Unilateral medial temporal lobe memory impairment: type deficit, function deficit, or both?

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Abstract—Previous research has characterized memory deficits resulting from unilateral hippocampal system damage as 'material specific', suggesting that left damage results in verbal memory impairment with preservation of visuospatial function and the converse with right damage. Implicit within this hypothesis are the assumptions that the systems are independent and memory is lateralized for each type of material. To test the verbal component of this hypothesis, unilateral hippocampal lesion and commissurotomy patients were compared with controls on a multiple-list free-recall task. The material specific hypothesis predicts severe impairment only with left lesions; right lesions and commissurotomy patients should be only minimally impaired. However, secondary memory was compromised at immediate recall for all patient groups, with both unilateral groups showing comparable and severe verbal episodic memory deficits. Final testing across all lists also revealed severe impairment in commissurotomy patients. Finding both unilateral groups to be similarly impaired for verbal material is taken as evidence against a material specific deficit during this verbal episodic memory task. Although previous data suggest that left patients are considerably more impaired during some verbal tasks, this may not be specific to the material, but rather the combination of material and task demands. Implications for the material specific hypothesis are discussed. © 1998 Elsevier Science Ltd. All rights reserved

Key Words: commissurotomy; episodic memory; medial temporal lobe; material specific; task demands; verbal recall.

Introduction

The severity of memory impairment following bilateral temporal lobe damage in humans has been heavily researched since Scoville and Milner [44] documented the profound impairment in patient HM resulting from bilateral resection of the hippocampus, uncus, and amygdala (with the associated cortical damage). In contrast to this marked deficit, Milner [28] reported that in cases of unilateral lobectomy “the anterior six cm. or so of one temporal lobe can be ablated, including not only the lateral neocortex, but also the underlying uncus, amygdala, hippocampus and hippocampal gyrus, without any more conspicuous neurological deficit resulting than a contralateral upper quadrant visual field defect. Careful testing does, however, reveal mild and highly specific [italics added] learning disabilities, which vary with the side of the lesion, but generalized memory disorders are rare, otherwise the operation would have been abandoned long ago.” (p.117). Furthermore, in two cases where unilateral lobectomy appeared to result in amnesic syndrome, Milner presented evidence suggesting that the syndrome was the result of previously undetected damage within the nonresected temporal lobe, effectively rendering the patient with bilateral damage. Thus, bilateral lesions were concluded to be necessary for amnesia to occur and persist.

This viewpoint is not without current proponents. For example, Warrington and Duchen [53] reported a reappraisal of a patient who seemingly became severely amnesic after a right temporal lobectomy for intractable epilepsy. This patient (NT) was initially reported by Dimsdale et al. [11] as evidence that unilateral lobectomy may in fact produce a severe and lasting amnesia. However, neuropathological postmortem analysis, conducted 25 years after the lobectomy, revealed sclerosis.
in the left, non-resected hippocampus. Warrington and Duchen suggested that the lesion predated NT’s lobectomy operation but was not identified at the time, and thus the removal of the epileptogenic tissue, in conjunction with the preexisting lesion was held responsible for the post-surgical development of severe amnesia. Consequently, Warrington and Duchen concluded that NT did not represent an exception to the bilateral ‘rule’, and, as yet, there was no evidence that the amnesic syndrome can result from a strictly unilateral lesion site. Similarly, Loring et al. [24] suggested that the development of severe amnesia in a right-language dominant patient (established via Wada testing) following right temporal lobectomy was the result pre-existing damage in the non-resected left lobe, discovered post-surgically using magnetic resonance imaging (MRI). Again, this result is consistent with the assertion that postoperative amnesia following unilateral lobectomy is the result of medial temporal lobe damage occurring in the non-operated lobe (e.g. [28, 36, 53]).

The model underlying the bilateral ‘rule’ has explicitly been referred to by Saykin et al. [43] as the material-specific, or ipsilateral deficit model. In short, the model asserts that memory function is lateralized with cerebral function. That is, the left hemisphere regulates verbal memory with the right regulating visuospatial memory (in left language dominant individuals). Consequently, severe amnesia does not typically follow unilateral resections because memory for the alternate material type is fully preserved in the remaining temporal lobe. In order to evaluate this model, Saykin et al. employed a large battery of visual and verbal memory tests administered pre and post surgically to unilateral lobectomy patients. When collapsed into two measures (verbal and visual memory change), a double dissociation was observed, with left lobectomy patients declining in verbal memory performance and improving on visual memory performance; the reverse pattern was observed for right lobectomy patients. These findings were held supportive of “the relative independence of changes in verbal and visual memory...with verbal memory lateralized to the left medial temporal region and visual memory to the homologous right MTL [medial temporal lobe] [29], and of the construct validity of material specific memory processes.” [43, p. 279].

