independently of the hippocampus, through repeated learning trials. However, hippocampal-dependent rehearsal would also normally contribute to slow neocortical learning. For this reason, in the absence of a normally functioning hippocampus, learning through repeated trials would result in above chance, but not necessarily normal, levels of memory performance (memory would be acquired by repetition only, rather than repetition and rehearsal). This view predicts that: (1) hippocampal lesions will impair the rapid acquisition of both episodic and semantic information; (2) hippocampal lesions will not prevent the acquisition of information through repeated exposure, although normal levels of performance may not be obtained; (3) pathology which disrupts neocortical slow learning will impair the transfer of information to the neocortex, but will not impair the rapid acquisition of episodic and semantic information (provided sufficient input to the hippocampus is still available).

In this paper, we report an investigation of semantic memory acquisition in a patient with relatively selective bilateral hippocampal damage (YR) which occurred when she was 48. YR has a clear episodic memory deficit. She shows impairment on laboratory tests that tap recall for contextual information, such as spatial and temporal features, that are critical for episodic memory as defined earlier [28,43]. In addition, informal assessment by our group has repeatedly confirmed that she is very impaired at recalling recent incidents from her daily life, i.e. at recalling episodic incidents. Importantly, YR's general pattern of anterograde amnesia (see [28,29,43,46]), is very similar to that of the three young subjects described by Vargha-Khadem et al. YR has impaired free and cued recall and impaired recognition memory for associations between information of different types, e.g. object–location, face–voice, picture–sound, word–temporal position [43,46]. However, her item recognition memory and memory for associations between items of the same type, e.g. word–word and face–face associations is relatively spared [29,30,43,46]. Any differences between YR and the three young subjects studied by Vargha-Khadem et al. in the acquisition of semantic memory cannot, therefore, be related to more general differences in their memory impairments.

In the experiments reported here we investigated YR's ability to learn new semantic information in three ways. First, we tested her ability to learn the meanings of several new words repeatedly presented within the experimental sessions (Section 2). This enabled us to confirm, with paradigmatically semantic materials, that YR resembled Vargha-Khadem et al.'s three young subjects in showing a deficit in fact learning after limited exposure to the stimuli. It also enabled us to investigate whether the severity of this deficit reduced as the number of learning trials increased, as might be expected if a slow learning mechanism was working normally in YR. Second, as YR's item recognition has been found to be intact for other information [29,43], in Section 3, we examined whether YR could distinguish studied definitions from new definitions, even after limited exposure, and whether such information could be maintained over a period of weeks. Third, we tested YR's knowledge of public information (including the meanings of new words) taken from the time of the onset of her episodic memory disorder (Section 4). In doing this, we took great care to construct the memory tests so as to avoid floor and ceiling effects on individual test items so as to maximize the sensitivity of the tests.

In Sections 3 and 4, we compared YR's performance not only with a group of matched control subjects, but also with

another patient, JL, who, as a result of a head injury, had damage to the anterolateral temporal cortex accompanied by temporal lobe epilepsy. This patient has shown normal memory on recall and recognition tests when memory is tested at delays of 24 h or less, but impaired performance after a delay of several weeks [44]. She therefore appears to have an impairment of the slow learning mechanism. We examined whether JL showed a similar pattern of accelerated forgetting for semantic material and whether her memory impairment for semantic information to which she had been repeatedly exposed over a period of years was more severe than YR's.

2. Experiment 1

2.1. Introduction

We investigated whether YR could learn the definitions of very rare words that neither she nor her controls had encountered before. Patient HM who suffered large bilateral MTL lesions has been found to be impaired on such tasks. He could not recognize which of a number of definitions had been paired with a particular word [17]. In contrast, Vargha-Khadem et al.'s three young patients who had suffered selective hippocampal damage acquired vocabulary to normal levels during their childhood and adolescence. They could recall the definitions of words from the English language and yet their free recall of episodic information was impaired. However, their initial acquisition of new factual information, such as the short stories which comprise the logical memory subtests of the Weschler Memory Scale-Revised [81], was impaired. We tested YR's memory for the definitions of new words following a single exposure to the material and after subsequent repetitions of the study list. Memory was tested by cued recall of the definitions, and recognition of the studied definition that corresponded to a particular word. We were interested in whether YR's initial acquisition of the word-definition pairs would be impaired and whether any deficit would be reduced by repeated exposure to the stimuli.

2.2. Method

2.2.1. Subjects

YR was 60 years old at the time of testing. In 1986, when YR was 48, she received an opiate drug to relieve a severe back pain and may then have suffered an ischaemic incident. Following this incident she suffered a memory impairment which has persisted until the present time. YR's performance was compared with that of 10 sex, age, and IQ matched female control subjects (mean age=59.1 (S.D. = 5.8), mean NART-R predicted full-scale IQ=104 (S.D. = 7.89)). Structural MRI has revealed bilateral hippocampal pathology with no visible pathology to other brain regions including the parahippocampal gyrus, frontal lobes and parietal lobes. There was some atrophy in the parietal region but this was comparable in extent to that seen in age-matched controls. Volumetric analysis of YR's MRI data is reported elsewhere [28]. YR's performance on standardized tests is summarized in Table 1. She has an IQ measured by the Weschler Adult Intelligence Scale-Revised [80] which is a little above average and is slightly higher for verbal than performance tests. The difference between her premorbid IQ (measured by the NART-R [56]) and present IQ was 13 points, which

Table 1
Performance of YR and JL on psychometric tests measuring premorbid IQ (NART-R) and present IQ (Weschler Adult Intelligence Scale-Revised), memory (Recognition Memory Test, the Wechsler Memory Scale-Revised, and the Doors and People Test) and executive functions (Wisconsin Card Sorting Test)[a]

Test	YR	YR percentile[b]	JL	JL percentile[b]
NART-R				
FSIQ	115	84	111	82
WAIS-R				
FSIQ	102	55	122	93
VIQ	108	70	118	88
PIQ	97	42	121	89
RMT				
Words	45	75	50	>75
Faces	48	>95	43	50
WMS-R				
GEN	66	1[c]	104	61
A/C	122	93	112	79
DEL	73	4[c]	105	63
D&P				
People	9	2.3[c]	36	95.2
Doors	18	36.9	19	36.9
Shapes	22	4.8[c]	36	74.8
Names	22	97.7	20	74.8
WCST				
CAT	3	6–10	6	>16
P.ERROR	6	88	0	>99

[a] IQ scores are provided for the NART-R and the Weschler Adult Intelligence Scale-Revised. Raw scores are provided for the Recognition Memory Test (maximum possible score 50) and the Doors and People Test (maximum possible score of 36 for People and Shapes and 24 for Doors and Names Subtests). Index scores are provided for the Wechsler Memory Scale-Revised. Number of categories and number of perseverative errors are provided for the Wisconsin Card Sorting Test. Percentile scores are also provided for each test. Key: FSIQ: full-scale IQ, VIQ: verbal IQ, PIQ: performance IQ, RMT: Recognition Memory Test, WMS-R: Weschler Memory Scale-Revised, GEN: general memory, A/C: attention/concentration, DEL: delayed memory, D&P: Doors and People, people: verbal recall, doors: visual recognition, shapes: visual recall, names: verbal recognition, WCST: Wisconsin Card Sorting Test, CAT: number of categories correct, P.ERROR: number of perseverative errors.

[b] The manuals of the Recognition Memory Test, Doors and People Test and Wisconsin Card Sorting Test provide tables of percentile equivalents for the scores on these tests. For the NART-R, WAIS-R and WMS-R the IQ/index scores are normally distributed with a mean of 100 and S.D. of 15. From this information and the subject's score, a *z*-score can be calculated and from the *z*-score one can determine the percentile score for the subject.

[c] Below fifth percentile.

indicates a fall of less than one standard deviation (S.D.) in IQ (one S.D. on the WAIS-R is 15 points). Her pattern of performance on the Weschler Memory Scale-Revised [81], Warrington Recognition Memory Test [79] and Doors and People Test [5] suggests that her recognition of visual and verbal items is relatively intact, but that recall is impaired. As shown in Table 1, YR's performance was at the fifth percentile or below on the two recall subtests of the Doors and People Test and on the general and delayed memory indices of the WMS-R. On the other memory tests, which all tapped item recognition, YR showed no indication of an impairment.

There was no evidence of impairment in YR's performance on tests of executive function. When compared with matched controls (mean age 59.6 years (S.D. = 3.6); mean NART-R 104.8 (S.D. = 7.15)) her verbal fluency (FAS; [7]) score of 42 was 0.11 S.D.s below the control mean of 43.9 and her score of 8 on the Cognitive Estimates Test [65] was 0.69 S.D.s below the control mean of 6. The number of categories which she correctly sorted in the Wisconsin Card Sorting Test [26] fell between the 6th and the 10th percentile because she avoided re-using previously correct categorization rules. On this test she made only six perseverative errors in 128 trials (performance was at the 88th percentile) which gave no suggestion of frontal dysfunction.