Although the results seem supportive of the material specific model, they should be interpreted with caution. Clearly there is some risk involved in ascribing memory deficits to a postmortem lesion discovered 25 years after onset of amnesia [53], and in the assumption that a reduced hippocampal volume is the causal agent in the post surgical amnesia reported by Loring et al. [24]. Furthermore, while changes in memory performance were related to side of resection in Saykin et al. [43], both groups were significantly impaired on verbal and visual memory prior to surgery. Given that their epileptic activity was focal and lateralized (making them good candidates for the procedure), it is not clear why the left and right groups failed to differ on the pre-surgical evaluation. Additionally, the MANOVA procedure was performed on composite measures, collapsed across different testing paradigms (e.g. recall versus recognition tests)—possibly obscuring task specific effects (see below).

Perhaps equally important, there is an apparent lack of consensus as to the criteria for establishing the presence of amnesia following unilateral medial temporal lobe damage. Given this state of affairs, we propose at least four criteria by which a claim of amnesia following unilateral medial temporal lobe damage should be examined: (a) the material specificity of the deficit, (b) the magnitude of deficit, (c) the permanence of the deficit, and (d) the nature of the test(s) used to assess the deficit.

It is often the case that unilateral patients are deemed merely to have a mild and material specific memory deficit (e.g. [28]). This assumes an independence between the medial temporal lobe memory systems; each working largely independently of the other on a specific type of information. We refer to this assumption, inherent in the ipsilateral deficit model of Saykin et al. [43], as the Laterality/Independence (LI) assumption.

If memory function is lateralized and specific to a particular type of material, prevention of communication between the two hemispheres, via corpus callosum and/or hippocampal commissures, should not impair memory. However, several studies (e.g. [20, 37, 38, 57, 58]) have demonstrated that callosotomy does in fact result in a memory impairment that is most noticeable with recall tasks. This suggests that the absence of communication between the hemispheres disrupts memory function; although it cannot be definitively ruled out that impairments observed in callosotomy patients are not the result of undetected epileptogenic neuropathology, antiepileptics may alter the fornices (see Clark and Geffen [6]).

Knight [22] provided further neuropsychological evidence against the hypothesis of functionally isolated and independent medial temporal lobe systems with respect to novelty detection. Patients with unilateral medial temporal lobe lesions showed diminished autonomic and electroencephalographic responses to novel somatic and auditory stimuli, regardless of laterality of lesion site, indicating that attentional orienting in normal subjects appears to require the joint participation medial temporal lobe structures.

Thus, the results of commissurotomy and orienting research weigh against the notion of functional independence between medial temporal lobe memory systems. Consequently, material specific deficits for unilateral medial temporal lobe patients during demanding tasks would be unlikely. Furthermore, if both left and right medial temporal lobe patients are severely impaired on the same type of material, then characterizations of material specificity or mildness are clearly inaccurate.

With regard to the permanence of deficit, there are many contributing factors such as edema and diaschisis,
which may render performance immediately following vascular accident or surgical intervention worse than is to be expected after extensive recovery. However, if a sizable difference between patient and control performance is documented one or several more years after onset, this could reasonably be termed a permanent deficit.

Finally, the task demands of the test used to assess performance are critical and a current neuropsychological review by Aggleton and Shaw [2] underscores this point. Aggleton and Shaw collected data from 33 studies reporting the performance of amnesics on the Recognition Memory Test (RMT, [52]). Although many of the patient groups, such as Korsakoff's, were impaired compared with the norms of the test, groups with relatively site-specific lesions (hippocampal ischemia, fornix surgery, and diencephalic/mamillary bodies) failed to differ from normal subjects for the verbal and faces components of the test. However, these patients all had Wechsler Memory Scale—Revised (WMS-R) general memory and delayed recall scores showing marked deficits, comparable to the other amnesias included in the study. Clearly then, one would not want to conclude that these patients were not amnesic, or only mildly impaired, simply because the RMT failed to differentiate them from normals. Given that both the Wechsler and RMT employ verbal material, the restricted lesion group's superior performance appears to be the result of something more than the type of material employed, and critically depended on the nature of the assessment task.