2.2.2. Procedure

Ten very uncommon concrete words were selected: moa, chamade, jacaranda, tsunami, haitu, torii, faldetta, pelota, basilisk, reredos, which were considered unlikely to already be familiar to our subjects. This was confirmed by feedback from both the control group and YR; none of the subjects had encountered any of the words before. Words were selected which had definitions which could be divided into four meaningful parts, e.g. haiku: a 17 line, often jesting, Japanese verse.

Each word, with its corresponding definition, was printed onto a separate index card. Subjects read the word and definition aloud and then placed the card face-down on the table. Once subjects had read all 10 word-definition pairs they were instructed to count backwards in threes from a number determined by the experimenter for 20 s. Cued recall of the definitions was then tested. Each studied word was presented to subjects in the center of an index card. In response to each word, subjects had to produce as complete a definition of the word as possible. The order in which definition recall was tested was different to that in which the definitions were studied.

This procedure was repeated so that subjects saw the set of words and definitions five times and, after each presentation of the list, recall was tested. A different study order and test order was used on each trial. Presentation and test order for each learning trial was the same for each subject.

A 30 min delay followed the study phase. This was filled by unrelated psychometric tests. Cued recall of the definitions was then tested in the same way as before. There was then a 5 min delay filled with a non-verbal task. Following this subjects were given a test in which they had to recognize the definition corresponding to each studied word. A four-choice forced-choice procedure was used. Each word was presented on an index card with four of the studied definitions below it (see Table 2). The subject had to select the definition which corresponded to that word. This test tapped memory for the associations between the words and their definitions, rather than merely familiarity with the definitions, as the foils were repairings of the studied word-definition pairs.

Table 2
A comparison of the format of the test materials for the recombination word-definition recognition test from Section 2 and the old/new definition discrimination test from Section 3[a]

The subject was asked "Which is the definition of this word?"
Haiku is:
A signal for retreat on drum and trumpet
A 17 line, often jesting, Japanese verse
A tree, native to Brazil, bearing large clusters of blue–violet flowers
A huge wave caused by an earthquake or volcanic eruption
Example of definition recognition from Section 3. The correct definition is marked here in bold
Studied definition:
Moa is an extinct, Ostrich-sized New Zealand bird
The subject was asked: "Which definition has the same meaning as one seen at study?"
Test choices for that studied definition:
A large bird from New Zealand which is rare
A large bird from New Zealand which has died out
A large bird from New Zealand which cannot fly
A large bird from New Zealand which is protected

[a] Example of word-definition recognition from Section 2. The correct definition is marked here in bold, the three incorrect definitions were also seen at study but paired with different words (chamade, jacaranda and tsunami, respectively).

Cued recall and definition recognition were tested again after a 24 h delay. As before, a 5 min filled delay intervened between the recall and recognition tests. Retest was immediately followed by five further learning trials of the word-definition pairs with cued recall being tested after each presentation of the list.

A final test session took place approximately 4 weeks later during which cued recall of the definitions was tested. Definition recognition was not tested in this session.

2.3. Results

To score the recall test each definition was divided into four points of information. One mark was awarded for each correct point of information, and half a mark was awarded for each partially correct point of information. This gave a maximum of four possible marks per word and therefore a maximum possible total of 40 for the set of 10 definitions. A section of the definition was considered correct if the correct meaning was conveyed. It was not necessary for

Table 3
The mean score of the control group, with S.D. in parentheses, for each of the cued recall tests (CUED RECALL), and the tests of the subjects' recognition of which studied definition corresponded to each studied word (WORD-DEFINITION RECOGNITION)[a]

Test	Control mean (S.D.)	YR	S.D. from control mean
CUED RECALL			
Session 1			
Learning trial 1	7.6 (3.74)	0.5	(−1.9)
Learning trial 2	15 (7.39)	1	(−1.89)
Learning trial 3	22.4 (9.46)	1.5	(−2.2)*
Learning trial 4	25.95 (10.74)	2.5	(−2.2)*
Learning trial 5	27.55 (9.05)	3.5	(−2.7)*
30 min delayed test	26 (10.75)	2.5	(−2.2)*
Session 2			
24 h delayed test	27.25 (10.08)	2	(−2.5)*
Learning trial 6	30.35 (10.67)	2	(−2.7)*
Learning trial 7	31.75 (10.55)	5.5	(−2.5)*
Learning trial 8	33.15 (9.7)	5.5	(−2.9)*
Learning trial 9	35.10 (6.9)	5	(−4.4)*
Learning trial 10	35.65 (6.36)	6	(−4.7)*
Session 3			
4 weeks delayed test	20.3 (7.4)	1	(−2.6)*
WORD-DEFINITION RECOGNITION			
Session 1			
30 min delayed test	9.3 (1.34)	3	(−4.7)*
Session 2			
24 h delayed test	9.3 (1.49)	5	(−2.9)*

[a] YR's scores on each of these tests is given along with the number of standard deviations that her performance fell above (+) or below (−) the control mean in parentheses (scores falling more than 1.96 S.D. below the control mean are indicated by an asterisk). Cued recall was scored out of a total of 40 points (see text for detail of scoring), both recognition tasks were scored out of a total of 10 points.

subjects to recall the exact wording of the definitions. If the main subject of the definition was wrong or omitted, half a mark was subtracted from the total score for that definition, e.g. the definition of moa is: an extinct, Ostrich-sized New Zealand bird, half a mark would be subtracted from the recall score if "bird" was omitted or replaced by, for example, "plant".

The results of the cued recall tests are shown in Table 3. We considered YR's performance to be impaired if it fell more than 1.96 S.D.s below the control mean, giving a type one error probability of 0.05, two-tailed. YR's cued definition recall was very poor after both the first and second presentations of the word-definition pairs but, because control subject performance was close to floor levels on these trials, YR's deficit just failed to reach our criterion for impairment (1.9 and 1.89 S.D.s below the control mean compared with our criterion of 1.96 S.D.s). On subsequent presentations of the word-definition pairings control performance improved considerably whereas YR's performance improved very little. On all of these trials YR's cued recall was significantly impaired and this impairment increased with increased repetition of the word-definition pairs (see Table 3). After the tenth learning trial (i.e. the final presentation of the word-definition pairs in test session two) YR's cued recall was 4.7 S.D.s below the control mean. YR's cued recall was also impaired at delays of 30 min and 24 h after the first five learning trials and at a delay of 4 weeks after all 10 learning trials.

The results from the recognition tests are also shown in Table 3. The recognition tests were scored as the number of correct choices out of a total of 10. YR was impaired at correctly selecting that definition which had been studied with a particular word from among definitions which had been studied with other words, 30 min and 24 h after five presentations of the word-definition pairings.

2.4. Discussion

YR was impaired at learning the definitions of new words. Her recall of word-definitions to which she had had limited exposure was very poor and, despite the near floor level of performance of the control subjects, was very close to our criterion of impairment after the first learning trial. Vargha-Khadem et al.'s three young patients were also impaired in the initial acquisition of semantic information. These young people showed poor recall of logical memory test stories after a single exposure. Therefore, like the recall of episodic information, the recall of semantic information to which there had been limited exposure, was impaired following hippocampal damage in YR.

The data also showed that YR's deficit did not decrease with repetition of the word-definition pairs. After 10 learning trials spread over two sessions YR's cued recall of the definitions was still severely impaired (4.7 S.D.s below the control mean).

An impairment was also seen when, after five learning trials, memory for the association between each word and its definition was tested by recognition rather than cued recall. Deficits in the recognition of associations between other types of material have also been found in YR when the information to be associated in memory has been of different kinds e.g. face–voice, object–location, picture–sound, picture–word, word–temporal order [43,46]. Therefore, rather than reflecting a specific impairment of semantic memory, YR's deficit in recognizing word-definition (orthographic-semantic) associations may reflect a more general deficit in associating in memory different types of information that are probably represented in different brain regions [49].

Extensive previous testing has shown that YR's recognition of individual items is intact under conditions which would enable a memory decision to be made on the basis of familiarity [30]. This suggested that YR would be able to distinguish studied definitions from unstudied definitions, even though her recall and recognition of the word-definition pairs is impaired. This was investigated in Section 3.

3. Experiment 2

3.1. Introduction

YR's ability to distinguish studied definitions from unstudied definitions was tested. As her performance on other forced-choice item recognition tests has been unimpaired, we predicted that YR should not show a deficit in definition recognition. We therefore not only tested YR's recognition memory after a short delay of 20 s, which was a retention interval of a similar length to those used in a number of the previously administered item recognition tests, but also assessed her recognition of the definitions after delays of 24 h and 3 weeks.

YR's recognition performance was compared with that of a patient, JL, who has no identifiable damage to the hippocampus but whose regions of pathology include the perirhinal and anterolateral temporal cortices. The perirhinal cortex has been suggested to be important for familiarity-based memory decisions [1] and, as a result, JL's recognition memory might be expected to be impaired. However, her hippocampus is intact and, as long as it still has appropriate input, may be expected to be able to support her recognition performance for a limited period of time [4,47,52,53]. In contrast, as she has damage to those regions proposed to be critical for long-term storage (anterior inferior temporal lobes), her memory may be impaired after longer delays. Consistent with this, JL has shown normal performance in recalling and recognizing stories and complex abstract patterns and in recognizing words 20 s and 30 min after a single exposure, but has shown impaired memory for this information after 3 weeks delay [44]. Here we investigated whether JL would show the same pattern of performance in recognizing definitions to which she had had repeated exposure.

3.2. Method

3.2.1. Subjects

YR's performance was compared with that of a female control group matched for age and IQ (mean control group age = 59.3 (S.D. = 5.03), YR's age = 61; NART-R full-scale predicted IQ = 106.4 (S.D. = 5.08).

Patient JL suffered a closed head injury as a result of a motor-cycle accident in 1976 when she was 17. She was unconscious for 11 days but subsequently made a good recovery. In 1977 she developed temporal lobe epilepsy, although before this she had complained of strange feelings often brought on by music, so it is likely that her epilepsy predated 1977. A CT scan carried out at this time revealed a probable low-density abnormality in the right anterior temporal area. In June 1978, an EEG showed a right sided posterior quadratic emphasis. JL currently experiences, on average, 35 complex partial seizures per month.

A T1-weighted 3D volume scan (RFAST) revealed bilateral damage to the superior, middle and inferior temporal gyri and the perirhinal cortex (see Fig. 1). The stereological point counting technique [24,62–64] was used to obtain quantitative estimates of the volumes of brain regions [44]. Volume measures of the entorhinal and perirhinal cortices were obtained using the boundaries defined by Insausti et al. [31]. The volume of JL's right perirhinal cortex was 6.3 S.D.s smaller than the mean of three matched control subjects. The volume of the left perirhinal cortex was within two S.D.s of the mean control volume but outside of the control range. However, estimated volumes of the left and right entorhinal cortex were above the control mean ($N = 3$). The volume of the hippocampus was also larger than the control mean ($N = 17$), bilaterally. Not only was the hippocampal volume normal, but a heavily T2-weighted scan, obtained using a fluid attenuated inversion recovery (FLAIR) sequence (see Fig. 1), showed a hippocampus of normal appearance. This is consistent with normal neuronal density and a normal proportion of glial cells in the hippocampus. However, we cannot exclude the possibility that other imaging techniques or postmortem examination may detect more subtle abnormality in this region in JL. There was evidence of partial damage to the amygdala on the right but it was not possible to obtain volume estimates for this structure because of the proximity of the cortical damage. Approximately 75% of the medial and lateral orbitofrontal cortex was damaged on the right and there was also damage to the anterior half of the gyrus rectus on the right.

JL's performance on standardized neuropsychological tests is shown in Table 1. Her IQ is above average and has not declined from estimated premorbid levels. JL's performance on a number of memory tests which tapped free and cued recall and recognition was almost entirely normal. There was a discrepancy between her score on the words and faces subtests of the RMT which fell at the 10th percentile. Although her performance was not impaired for either subtest it was worse for faces than words. On tests of frontal lobe functioning JL's performance was normal. JL's pathology and neuropsychological profile are discussed in more detail by Mayes et al. [44].

JL's performance was compared with that of a female control group matched for age and IQ. JL was aged 40 years at the time of testing which was 0.36 S.D.s below the control mean age of 41.1 years (S.D. = 3.03). The NART-R predicted full-scale IQ of the group was 113.5 (S.D. = 8.2), JL's predicted IQ from the NART-R was 114 which was 0.06 S.D.s above the control mean predicted IQ and her WAIS-R full-scale IQ of 122 was 1.04 S.D.s above the control mean predicted IQ.

3.2.2. Procedure

Thirty-three new words were selected which were unlikely to have been encountered before by the subjects. As in Section 2, feedback confirmed this to be the case. The words were assigned to four sets: three sets of nine words and one set of six words. Each word and its definition was printed on an index card. Presentation of the word-definition pairs

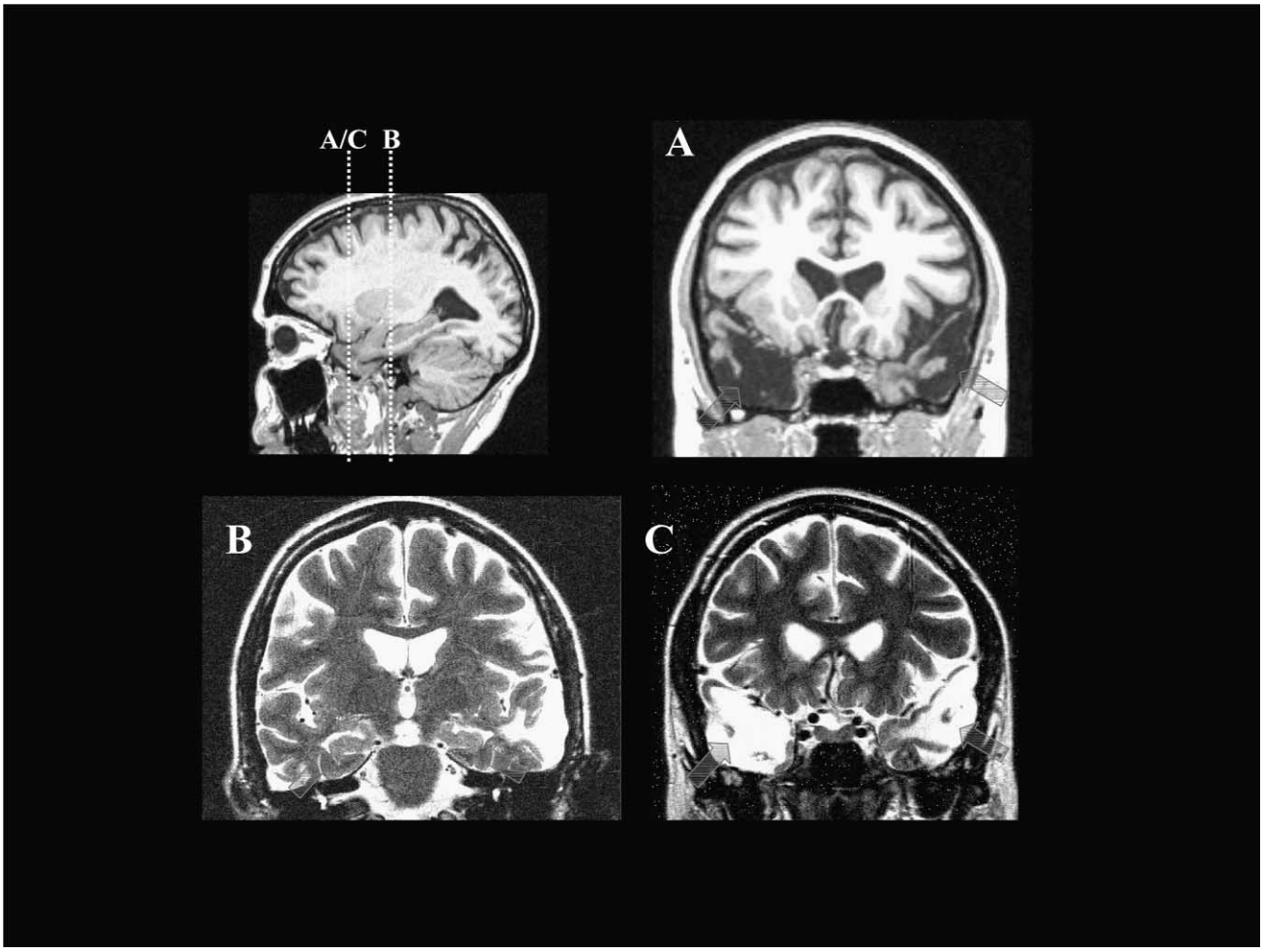

Fig. 1. MR images for patient JL. Sagittal T1-weighted image (top-left) showing the location of images A/C. (A) Coronal T1-weighted image showing extensive damage to the anterior temporal lobes bilaterally (arrows); (B) heavily T2-weighted image obtained with fluid attenuated inversion recovery (FLAIR) sequence that shows the hippocampus appears to be normal bilaterally (arrows); (C) a FLAIR image, corresponding to (A), which shows the abnormal appearance on a heavily T2-weighted image of the anterior temporal lobes bilaterally. The images follow radiological convention, i.e. the left side of the image corresponds to the right side of the individual's brain.

took place in three blocks within a single test session. Memory was tested after delays of 20 s, 24 h and 3 weeks. The stimuli corresponding to these test delays were intermixed within the three study blocks.

Each word-definition pair was presented more than once at study. The stimuli for which memory was tested after a 20 s delay were presented twice, those for which memory was tested after a 24 h delay were presented five times, and those for which memory was tested after a 3-week delay were presented 10 times. Greater exposure was given to the items which would be tested after a longer delay in an attempt to match control subject performance at the three delays. Control subjects and patients had the same amount of exposure to the word-definition pairs.