In most circumstances, recognition memory is clearly superior to recall. In addition, signal detection theory predicts that two alternative forced choice (2AFC) recognition will be less difficult than that of yes/no procedures by a factor of square root of 2 [26], and even this may underestimate the relative ease of 2AFC discrimination (e.g. [19, 9]). Aggleton and Shaw [2] note that the 2AFC procedure closely resembles the delayed match to sample and delayed non-match to sample procedures employed in non-human primate research and cite several studies which suggest no impairment, or a relatively mild impairment on this task with hippocampal, or diencephalic lesion sites. As a whole then, it seems reasonable to postulate that 2AFC testing procedures may be insensitive to the episodic memory impairment resulting from relatively pure hippocampal or diencephalic damage. Along similar lines, Saing et al. [42] have suggested that the apparent laterality of verbal memory is conditional upon the task requirements and not solely a function of the material type. Although retrospective analysis of paired associate learning scores was associated with larger deficits for left than right hippocampal sclerosis, the same was not true of the logical memory subtest of the WMS-R, with both groups similarly impaired compared to controls. Thus the difficulty, or more accurately the specificity, of the test is crucial when determining the magnitude and laterality of presumed memory deficit.

If one were interested in the potential episodic or event memory deficit resulting from unilateral medial temporal lobe lesion, tests which place heavy demands on recall of event context would seem most appropriate. One such test, free recall of lists, has been studied extensively, and yields stereotypical response patterns for both immediate and delayed recall tasks (i.e. the serial position curve). While the strict two store account of the curve (e.g. [56]) has received criticism, Moscovitch [30] notes that a relaxed version relating primary memory (i.e. recency) to information that is currently conscious and secondary memory (i.e. primacy) to information which must be retrieved from a larger more permanent store is defensible. Accordingly, numerous researchers have reported that it is only secondary memory (SM) that is impaired in amnesia (e.g. [3, 5, 25, 51, 54]) and that primary memory (PM) is preserved. Moscovitch [30] found this same pattern in the serial position curves of unilateral left temporal lobectomy patients, with some evidence that these groups may also be impaired in primary memory, using the dichotomous scoring method of Tulving and Colotla [48].

The Tulving/Colotla scoring procedure uses the intertrial retention interval (ITRI), or the number of words between an item's occurrence in the study list and its report by the subject to determine its classification as PM or SM. For example, if a study list consisted of items W1, W2, W3, W4, W5, and W6, and the subject recalled W6, W5, W3, and W1, in that order, the ITRIs for these four items would be 0, 3, 6, and 8, respectively. Items with ITRIs of seven or less are categorized as PM, those with intervals of eight or greater, SM. Watkins [55] compared this procedure with three earlier procedures and found that it provided the most stable estimates of PM across various experimental conditions.

Moscovitch [30] demonstrated the anticipated reductions in secondary memory performance in unilateral amnesics compared with controls and that the degree of impairment was related to the caudal extent of medial temporal lobe damage. From this, Moscovitch concluded that, although primary memory may not be intact in amnesics, secondary memory deficits are the principle contributor to the syndrome (cf. [3, 51]). The apparent lack of normal primacy effects in the serial position curve of amnesics suggests that experimental or stimulus manipulations previously shown to improve secondary memory in normal subjects may be ineffective in amnesic populations (e.g. ‘deepening’ levels of processing [8]; slowing presentation rate [32]; and increasing item concreteness or meaningfulness [39]). Moscovitch [31] contends that a major function of the hippocampal dependent memory system is the process of cohesion, which involves the binding of event elements into a memory trace and specifically suggested that the primacy effect (i.e. secondary memory) is hippocampally mediated.

Given the uncertain nature of material specificity of memory impairment in unilateral medial temporal lobe damage, and the evidence for impairment following hemispheric disconnection, the goal of the current study was
to contrast three patient groups (unilateral left and right medial temporal lobe damage and commissurotomy) with controls on a verbal memory task sufficiently demanding to reveal any differences. If the material-specific hypothesis is correct, one should expect to find large impairment in only the left medial temporal lobe group. Since the right medial temporal lobe would not be required for the verbal task, neither lesion or disconnection should result in impairment. Furthermore, if the left medial temporal lobe mediates the task, then manipulations which improve secondary memory in normal controls, should also result in improvements in right medial temporal lesion and commissurotomy patient groups. In order to test this, we employed a variant of the multiple-list free-recall task [7, 48], manipulating both item concreteness and presentation rate while contrasting the groups on both primary and secondary memory. In addition, we added a final free recall at the end of the experimental session, testing the subject’s recall for all experimental items after a prolonged retention interval. It was hoped that the results would speak directly to the issues of material specificity and medial temporal lobe independence by contrasting any observed impairments following unilateral medial temporal lobe system damage and callosotomy.