Subjects were not told that their memory would be tested for the word-definition pairs after the 24 h and 30 min delays. Subjects were told that after the 20 s delay their memory would be tested for some of the items they had seen at study. A surprise test was used for the longer delays because we did not want subjects to write down the definitions on leaving the first test session or to engage in systematic rehearsal. This may have occurred if they had known that their memory would be tested for the material after the longer delays.

The 20 s delayed test assessed subjects' memory for the items they had seen twice at study. However, we were concerned that, if memory was only tested at that delay for items which had been studied twice, then, during the second and third study blocks, subjects would not attend properly to items after their second presentation (as they would presume that memory for those items would not be tested). To ensure that subjects attended to all definitions even when they were presented more than twice, we included two filler items in each study block. One filler item was presented five times at study and the other was presented 10 times at study. Memory for these filler items was tested after the 20 s delay but subjects' responses to the filler items were not scored.

So in summary, subjects were presented with three study blocks each containing 11 words and their definitions. Each block comprised: three word-definition pairs to be tested after a 20 s delay, three word-definition pairs to be tested after a 24 h delay, three word-definition pairs to be tested after a 3-week delay and two filler words to be tested after a 20 s delay.

At study the word-definition pairs were presented to subjects on index cards. They read the word and its definition aloud and placed the card face-down on the table before reading from the next. On completion of the study phase, subjects were instructed to count backwards in threes for 20 s from a number determined by the experimenter. Definition recognition was then tested for five of the 11 definitions (the three items which had been presented twice (real test items) and the two fillers). Subjects were shown cards on which there was a reworded version of one of the studied definitions (which maintained that definition's meaning) along with three similar definitions formed by changing just one point of information in the definition (see Table 2). The target word did not appear with the definition at test. The memory decision could therefore be based on discriminating old from new semantic features. After this test there was a break of 5–10 min filled with conversation and then the next block of definitions was presented and tested in the same way; this was then repeated for the third block.

Subjects returned 24 h later and their recognition of the definitions which had been presented five times at study was tested. In this recognition test the foils differed from the target definition by two points of information.

Subjects returned a final time 3 weeks later and their recognition of the definitions which had been presented 10 times at study was tested. In this recognition test the foils differed from the target definition in all four points of information.

The difficulty of the discrimination of target definition from foil definitions was varied over the three test delays in an attempt to match control subject performance at the three delays and avoid problems of floor effects.

3.3. Results

The results for YR and JL are shown in Table 4 as the number of S.D.s that their performance fell above or below the means of their respective control groups. Although YR's definition recognition fell numerically below the control mean, it was not impaired at any of the three delays. Her performance was within the control range even at the longest delay where she scored 44% correct and the control performance ranged from 33 to 100% correct (chance = 25% correct). It should be noted though that despite our best efforts to match control performance over the three delays, YR's control subjects were performing at close to floor levels after a 3-week delay and, as a result, any deficit in YR's performance at this delay may have been underestimated. However, we consider this to be unlikely because on a comparable test using the definitions from Section 2, which was carried out 4 weeks after YR and her controls had received the 10 learning trials described in the Section 2.2, YR's performance was again unimpaired (YR scored 6 out of a possible 10 correct; control mean number correct was 8.2 (S.D. = 1.69); control range 4–10 correct; chance was 2.5 correct). In that case, the control subjects were not performing at floor levels.

JL's definition recognition was unimpaired after both delays of 20 s and 24 h. In fact, her performance was numerically better than the mean of her control group at these two delays. In contrast to YR and to her own performance after the shorter delays, JL's performance was severely impaired after a 3-week delay. Examination of Table 4 shows that the experimental manipulations (see Section 2.2) which were used to avoid control subjects performing at floor levels after the long delay were so successful that the performance of the control subjects was better after the longer than the shorter retention intervals. However, this improved control subject performance could not explain JL's memory deficit after the 3-week delay. JL's performance did not remain stable over the three delays while the control subject performance improved. Rather, her old/new definition recognition fell from 78% correct at the 24 h delay to chance (22%) at the 3-week delay, which was well outside her control group's range (78–100% correct).

The interpretation of JL's apparently accelerated forgetting of semantic information is limited by the close to ceiling level of performance of the control group at the 24 h delay. The ceiling effect could have hidden any forgetting that the control group may have shown between the 24 h and 3-week delay. However, examination of the performance of only those control subjects who gained the same score (78% correct) or less than JL at the 24 h delay showed that these

Table 4
The mean percent correct score (S.D. in parentheses) for YR's control group, JL's control group and percent correct scores for YR and JL for each of the three delays of the definition recognition test. Also provided are the number of standard deviations that YR's and JL's performance fell above (+) or below (−) the mean of the matched control group for each delay (scores falling more than 1.96 S.D. below the control mean are indicated by an asterisk)[a]

Test delay	YR controls	YR	S.D. from control mean	JL controls	JL	S.D. from control mean
20 s	73.5 (15.9)	67	(−0.4)	83.5 (13)	100	(+1.26)
24 h	63.4 (25.3)	44	(−0.77)	74.8 (21.6)	78	(+0.15)
3 weeks	72.2 (26.5)	44	(−1.06)	92.3 (7.4)	22	(−9.5)*

[a] Chance performance is 25% correct.

control subjects produced a very different pattern of performance to JL. Seven control subjects obtained a score at the 24 h delay which was equivalent to or worse than JL (control mean score 63.7, S.D. = 15.5). In contrast to JL, whose performance dropped to chance at the 3-week delay, the mean performance of these seven control subjects was 90.6% correct (S.D. = 7.6) at the 3-week delay. Therefore, the data convincingly indicate that JL loses her memory for the definitions at an accelerated rate relative to matched controls between the 24 h and 3-week delay.

3.4. Discussion

As discussed in the Section 1, it has been proposed that the neocortex is not capable of rapid learning [4,47,52,53]. However, although the neocortex learns slowly, it has been proposed that studying an item, even once, produces small but measurable changes in the way that item is represented in the neocortex [58,59]. Familiar stimuli strongly activate a small number of units whereas unfamiliar stimuli weakly activate a large number of units. As a result a measure of an item's familiarity can be determined from its neocortical representation. Aggleton and Brown [1] have highlighted the perirhinal cortex, in particular, as being capable of supporting recognition memory when memory decisions can be made on the basis of familiarity.

YR's results support this view and indicate that successful discrimination of studied from unstudied definitions is not dependent on the hippocampus. This is consistent with her unimpaired memory on a wide range of item recognition tests for which, it could be plausibly argued, a memory decision could be successfully made on the basis of familiarity [29,43,45]. Relative sparing of forced-choice item recognition has also been reported following relatively selective hippocampal damage in other patients ([2,77], see also [60]) and in animals (for review see [1] and [84]).

The finding that YR's recognition of definitions was unimpaired even though she had considerable pathology to her hippocampus does not eliminate the possibility that this structure is able to support and is sometimes critical for recognition memory. One suggestion that this may be the case was the trend for YR's performance to worsen relative to the controls as the retention interval increased. This may suggest that although non-hippocampal regions may support item recognition well at short delays, long-term storage may benefit from hippocampal processing.

JL could discriminate studied from unstudied definitions at a normal level. This normal recognition memory may have been mediated by her intact hippocampus or, less likely, by her residual perirhinal cortex. However, long-term maintenance of this information in memory was impaired. JL's pattern of memory performance is consistent with the view that over a period of time storage of information is transferred from the MTL to the neocortex and suggests that, for JL, this transfer from temporary to long-term storage is not occurring successfully. JL's definition recognition is intact after delays of 20 s and 24 h but is severely impaired after 3 weeks. Other cases of long-term forgetting have been reported in the literature. Like JL, these patients have shown intact memory for a period of hours, but impaired memory after longer delays [3,14,32,34,35,38,40,57]. This deficit may result from damage to the neocortical storage sites and, as we have already noted, the main region which is damaged in JL is the anterolateral temporal cortex which has been linked to long-term storage by Kapur [32]. Evidence supporting this possibility is provided by a patient with semantic dementia and damage to the inferior temporal lobe, particularly in anterior regions [22]. Through daily practice he rapidly re-learnt vocabulary which had been familiar, but had been lost during the course of his dementia; however, when he stopped practicing he forgot this vocabulary over a period of weeks. An alternative explanation is that epileptic activity which is present in JL, and the majority of the other patients who have shown her pattern of abnormal long-term forgetting [3,32,34,35,38,40,57], may have disrupted the processes necessary for maintaining long-term storage. This disruption may be of the interaction between the MTL and the neocortex as well as of the processing occurring at the neocortical storage sites.