Method

Subjects

Hippocampal patients. Four patients with lesions to their left hippocampal formation (LHC), and five with lesions to their right hippocampal formation (RHC), resulting from stroke, were tested. By the term ‘hippocampal formation’ we refer to the area designated by Eichenbaum et al. [12, pp. 450–451], which includes the hippocampus proper, the dentate gyrus, and subiculum. In addition, damage extended into surrounding cortical areas including parahippocampal and temporal–occipital areas.

All strokes were due to infarction of the posterior cerebral artery, including the artery of Uchimura which serves the posterior hippocampal region, from embolus or atherosclerotic occlusion except for one patient (DR) whose stroke was due to vasospasm after a subarachnoid hemorrhage. All patients suffered from variable degrees of anterograde amnesia. The LHC patients tended to show more severe anterograde amnesia symptoms than the RHC patients, both in terms of standardized tests, such as the WMS-R, and in terms of informal discussions of their recent past (see [23]). Aside from these memory problems, all patients were capable of understanding complicated instructions and of carrying on intelligent conversations with the examiner. However, the patients with the more severe symptoms are unlikely to remember these conversations a short time later. The effects of unilateral posterior cerebral infarction and the resulting anterograde amnesia have been reviewed elsewhere ([10, 34, 50]).

The infarct patients all had variable degrees of homonymous field defects due to calcareous damage. Two of the LHC patients also suffered some damage to their splenium resulting in some degree of alexia without agraphia. Patient (AL) could read only a few letters at a time and the other (EM) only a syllable at a time. Patients were asked to look at the screen while the words were read to them. Previous testing sessions had demonstrated that they were capable of reporting when the experimenter said a word different than the one shown on the screen.

Commissurotomy patients. Four callosotomy patients served in the experiment. Magnetic resonance (MR) brain scans of three of these subjects are presented elsewhere ([15, 38]).

Callosotomy patient histories

JW is a 42-year-old right-handed man who has had intractable epilepsy since the age of 19. Although there was no known family history of neurologic disorder and his developmental milestones were appropriately achieved, JW began experiencing brief absence spells at the age of 13, years after a concussive head injury. He graduated from high school at 18 years and experienced a major motor seizure one year later. After this seizure, a complete neuropsychologic evaluation revealed normal blood chemistries, brain scan, skull films, and lumbar puncture. However, EEG revealed irregular polyspike and high voltage repetitive 3 cps spike and wave bursts during sleep. JW was placed on antiepileptic medication. During the next 7 years, in spite of adequate serum levels, EEGs continued to reveal irregular polyspike activity. In 1979, JW underwent a two-stage microsurgical section of his corpus callosum. Eight months after his surgery, he appeared alert and able to converse easily about the past and present. Results from neurologic examination from that period appeared were normal. Although he appeared to have normal ‘everyday memory’ following his callosotomy, JW and his family members are quite aware of his memory problems. For example, when asked about specific events in the recent past, several retrieval cues are necessary before he describes the event. His mother describes this phenomenon by saying “he has a lazy memory”. JW has been studied extensively over the past 14 years on a variety of perceptual, cognitive, and attentional tests (e.g. [14]).

VP is a 44-year-old right-handed woman. Like JW she has no family history of neurologic disorder, and she reached developmental landmarks normally. At the age of 9 years she experienced seizures following febrile illness. Medication controlled the seizure activity and she was able to graduate from high school. By 1976, she was experiencing periods of blank staring lasting for seconds. EEG recordings from this period revealed bilateral 4 cps spike and slow-wave activity, and sharp activity with left temporal predominance. In 1979, while on medication, she experienced major motor, absence, and myoclonic seizures. She underwent partial anterior callosal section in early April 1979, and the resection was complete in a second operation 7 weeks later. Following the surgery, the neurologic exam revealed no focal findings. Her Wechsler IQ scores were in the normal range.

DR is a 52-year-old right-handed woman. Though there is no family history of neurologic disorder and her developmental milestones were appropriately achieved, she began experiencing brief episodes of altered consciousness which involved unpleasant olfactory hallucinations and motor automatisms. Abdomsant drugs were able to abolish these secondary effects; however, she continued to have several complex partial seizures per day. DR not only graduated from high school, but went on to get a Bachelor of Science in accounting. She was employed as an accountant until her mid-thirties when her seizures impaired her job performance. In 1983, she underwent a single stage callosotomy for these intractable primary complex partial seizures. Eleven years since callosotomy, she continues to experience complex partial seizures though no generalized convulsions have occurred.