4. Experiment 3

4.1. Introduction

Experiments 1 and 2 investigated new learning of factual information following repeated presentation within one or two test sessions. Although YR's forced-choice recognition of definitions was unimpaired even after relatively limited exposure, her recall of the definitions and recognition of the pairings of words and their definitions was impaired even after 10 repetitions of the stimulus material. However, further repetition and greater spacing between repetitions may have been required for successful slow neocortical learning of this associative information without a normally functioning hippocampus. Public information provides one means of addressing this issue as examples can be selected to which there would have been extensive, repetitive, exposure.

Section 4 assessed YR's knowledge of three types of public information from the postmorbid period. These were knowledge about people who had become famous, knowledge about famous events, and knowledge of terms which were new to the English language. YR would have been exposed to this information repeatedly over a number of years. Thus, this enabled us to test whether repetition is sufficient to support normal slow learning in the neocortex or whether hippocampal-dependent processes, which probably mainly take the form of recall-dependent rehearsal, are also critical for slow learning.

We also tested JL's knowledge on a subset of the public information tests. If JL's impairment in the long-term retention of information is due to disruption (either as a result of damage or epilepsy) at the neocortical storage sites, this

would be expected to reduce the effectiveness of both repeated stimulus exposure and rehearsal in producing slow learning. As a result, JL's knowledge of public information would be expected to be more severely impaired than YR's.

4.2. Method

4.2.1. Subjects

YR and JL's performance was compared with matched control subjects. The control group varied slightly for each task as some subjects were not available for all test sessions. Details of each control group will be provided in the results section for that task.

From our long experience with the two patients we would judge that they both have average levels of interest in current public affairs. They watch television news broadcasts and read newspapers, and are therefore likely to have had a comparable amount of exposure to news media to their respective control groups.

4.2.2. Procedure

YR was tested on updated versions of the famous names and famous events questionnaires developed by Mayes et al. [42] and on three new tests. These new tests required subjects to provide detailed information about people who had become famous, famous events, and terms which have entered the English vocabulary since 1986 (the year in which YR's memory disorder began). JL was also tested on the three latter tests as these were considered to be the most sensitive in revealing a deficit if present.

4.2.3. Famous names questionnaire

This tested subjects' memory for people who had come to fame for a limited period between 1950 and 1995. For each famous person there were three questions. Subjects were first required to select the famous name from among three similar foil names which had been constructed by the experimenter. The subjects then provided enough information about the famous person in order to categorize them as: (1) a leader; (2) a criminal, spy or terrorist; (3) involved in entertainment; (4) a victim; (5) an explorer; (6) a sports personality. These categories were visible to subjects while they were providing this information. Finally subjects were asked to select a year between 1950 and 1995 when that person was at the peak of their fame. Category assignment and dating were only scored for those names which were correctly recognized.

For YR and her controls questionnaire items were grouped into three blocks and separate scores obtained for each block. These were: postmorbid period (1986 onward), recent premorbid (1976–1985), and remote premorbid (1950–1975). There were 14 items in the postmorbid block, nine items in the recent premorbid block and 16 items in the remote premorbid block.

4.2.4. Famous events questionnaire

This took the same format as the famous names questionnaire. A verbal label denoting a famous event (usually a place name) had to be selected from among three foils. Information was provided about the event by the subject in order to categorize it as: (1) an act of terrorism; (2) associated with war; (3) a natural disaster; (4) an accident; (5) an achievement; (6) a criminal act other than terrorism; (7) a scandal. The year in which the event occurred had to be selected from the period 1950–1995.

Questionnaire items were assigned to blocks in the same way as the famous names questionnaire. There were 18 items in the postmorbid block, nine items in the recent premorbid block and 13 items in the remote premorbid block.

4.2.5. Post-1986 personalities, events and terms

Three questionnaires were constructed. One consisted of the names of people who had come to public attention since 1986. These personalities were drawn from politics, sport and entertainment (film and television). The second questionnaire consisted of the names of places at which a major event had occurred since 1986. Finally, the third questionnaire comprised terms which had come into use in the English language since the middle of the 1980s.

For each questionnaire item subjects were asked to provide as much information and detail about that person, event or the meaning of that term as possible.

The questionnaires were administered to the control subjects before being given to YR and JL. All of JL's controls could provide at least one piece of information about all of the test items on the person and event questionnaires, so the complete questionnaires were administered to JL. However, for some of the questionnaire items no information could be provided by a number of YR's control group. As the aim of these questionnaires was to provide a sensitive measure of semantic memories acquired in the postmorbid period we selected just those personalities and events for which all 10 control subjects could provide at least one piece of information. This resulted in 13 out of 20 original personality items and four out of seven original events items being used for YR.

Subjects' responses to each item were scored by an individual who did not know the identity of the subjects. For each item two marks were awarded for each correctly recalled piece of information. For example, two marks would be awarded for each of the following pieces of information about John Major "ex prime-minister", "Conservative" and "prime-minister after Thatcher". One mark was awarded for a piece of information that was correct but incomplete or imprecise. For example, one mark would be awarded for each of the following pieces of information about John McCarthy "something to do with the Middle East" and "had a girlfriend—Gill somebody". Although we only included items in the test for which all control subjects could provide at least one piece of information, this did not result in a ceiling effect. The test required subjects to provide as much information as possible for each item and yielded a score commensurate with the amount of information they could provide.

There is less potential information which subjects may provide about new terms and words than events and personalities. So a sensitive measure of YR's learning of new terms was gained by using a larger set of items. A larger number of control subjects were also tested. YR's knowledge of new terms was tested if at least 75% of the control subjects could provide a correct definition of that item. This resulted in 17 of the original 21 items being used. The same criterion was used for the inclusion of terms in the questionnaire completed by JL. This resulted in 18 of the original 21 items being used. Responses to this questionnaire were also scored by a marker who did not know the identity of the subjects.

4.3. Results

4.3.1. Famous names and famous events questionnaires

The results for YR and her control subjects are shown in Table 5. Thirteen matched controls were tested on the famous events questionnaire (mean age: 58.5 (S.D. = 4.0), mean NART-R IQ: 107.2 (S.D. = 9.1)). Twelve matched controls (mean age: 58.6 (S.D. = 4.2), mean NART-R IQ: 107.8 (S.D. = 9.5)) completed the famous names questionnaire because one of the subjects was unable to attend that session.

YR's memory for famous events and people from the premorbid period was not significantly impaired. Recognition of the famous event or person, categorization of the event or person according to the nature of their fame, and recall of the year in which the event occurred or the personality was at the peak of their fame were all spared.

For the postmorbid period, YR could also correctly select famous names and famous events from among non-famous names and events as shown by her normal recognition scores. YR could also categorize famous people according to the reason for their fame, e.g. politician, sport, entertainment as well as her controls. However, her categorization of events was significantly impaired (4.7 S.D.s below the control mean). Her dating of events and names from the postmorbid period was also impaired: 4.02 S.D.s below the control mean for names and 2.07 S.D.s below the control mean for events.

Table 5
YR's scores and the mean scores of her matched control group for the recognition, categorization and dating question for each of the famous names and famous events questionnaires[a]

Test	YR controls	YR	S.D. from control mean
Names recognition			
Postmorbid	0.86 (0.14)	1	(+1.00)
Recent premorbid	0.88 (0.13)	0.89	(+0.08)
Remote premorbid	0.82 (0.14)	0.94	(+0.86)
Names categorization			
Postmorbid	0.87 (0.14)	0.86	(−0.07)
Recent premorbid	0.58 (0.15)	0.75	(+1.13)
Remote premorbid	0.73 (0.13)	0.8	(+0.54)
Names dating			
Postmorbid	3.21 (1.21)	8.08	(−4.02)*
Recent premorbid	12.78 (6.76)	9.75	(−0.45)
Remote premorbid	8.12 (3.5)	5.4	(−0.78)
Events recognition			
Postmorbid	0.85 (0.16)	1	(+0.94)
Recent premorbid	0.75 (0.19)	1	(+1.32)
Remote premorbid	0.83 (0.14)	0.85	(+0.14)
Events categorization			
Postmorbid	0.84 (0.09)	0.4	(−4.89)*
Recent premorbid	0.69 (0.17)	0.78	(+0.53)
Remote premorbid	0.77 (0.17)	0.73	(−0.24)
Events dating			
Postmorbid	4.14 (2.0)	8.28	(−2.07)*
Recent premorbid	10.22 (6.37)	5.5	(−0.74)
Remote premorbid	8.21 (4.28)	11.6	(+0.79)

[a] For the recognition and categorization questions scores are shown as proportion correct. For the dating question a difference score was calculated which was the difference between the year provided by the subject and the actual year in which that person was at peak fame or that event occurred. The number of standard deviations that YR's performance is above (+) or below (−) the control mean is also given. Impaired performance (greater than 1.96 S.D. below the control mean) is indicated by an asterisk.