VJ is a 42-year-old left-handed female who was the product of a normal pregnancy. Her mother, her only sister, and her only daughter are all left-handed. She had no history of learning disorders or any neuropsychological dysfunction. There is no
family history of seizures or learning disability. Her first seizure occurred at the age of 17. Her seizures have remained intractable despite multiple trials of different epileptic medications. She elected to undergo callosal section after a drop-attack caused her to fall onto the open door of a hot oven, resulting in second degree burns over her arm and hand. The pre-operative neuropsychological examination was done while her dominant hand was still bandaged. She had a complete two-stage callosotomy. The anterior callosum was cut initially, followed by a complete cut of the splenium after a delay of 8 months.

Subject characteristics

In order to provide some indication of the severity of their anterograde amnesia, Table 1 presents the available standardized scores for the patients on the WMS-R and Wechsler Adult Intelligence Scales—Revised. Table 1 also gives the sex and age compositions of the normal groups. Computerized reconstructions of computed tomography (CT) or magnetic resonance (MR) brain scans of the hippocampal patients are presented in Fig. 1.

Healthy control subjects. Two groups of healthy controls were tested. One was a group of 18 older adults who lived in Davis, California and who were contacted via a newspaper advertisement. These subjects, like the patients, were paid $10/hour for their participation. The other controls consisted of 24 students from introductory psychology courses at the University of California, Davis. These subjects received minor course credit for their participation.

Design and procedure

Twenty lists of 16 items each were constructed using concreteness ratings provided in Paivio, Yuille, and Madigan [35]. Of these, ten lists were constructed using concrete items with ratings greater than 6.2, the remaining ten consisted of abstract items with ratings below 3.0 (for rating methods see [35]). Furthermore, half of each list type were presented at a fast rate (1.5s) and half were presented slowly (3.0s). This resulted in four concreteness by presentation rate conditions: 1, concrete/fast; 2, concrete/slow; 3, abstract/fast; 4, abstract/slow. The order of list types was held constant for patient groups and age-matched controls. For these subjects the order was [4,1,2,3,4,2,1,4,3,1,2,4,2,1,4,3,1,2,3] for the 20 lists. Student controls received a randomized order of experimental conditions. Additionally, all subject responses were categorized as coming from either primary (PM) or secondary (SM) memory following Tulving and Colotla [48] (see our introduction for description). When considering each subject group separately, this resulted in a $2 \times 2 \times 2$ within-subjects design with independent variables of concreteness (concrete/abstract), presentation rate (fast/slow), and memory component (primary/secondary).

Stimuli were presented via computer with students reading the words to themselves, but patient groups and age-matched controls were instructed to watch the stimuli while the experimenter read them aloud. Immediately following the presentation of each list, subjects were asked to recall all of the members of the preceding list, giving the most recent items read/heard first (immediate recall). Student controls typed their responses on the computer keyboard; the patient groups and age-matched controls gave them verbally and the experimenter recorded them via keyboard. Subjects were given 30 s to recall as many items as possible from each list, after which there was a 30 s delay prior to beginning the next study list. This pattern was repeated for each of the 20 lists. Following immediate recall of the final list, subjects were again given a 30 s break and then asked to report any of the items they could recall from the entire experiment (final delayed recall).

Table 1. Standardized test scores and patient demographics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Test</th>
<th>Age at</th>
<th>WMS-R Verbal</th>
<th>WMS-R Delayed</th>
<th>WAIS-R Verbal</th>
<th>WAIS-R Perf.</th>
<th>WAIS-R Full</th>
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</thead>
<tbody>
<tr>
<td>AL</td>
<td>m</td>
<td>62</td>
<td>58</td>
<td>73</td>
<td>69</td>
<td>96</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>WM</td>
<td>m</td>
<td>71</td>
<td>56</td>
<td>71</td>
<td>63</td>
<td>118</td>
<td>112</td>
<td>117</td>
</tr>
<tr>
<td>JS</td>
<td>m</td>
<td>72</td>
<td>55</td>
<td>81</td>
<td>82</td>
<td>103</td>
<td>103</td>
<td>103</td>
</tr>
<tr>
<td>EM</td>
<td>m</td>
<td>78</td>
<td>76</td>
<td>82</td>
<td>69</td>
<td>113</td>
<td>109</td>
<td>112</td>
</tr>
<tr>
<td>JC</td>
<td>f</td>
<td>55</td>
<td>perinatal</td>
<td>100</td>
<td>96</td>
<td>89</td>
<td>81</td>
<td>85</td>
</tr>
<tr>
<td>FN</td>
<td>m</td>
<td>56</td>
<td>50</td>
<td>125</td>
<td>125</td>
<td>119</td>
<td>131</td>
<td>120</td>
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<td>CB</td>
<td>m</td>
<td>72</td>
<td>49</td>
<td>76</td>
<td>85</td>
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<td>na</td>
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<tr>
<td>DO</td>
<td>m</td>
<td>70</td>
<td>?</td>
<td>78</td>
<td>84</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>DR</td>
<td>m</td>
<td>43</td>
<td>41</td>
<td>106</td>
<td>118</td>
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<td>95</td>
<td>96</td>
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<td>f</td>
<td>52</td>
<td>18</td>
<td>121</td>
<td>83</td>
<td>105</td>
<td>72</td>
<td>89</td>
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<tr>
<td>VP</td>
<td>f</td>
<td>44</td>
<td>9</td>
<td>83</td>
<td>88</td>
<td>95</td>
<td>88</td>
<td>91</td>
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<tr>
<td>VJ</td>
<td>f</td>
<td>43</td>
<td>17</td>
<td>95</td>
<td>88</td>
<td>94</td>
<td>73</td>
<td>88</td>
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</tbody>
</table>

Non-patient groups

<table>
<thead>
<tr>
<th>Age-matched</th>
<th>Female/male</th>
<th>Age</th>
<th>Age range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Students</td>
<td>11/7</td>
<td>56.7</td>
<td>40-70</td>
</tr>
</tbody>
</table>

Notes: See patient summary in subjects section for etiology and surgery information: na, WAIS-R scores unavailable; Perf., performance.
Fig. 1. Computerized reconstructions of CT or MR brain scans for nine patients with unilateral hippocampal system lesions resulting from infarctions of the posterior cerebral artery. Black areas represent site of lesion on transverse sections. The lateral view illustrates the level and orientation of each section from the most ventral section (1) to the most dorsal section (7).

Results and discussion

For ease of interpretation, three separate analyses were conducted. The purpose of the first analysis (within groups) was to determine if the effects of the independent variables on the performance of controls was in keeping with prior research. Additionally, patient groups were examined to determine if the variables affected their memory performance. The second analysis (between groups) contrasted the subject groups on overall primary (PM) and secondary (SM) memory measures. In order to determine if PM or SM differentially carried the between group performance variability, and to demonstrate that different conclusions regarding group performance would be drawn if the PM/SM metric had not been employed. The final between groups analysis contrasted subject groups on final recall (i.e. memory for items across all lists) to determine if the groups differed, irrespective of their immediate recall performance.

Analysis one

Age matched controls. A 2 × 2 × 2 within-subjects ANOVA with independent variables of word type, presentation rate, and memory component yielded significant main effects for word type, presentation rate, and memory component. More importantly, there were significant word type by memory component, and presentation rate by memory component interactions. A summary of the
Table 2. ANOVA summaries and within-groups analysis of variance for the control groups

<table>
<thead>
<tr>
<th>Effect</th>
<th>Age-matched [df(1,17)]</th>
<th>Students [df(1,23)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Word type (concrete/abstract)</td>
<td>0.31</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>29.71***</td>
<td>50.25***</td>
</tr>
<tr>
<td>2. Presentation speed</td>
<td>0.21</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>42.93***</td>
<td>13.71**</td>
</tr>
<tr>
<td>3. Memory component (PM/SM)*</td>
<td>1.32</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td>7.06*</td>
<td>11.21**</td>
</tr>
<tr>
<td>1 x 2</td>
<td>0.17</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>0.08</td>
<td>0.68</td>
</tr>
<tr>
<td>1 x 3</td>
<td>0.41</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>13.56*</td>
<td>35.81***</td>
</tr>
<tr>
<td>2 x 3</td>
<td>0.38</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>27.07***</td>
<td>15.79***</td>
</tr>
<tr>
<td>1 x 2 x 3</td>
<td>0.34</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>0.21</td>
<td>0.12</td>
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</tbody>
</table>

*PM/SM, primary and secondary memory scores
*p < .05; **p < .01; ***p < .001

ANOVA for this group is provided in Table 2. Post hoc comparisons revealed improvements in recall with concrete vs. abstract words, and slow vs. fast presentation rates occurred only for secondary memory [Tukey’s HSD, p < .001]. Primary memory was not affected by these manipulations. Figure 2 displays these interaction effects. These results are in keeping with previous research in demonstrating that for normal populations, experimentally induced improvements in recall occur primarily via secondary memory; primary memory performance remains relatively invariant across conditions (e.g. [16]).