4.3.2. Post-1986 personalities, events and terms

For the post-1986 personalities and events test YR's performance was compared with that of a group of 10 female control subjects matched for age and IQ (mean age = 58 S.D. = 3.68 compared with YR's age of 60 years; mean NART-R IQ = 102.8, S.D. = 6.3). Her performance on the post-1986 terms test was compared with a group of 16 matched female controls (mean age = 59.9, S.D. = 4.02; mean NART-R IQ = 104.1, S.D. = 7). The results are provided in Table 6. YR was significantly impaired at recalling the meanings of new terms (2.02 S.D.s below the control mean) and at recalling events cued by the name of the place

Table 6
Scores for YR and JL and mean scores of their respective control groups (S.D. in parentheses) for each of the post-1986 personalities, events and terms questionnaires. The number of standard deviations that YR and JL performance was above (+) or below (−) the control mean is also given for each questionnaire[a]

Test	YR	YR controls	S.D. from control mean	JL controls	JL	S.D. from control mean
Personalities	86.9 (11.66)	65	(−1.87)	137.7 (19.98)	34	(−5.19)[b]
Events	26.75 (7.10)	10.5	(−2.29)[b]	46.6 (9.5)	11	(−3.75)[b]
Terms	31.53 (5.46)	20.5	(−2.02)[b]	55.5 (7.37)	23	(−4.41)[b]

[a] JL and her controls completed a larger number of items in the three questionnaires than YR and her controls (see text for detail).
[b] Indicates performance which was more than 1.96 S.D. below the control mean.

where they occurred (2.29 S.D.s below the control mean). There was also a strong trend for an impairment at recalling information about personalities who had come to public attention since 1986 (1.86 S.D.s below the control mean which was just below our cut-off for impairment of 1.96 S.D.s below the control mean).

JL's scores were compared with a group of 10 female controls matched for age and full-scale IQ (mean age = 40.5, S.D. = 3.1; mean FSIQ = 113, S.D. = 8.3). JL's performance ranged between 3.75 and 5.2 S.D.s below the control mean on these questionnaires and so was clearly impaired for all three types of semantic information.

4.4. Discussion

YR can discriminate famous events and names from non-famous events and names as well as controls for both the post and premorbid period. This is consistent with her preserved forced-choice item recognition which was reported in Section 3 for definitions and has been reported elsewhere for other information [29,43]. Considering the postmorbid period further, she also had some knowledge about the famous people whose names she recognized as she could correctly categorize them according to the nature of their fame. However, her categorization of events was impaired. When more detailed information had to be provided, e.g. dating an event or the year of peak fame of a famous person or providing as much information as possible about a particular event, person or term, she was impaired.

JL's performance on the post-1986 personalities, events and terms questionnaires was also impaired and this deficit was greater than that shown by YR. This contrasts with the pattern of JL and YR's recall of new factual information after limited exposure and short delays. This is well illustrated by their recall of the short stories which comprise the logical memory subtests of the WMS-R and require recall of very similar factual information to that retrieved in the post-1986 events questionnaire. These stories consist of non-personal factual information and are very much like the descriptions of real events heard in news broadcasts on the radio and television. The short stories, therefore, require subjects to recall the same kind of information as that which comprises recent historical events which form part of our general knowledge and was tested by the post-1986 events questionnaire. On the logical memory subtests of the WMS-R YR's story recall was severely impaired at both immediate (4.7 S.D.s below the control mean) and 30 min delayed (4.9 S.D.s below the control mean) tests (control group: mean age 61 (S.D. = 5.3); mean NART-R 106 (S.D. = 5.9)), whereas, JL's story recall was unimpaired relative to matched controls (0.19 and 0.35 S.D.s below control mean at 0 and 30 min delays, respectively; control group mean age 41.9 (S.D. = 5.4), mean WAIS-R IQ 114.9 (S.D. = 8.1)). This partial double dissociation between JL and YR's short-term recall of material to which there had been a single exposure (logical memory test stories) and long-term recall of repeatedly exposed information (post-1986 public information questionnaires) is shown in Fig. 2. It suggests that the brain dysfunction suffered by these two patients has qualitatively different effects on memory.

This finding is consistent with the double dissociation reported by Kapur [32] between the effect of mammillary body damage and non-MTL damage on the rapid acquisition of name-occupation paired associates and the potentially slow acquisition of new public information through repeated exposure. Unlike Kapur et al. we found a partial rather than a full double dissociation. There are two possible explanations for this. One is that there is a difference in the importance of the normal contributions of the hippocampus and the mammillary bodies to slow learning. The other is that the deficit in the slow acquisition of new public information following damage to structures in Papez circuit is small and may be missed unless measures are very sensitive. In order to produce tests that are maximally sensitive, floor and ceiling effects need to be avoided for individual items and we ensured that this was the case for the tests used in our study.

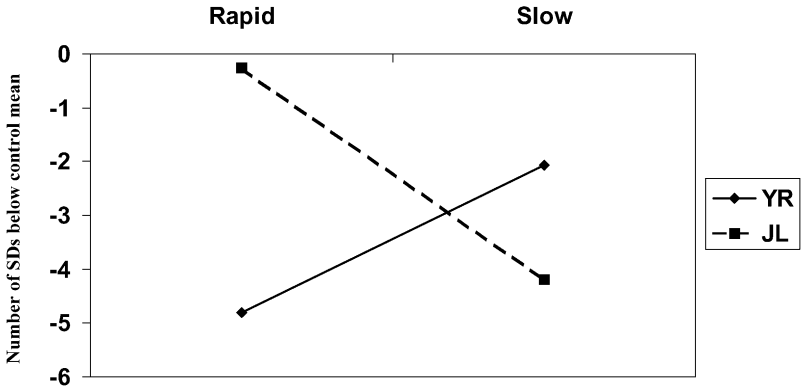

Fig. 2. The mean number of standard deviations that YR and JL performance fell above (+) or below (−) the control mean for two tests of rapid learning (immediate and delayed story recall) and three tests of slow learning (knowledge of famous events, personalities and English terms from the postmorbid period).

Our findings indicate that, although YR's hippocampal damage clearly impaired both the rapid acquisition and slow acquisition of new semantic information, it did not prevent her acquiring some new semantic information as a result of repeated exposure. These results suggest that the gradual neocortical changes proposed to underlie slow learning can occur in the presence of considerable hippocampal damage (around 50% volume loss in YR's case). However, YR's learning of new semantic information following repeated exposure was not normal. One possible explanation for this is that hippocampal damage reduces the learning opportunities of the neocortex. As we discussed earlier, slow learning probably depends on rehearsal as well as repeated learning trials, and rehearsal, but not necessarily the effect of repeated learning trials, is likely to be mediated by the hippocampus. If this is the case, YR's hippocampal damage may have reduced the opportunity of her neocortex to learn through rehearsal making slow learning reliant to a much greater extent, than in healthy subjects, on repeated learning trials.

The fact that JL shows a greater deficit than YR on the tests of memory for public information supports the conclusions which were drawn from JL's results in Section 3 and indicates that the integrity of neocortical processing may be more critical than hippocampal processing for the slow learning processes which result in very long-term retention of information.

5. General discussion

Previous testing [28–30,43,45,46] has shown that YR's general pattern of anterograde amnesia is very similar to that of the three young patients reported by Vargha-Khadem et al. [77]. All four patients showed impaired recall and impaired recognition of associations between information of different types, e.g. object–location associations, whereas, item recognition and recognition of associations between items of the same type, e.g. word–word associations, were spared. However, the experiments reported here have shown that, unlike Vargha-Khadem et al.'s patients, YR is impaired, not only at rapidly acquiring new factual memories, but also at acquiring such memories when slow, repetitive, learning processes could have been used. YR's impairment in the rapid learning of factual information was revealed by deficits on both recall and associative recognition tests (the latter using recombination foils). YR's slow learning impairment was indicated by her impaired free recall of factual information to which she had been repeatedly exposed either within the limited time period of the test sessions or within the longer time period provided by daily life. YR's associative recognition of factual information which could have been learnt, slowly, through repeated exposure remains to be tested but we predict that this should also be impaired.

The major exception to this semantic learning deficit was YR's preserved ability to discriminate, in forced-choice recognition tests, between briefly encountered definitions, repeatedly encountered events and people, and novel definitions, events and people. The sparing of this kind of recognition of factual items in YR is consistent with her intact performance on a wide range of other item recognition tests which have required studied and unstudied items to be discriminated [29,43,45]. Included amongst these were tests of face recognition (see RMT performance, Table 1) and scene recognition (Isaac and Mayes, unpublished data). As experienced episodes are often composed of people (who are mainly identified through their faces) acting within scenes, such information would be an important component of episodic as well as factual memories. Our results suggest that this kind of item recognition has been relatively spared by YR's hippocampal damage and that this sparing occurs both when the item forms part or all of a fact and when it forms part of an experienced episode. This ability to discriminate studied from unstudied items may be mediated by a circuit involving the perirhinal cortex, dorsomedial nucleus of the thalamus and frontal regions. This circuit has been proposed to support recognition memory when this can be based on the familiarity of an item [1].