Student controls. Table 2 provides a summary of the ANOVA for this group. Again, post hoc comparisons revealed improvements in recall with concrete vs. abstract words, and slow vs. fast presentation rates occurring only for secondary memory [Tukey’s HSD, p < .001, see Fig. 2]. This similarity to age-matched controls does not mean that students and age-matched controls are identical in performance. When compared directly in a two-way subject group by memory component mixed ANOVA, students are superior to the age-matched controls [F(1,40) = 5.92, MS = .51, p < .05], with no interaction

Fig. 2. Word type (concrete/abstract) and presentation rate (fast/slow) interactions with primary and secondary memory for student and age-matched controls. The left side of each panel represents the effect of the variables on primary memory; the right side the effect on secondary memory.
between subject group and memory components. Thus subject age is an additive factor, and the magnitude of impairment for primary and secondary memory is similar for the age-matched controls compared with students.

**Patient groups.** For all three patient groups, the only effect that reached significance was that of memory component. For Commissurotomy $[F(1,3) = 16.46, MS = .07]$, Right Hippocampal $[F(1,4) = 109.75, MS = .30]$, and Left Hippocampal $[F(1,3) = 14.25, MS = 1.22]$ patients, performance deteriorated in transition from primary to secondary memory ($p's < .05$, see Fig. 3). Notably, this trend is in the opposite direction to the performance for normal controls, whose secondary memory scores are higher than primary memory.

**Analysis two**

This analysis consisted of a $4 \times 2$ mixed ANOVA with independent variables of subject group and memory component. Student control data were omitted since any effects would be confounded with the age difference of this group. Results yielded significant main effects for subject group $[F(3,27) = 9.80, MS = .51, p < .001]$ and memory component $[F(1,27) = 25.85, MS = .25, p < .001]$, with a significant subject group by memory component interaction $[F(3,27) = 18.73, MS = .25, p < .001]$. Inspection of the subject group by memory component interaction (see Fig. 3 and Analysis one), shows that the trend across primary and secondary memory is inconsistent.

For example, although secondary memory is greater than primary memory for control groups, the opposite is true for hippocampal and commissurotomy patients, with decreases in secondary compared with primary memory. Simple effects analysis of the interaction showed no significant differences for primary memory across the groups ($p = .19$), but a significant difference for secondary memory $[F(1,3) = 19.53, MS = .42, p < .001]$. Pairwise comparisons of secondary memory across groups were conducted at an alpha of .05 (modified Bonferroni, [21]) for three post hoc comparisons. Post hocs revealed that the age-matched controls ($M = 3.07$) scored higher than commissurotomy patients ($M = 2.25$), who in turn scored higher than right hippocampal patients ($M = 1.15$). Finally, right hippocampal patients were not significantly different from left hippocampal patients ($M = 0.67$) in secondary memory. Figure 3 illustrates the differences in secondary memory. Age matched controls were superior to all patient groups in secondary memory, with commissurotomy patients performing better than both hippocampal groups.

**Analysis three**

The commissurotomy patients appeared only mildly impaired on the overall immediate recall task in comparison with age-matched controls, and considerably better than hippocampal patients. The next analysis was
conducted on the pattern of performance on the final recall of all items across lists.

A one-way ANOVA was conducted on final recall scores with an independent variable of subject group. Results yielded a significant difference between groups \( F(3,27) = 16.75, MS = 48.27, p < .001 \). Figure 4 shows the main effect with group means. Pairwise comparisons of final recall across groups were conducted at an alpha of .025 (modified Bonferroni, [21]) for six post hoc comparisons. Age-matched controls scored higher than all three patient groups which were not significantly different from one another. Thus, despite their relatively normal appearance at immediate recall, it is clear that the commissurotomy patients are severely impaired at final recall and statistically indistinguishable from hippocampal patients.