Our findings show that YR's memory for newly encountered factual information paralleled her pattern of spared and impaired memory on other anterograde memory tests even when this semantic knowledge could have been acquired slowly through repeated exposure. YR's pattern of performance therefore contrasts with that of Vargha-Khadem et al.'s patients who showed relatively preserved recall of factual information to which there would have been repeated exposure, and therefore opportunity for slow learning, over a number of years. This preservation of slow learning in Vargha-Khadem et al.'s patients dissociated from their impaired recall of briefly encountered facts and experienced episodes, memory for which would have depended on a rapid acquisition process.

One possible reason for this discrepancy is that our tests may have been more sensitive at revealing deficits in semantic memory than those used by Vargha-Khadem et al. since they eliminated items for which healthy subjects performed near ceiling and floor levels. Alternatively, the discrepancy may be explained by the difference in the age of onset of hippocampal damage in YR and Vargha-Khadem et al.'s patients. As discussed in the Section 1, early age of onset, such as that suffered by Vargha-Khadem et al.'s patients makes it possible that some form of re-organization of function may have occurred [39].

Another study which appears to support the latter interpretation [78] found generally impaired slow learning of semantic information in a patient (PS) who had apparently selective hippocampal damage of adult onset. This was revealed by impairments on three of four tests of postmorbid public information (two recall tests and one recognition test) and a trend for an impairment on the fourth test (recognition).

In a similar way to our comparison between YR and JL, patient PS's performance was also compared with that of

another patient (SS) who had more extensive MTL damage. PS's deficit on the semantic learning tests was reported to be less severe than the deficit shown by SS. However, this dissociation is difficult to interpret because PS was also less severely impaired at rapidly acquiring new information (as indicated by a smaller discrepancy between WAIS-R full-scale IQ and WMS-R general memory index than SS). In contrast, our study has revealed a partial double dissociation between the rapid and slow learning achieved by JL and YR which strongly suggests that separable mechanisms contribute to each type of learning. Rapid acquisition of new semantic information was impaired in YR but normal in JL, who also retained this information normally for up to 24 h. In contrast, knowledge of information which could have been slowly learned through repeated exposure was more severely impaired in JL than YR. This severe impairment in JL was most likely due to either the disruptive effect of seizure activity on interacting neocortical and MTL processing, damage to the anterolateral temporal lobe long-term storage sites, or both.

A study, reported by O'Connor et al. [57], provides support for the first possible explanation of JL's long-term memory impairment. O'Connor et al. described a case of a patient with temporal lobe epilepsy, who, like JL, could retain information in memory for a few hours or days but then rapidly lost this information over a period of weeks. Interestingly, these authors reported that less information was retained when more seizures were experienced during the retention interval. This was particularly evident when the patient's medication was changed, which reduced seizure frequency, and this was accompanied by slower forgetting over a 7-day period. Similarly, in a study of remote memories, Bergin et al. [8] found a correlation between the number of seizures that patients with complex partial seizures had experienced since 1980 and how much they remembered about public events that occurred between 1980 and 1991, such that worse memory was associated with more seizures. It should be noted however, that this correlation was not found when only patients with temporal lobe epilepsy were considered. The findings of these studies clearly indicate that seizures can have a disruptive effect on memory. However, they leave open whether seizures disrupt memory when they occur shortly after first exposure (initial consolidation disruption), when they occur over an extended time period that begins hours or days after first exposure (slow consolidation disruption), or both.

The animal literature provides preliminary evidence that seizures disrupt both initial and slow consolidation. Knowlton et al. [37] showed that memory was disrupted by seizures which occurred immediately after learning. They stimulated the hippocampus in rats immediately after the study phase on a radial arm maze task until a seizure occurred. These rats showed impaired memory for the arms they had entered prior to the seizures; however, they showed normal retention of arms entered following the seizures and thus unimpaired new learning. However, a study by Cook and Persinger [13] suggested that even subclinical seizures, caused by lithium and pilocarpine injections, may disrupt slow consolidation. They showed that injection of lithium and pilocarpine caused a subtle disruption of the long-term maintenance of memories that were acquired during the training phase, 2 weeks earlier.

A potential mechanism which could explain how seizure activity may affect the maintenance of memory over relatively long time periods has been suggested by a recent study by Riedel et al. [61]. These researchers produced temporary disruption of hippocampal function in rats by blocking fast glutamatergic synaptic transmission using an AMPA/kinate receptor antagonist for a 7-day period. They found that this disruption impaired long-term memory for spatial information that had been normally encoded 1 or 5 days before the intervention [61]. It is plausible that hippocampal seizures would have a similar effect. This study suggests that normal hippocampal activity is necessary either for the temporary or permanent maintenance of a hippocampal memory or for the creation and possibly the maintenance of a slowly developing neocortical memory that depends on regular hippocampal–neocortical interactions. A study by Frankland et al. [15], which showed that mice with a selective neocortical consolidation impairment failed to create slowly developing stable long-term memories, supports the view that hippocampal–neocortical interactions may be critical for the development of stable memories. Frankland et al. found that mice which were heterozygous for a null mutation of α-calcium-calmodulin kinase II (α-CaMKII+) showed impaired cortical, but unimpaired hippocampal, long-term potentiation. These animals showed normal acquisition and retention for between 1 and 3 days for two tasks sensitive to hippocampal damage, but showed severely impaired retention for these tasks after delays of between 10 and 50 days. Taken together, the findings of Riedel et al. and Frankland et al. suggest that the establishment of stable long-term memories depends on normal hippocampal–neocortical interaction for some time following encoding and normal consolidation processes in the neocortex.

In the experiments reported in the present paper we cannot look for a correlation between number of seizures and memory test performance in JL. As we are studying a single patient, whose seizure activity has remained stable since onset, we cannot examine whether there is a relationship between seizure activity and knowledge of public information. Furthermore, JL only completed one experiment in which the times of initial exposure to the information and test were known (Section 3). Although JL will have experienced more seizures between study and the 3 weeks test than the 24 h test, number of seizures is confounded by length of delay and either factor could have explained her drop in memory performance. To examine whether there was a relationship between the number of seizures she experienced and the amount of information she retained in memory, we would have had to have performed multiple tests at comparable delays.

Other studies, however, have failed to find a correlation between seizure activity and memory [9,10,38]. Furthermore, the patient reported by De Renzi and Lucchelli [14] showed a similar pattern of accelerated forgetting to that observed in the temporal lobe epilepsy patients but did not have seizures. A similar memory pattern has also been found in a patient we have studied who does not suffer from epilepsy (Downes, personal communication).

The alternative explanation of JL's long-term memory deficit is that her drop in performance over a period of weeks may be due to damage to anterolateral temporal regions involved in long-term storage of information. Evidence supporting this explanation is provided by the study of Graham et al. [22] which was described briefly in the discussion of Section 3. The patient (DM), described by Graham et al. had semantic dementia and atrophy of the left temporal lobe which affected the temporal pole and, to a lesser extent, extended into the posterior inferior temporal region. Through daily practice, DM rapidly relearned vocabulary which had previously been familiar, but which had been lost during the course of his dementia. However, when he stopped practicing he forgot this vocabulary over a period of weeks. Like DM, JL has damage which includes the inferior temporal lobe and, also like DM, she rapidly acquires new information but rapidly forgets this over a period of weeks when it is not rehearsed.

DM's vocabulary knowledge was assessed using a category fluency test in which he was asked to produce as many exemplars as possible for each of a number of studied semantic categories. We have not tested JL on a comparable test but would predict that she would rapidly acquire new vocabulary and would lose this once daily practice was prevented. In contrast to JL and DM, we would predict that, due to her hippocampal damage, YR should be impaired at rapidly learning new associations between semantic categories and exemplars, and so should be impaired on this task. However, some evidence of new vocabulary learning may be apparent following extensive practice if this were sufficient to enable slow cortical changes to occur.

Interestingly, Graham et al. noted that DM appeared to have used a rote learning strategy to acquire the new vocabulary because, at test, he produced the exemplars in the order in which they had been studied. This use of a rote learning strategy is likely to be due to two things. First, the destruction of the cortical representing (and storage) sites makes it difficult to encode and store new semantic information even when the hippocampal system is functioning normally. Second, the disruption to pre-established semantic memories makes it difficult to encode any newly encountered information in a rich meaningful fashion.

Unlike DM, there is no indication that JL has disruption of previously established semantic memories. For example, she shows no word finding or picture naming difficulties and does not show the reversed gradient of retrograde amnesia, which is usually reported for patients with semantic dementia. She also performs normally on the Pyramids and Palm Trees Test. This is surprising given the similarity in the cortical regions damaged in JL and in patients with semantic dementia. However, although patients with semantic dementia have major atrophy to the anterolateral temporal neocortex, it is possible that there are also more subtle atrophic changes in other neocortical regions. If so, this could cause more widespread disruption to the distributed system representing and storing semantic information long-term than damage restricted to anterolateral temporal neocortex. Given that JL's well-established semantic memories are intact, we would expect that she would encode new vocabulary in a rich and meaningful way and would not rely on rote learning. As a result we would predict that JL's category fluency performance for newly encountered categories should be higher than DM's.

Radionecrosis resulting from radiation therapy for the treatment of nasopharyngeal carcinoma also often causes damage to the anterolateral temporal neocortex but can, in addition, cause damage to the MTL [11,33]. Damage to the MTL was probably present in many of the necrotic patients of Cheung et al. [11] as these patients showed the impaired learning and rapid forgetting of organic amnesia. However, the patient described by Kapur et al. [33] was shown to have damage that primarily affected the anterior temporal neocortex, but apparently left the hippocampus and MTL cortices largely intact. This patient showed a pattern of memory impairment which was similar to that shown by JL. His performance on anterograde memory tests was relatively normal, but patchy, with performance in the normal range for some tests but mild to moderate impairments on paired associate learning and a severe impairment in face recognition. Notably, he also showed loss of memory for factual information acquired both before and after his illness. This pattern of performance is similar to that of JL, who also showed a retrograde amnesia (Mayes et al., submitted for publication), and is consistent with disruption to the cortical storage sites for long-term memories. As already indicated, this patient resembled JL in a specific respect. Both patients showed preserved rapid acquisition of new information, but impaired slow acquisition of new information through multiple repetitions relative to a matched patient who had selective damage to a Papez circuit structure [32]. Unfortunately, unlike JL, the patient described by Kapur et al. was not formally tested to determine whether he showed initially normal memory for new factual information and then forgot it abnormally fast over a period of weeks.

The comparison of YR and JL performance draws attention to the fact that YR had acquired some knowledge of public information to which she would have had repeated exposure over a number of years even though this was significantly below normal levels. This new learning is unlikely to be an artifact of our methodology and tests. The conditions for new semantic learning were not more favorable for this patient than for JL or for the control subjects. All participants in the study had exposure to various news media but as far as we could determine this exposure was not greater

for YR than for the other participants. Similarly, she did not report excessively rehearsing or repeatedly exposing herself to this information. The other explanation we can rule out is that the tests were not sensitive enough to detect a deficit if present. As discussed in Section 4.2, great care was taken to ensure that floor and ceiling effects were avoided on an item by item basis in the tests of slow learning (public information), thus producing sensitive measures of this aspect of memory. YR's and JL's performance on these tests confirmed this sensitivity; both were impaired and a greater impairment was revealed for JL than YR. However, favorable learning conditions and poor test sensitivity may explain the reported sparing of new semantic learning in other patients such as the young patients described by Vargha-Khadem et al. [77].

As discussed earlier in the paper, the spared learning shown by the young patients reported by Vargha-Khadem et al. has been attributed by others to re-organization of function due to the early age of their pathology [39]. YR's data suggest that, even when hippocampal pathology occurs in adulthood, acquisition of some new information to which there has been repeated exposure may be possible. This new semantic learning could have been mediated by residual hippocampal processing because hippocampal destruction was incomplete in both YR and the young patients reported by Vargha-Khadem et al. [77]. Total destruction of the hippocampus may impair rapid and slow learning of new factual information more severely than the partial damage suffered by YR and the patients reported by Vargha-Khadem et al. The nature of the relationship between level of memory impairment and extent of hippocampal damage is controversial. It still needs to be determined whether there is a negative relationship [6], a positive relationship [50,51], or whether the relationship varies depending on factors such as the kind of memory and the range of volume reductions considered. For example, it has even been speculated that 20% destruction of the hippocampus may be sufficient to completely prevent it from working, so further damage to it should have no greater disruptive effect [83].

Alternatively, and consistent with many computational models, the slow acquisition of new factual information may be mediated by slowly occurring changes in medial temporal cortex regions, such as the perirhinal, entorhinal and parahippocampal cortices, or in neocortical regions. However, it could also be argued that it is mediated by other parts of the limbic system which are not strongly connected to the hippocampus. Finally, it may be that changes in a number of these brain regions underlie new learning of semantic information following partial hippocampal damage. Whichever of these explanations is correct, it should be emphasized that YR's performance is impaired which indicates that hippocampal processing normally contributes to the acquisition of semantic information and that, following adult onset hippocampal pathology new semantic memories are not acquired normally, even through the slow learning process. This could be because the hippocampus is critical for recollection and thus rehearsal, a factor proposed to contribute to slow learning [4].

Our data indicate that, in addition to impairing the rapid acquisition of new episodic memories, hippocampal damage impairs the rapid formation of memory representations for semantic information. However, whether the deficit in rapidly learning new semantic information should be interpreted as an episodic memory deficit, because of its dependence on hippocampal damage, is debatable. According to the influential view expressed by Squire and Zola [69], the acquisition of factual memories (semantic memories) depends on the acquisition of the episodes of which they form part (episodic memory). Rapid acquisition of both of these types of information has been argued to depend on the MTL [4]. This view suggests that factual information is initially represented in memory as an integral part of the associated episodic memory and it implies that retrieval of the factual information is facilitated by retrieval of the associated episode.

An alternative view is that, although memory representations for semantic information will form part of the representations of the episodes in which they were encountered, the semantic and episodic components of the representations can be separately retrieved. So, retrieval of rapidly learned facts need not involve retrieval of the personal episode in which they were encountered. However, following limited exposure, retrieval of associated episodic information may accompany fact retrieval. If so, this may help fact retrieval by providing additional retrieval cues as suggested by context-dependent forgetting effects [19]. The extent to which such episodic retrieval boosts semantic memory and the frequency and variability with which such boosting occurs is, however, unknown. For this reason it is equally unknown whether impairments in acquiring new factual memories reflect a pure fact memory deficit or result partly or solely from an episodic memory deficit.

How do our findings relate to the debate as to whether episodic and semantic memory can be dissociated? Taking the definition we use in Section 1, which distinguishes episodic and semantic memory in terms of the kind of information which has to be remembered, our findings do not suggest a dissociation between semantic and episodic memory. However, we have found two other dissociations. The first dissociation was found when considering memory for material to which there had been limited exposure. For both semantic and episodic information, YR's hippocampal damage impaired recall and recognition of associations between information of different kinds. In contrast, hippocampal damage did not impair recognition (old/new discrimination) of individual items. Such items could form part of either a semantic or an episodic memory. Hippocampal damage would, therefore, be expected to impair the encoding and/or storage in memory of associations between different kinds of information. Storage of such associations is not only critical for episodic memory (e.g. contextual associations), but also for semantic memory (e.g. orthographic-meaning

associations). In contrast, non-hippocampal regions would be expected to be sufficient to support recognition of the individual items, the storage of which is critical for episodic as well as semantic memory.

The second dissociation is between memory for information to which there has been limited exposure and memory for information to which there has been repeated exposure. The partial double dissociation between YR's and JL's pattern of memory deficits suggests that the hippocampus is critical for associative recognition and recall of information to which there has been limited exposure, whereas the neocortex may be able to mediate such memory for repeatedly presented material and may be more important than the hippocampus for the slower learning processes which result in long-term retention of information. However, the double dissociation is only partial, indicating that the hippocampus normally makes an important contribution to slow learning, probably via recollection-dependent rehearsal.

Our data suggest that the distinction between semantic and episodic memory that has been made on the basis of findings from studies of amnesia and cases of focal hippocampal damage may be unsupported. Rather, the findings may actually reflect a distinction between the neural mechanisms underlying the rapid acquisition of information to which there has been limited exposure and the slow acquisition of information to which there has been repeated exposure over a long period of time: semantic information is usually experienced many times whereas episodic information is usually experienced only once. Studies purporting to show a dissociation between semantic and episodic memory have confounded the episodic/semantic distinction with the amount of exposure. In the present series of experiments we kept the type of information for which memory was tested constant. All three studies required subjects to retrieve semantic information. However, we varied the amount of exposure subjects had had to the material before they were asked to remember it. Although we only tested the recall of factual (semantic) information to which individuals would have been repeatedly exposed, we predict that any repeatable information could be learnt slowly through repetition by the neocortex irrespective of its personal or non-personal nature. As a result, we predict that repeated exposure to a personally experienced episode would enable those aspects of that episode which are repeated to be learnt in the absence of a functioning hippocampus (although, as for factual information, performance would not be expected to reach normal levels). This could be tested by recording on video a staged incident which is witnessed by the patient and then replaying the video to the patient at regular spaced intervals over a period of months. We would predict that patients such as YR would show only a mild recall deficit for the material on video after such repetition. In contrast, Nadel and Moscovitch's view [54,55] would predict a large memory deficit for such repeated episodic information following hippocampal damage.

Some aspects of an episode are clearly not repeatable, such as temporal context including preceding and following incidents, and the internal state/thoughts of the participant. We predict that memories for such information would not be acquired by patients with hippocampal damage because this information is experienced on a single occasion and therefore its acquisition would depend on rapid hippocampal learning.

In summary we are proposing that it is the extent to which information is repeatedly experienced, rather than the kind of information, that may be the crucial determinant of the success of new learning following selective hippocampal damage.

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