Despite the statistical equivalence of the patient groups in the earlier analysis, the group means still appear different. In fact, when only the patient groups are entered into the analysis, the omnibus \( F \) approaches significance \( F(2,10) = 3.82, MS = 8.10, p = .059 \) and LSD \( t \)-tests suggest that both the commissurotomy and right hippocampal groups are superior to the left hippocampal group, without being significantly different from one another \( (p < .05) \). (See Fig. 4.)

Given that secondary memory for the right hippocampal group was considerably worse than the commissurotomy group at immediate recall, we wondered if their pattern of responding may be different at final recall. Despite having numerically similar totals, the right hippocampal group drew 45% of their delayed final recall responses from the last list, whereas the commissurotomy patients only drew 19%. This suggests that although the groups have similar overall final recall scores, they may be employing different retrieval strategies, with the right hippocampal group relying more heavily on their most recently given responses.

**Summary**

Contrary to the predictions of the material specific hypothesis, all three patient groups were significantly impaired in secondary memory during immediate list recall. Furthermore, their trend of performance from primary to secondary scores was qualitatively different from control, showing a decrease during the transition. This, in conjunction with the failure of the word type and presentation speed manipulations to significantly affect performance in the right hippocampal and commissurotomy patients, shows that these subjects have a sizable verbal episodic memory deficit. Although the commissurotomy patients are somewhat less impaired than the right hippocampal patients at immediate recall, both are heavily impaired at final recall, and not statistically distinguishable from one another. Furthermore, their final recall scores are only slightly higher than those of the left hippocampal group whose performance was uniformly poor throughout testing.

**General discussion**

The results of this study speak directly to two important and related questions. First, can unilateral medial temporal lobe verbal episodic memory impairments be accurately characterized as lateralized? Second, what do the verbal memory deficits observed in the patient groups tell us about the possible relation between medial temporal lobe memory systems in normal individuals? Several authors have suggested (e.g. [28, 36, 43, 53]) that impairments observed following unilateral damage are relatively mild, and specific to certain material types. We refer to the assumption underlying this characterization, in its strong form, as the Laterality/Independence (LI) assumption and view it as suspect for at least two reasons.
First, it suggests that the medial temporal lobe memory systems do not normally interact either directly via the dorsal hippocampal commissure or indirectly through cortical interactions taking place via the corpus callosum during event encoding and/or retrieval. Instead, the LI assumption rests on the idea that because cortical processing/representation in humans is lateralized and specialized for particular materials or inputs (e.g. [14]), episodic memory for these same representations must likewise be lateralized and modular. Given the presence of an apparently functional dorsal hippocampal commissure [18], and the massive cortical interconnectivity provided by the corpus callosum, there is no a priori reason that this should be the case. Second, the LI hypothesis implies that some events (e.g. a verbal memory task) can be fully represented by one half of the cerebral cortex and thus be adequately encoded into secondary memory by the medial temporal lobe system which 'serves' that hemisphere. We contend, as have others (e.g. [42]), that this outlook places too much consideration on the nature of the stimulus material per se, and not enough on the task demands of the experiment.

For example, Saling et al. [42] found that left hippocampal sclerosis patients were significantly worse than right patients at verbal paired associate learning, with right hippocampal patients scoring within the normal range. At first glance, this finding would be supportive of the notion that left hippocampal patients have a material specific verbal memory deficit, but right patients are unimpaired at verbal memory. However, both groups were significantly and similarly impaired in the recall of passages; clearly a verbal memory task. Saling et al. suggested that this pattern of findings underscores the point that the laterality of verbal memory is conditional on specific task demands in patients with damage to medial temporal lobe systems. Similarly, Kroll et al. [23] found that unilateral medial temporal lobe infarction patients were more likely than controls to make false alarms to familiar conjunctions of facial features in a recognition task, regardless of the laterality of damage. Again, this runs counter to any idea of a lateralized memory deficit for facial stimuli. However, in both these cases where left and right unilateral groups were substantially impaired ([23, 42]), one could argue that the medial temporal lobe memory systems were still independent, but the tasks employed normally require bilateral cortical processing. For example, one could assert that facial processing normally involves both spatial/structural-relational processing of the features and semantic processing of the affect, or ethnicity, etc. A similar argument could be made in the case of encoding a story. From this perspective, the LI hypothesis would predict that both groups would perform poorly, but these deficits would be due to different types of independent encoding failures. In short, one could suggest that the task and materials employed were not process (hemisphere) specific. In the current study, this explanation seems strained. Indeed, it would be unlikely that one could find a more 'purely' verbal memory task than list learning of unrelated words. However, if it is the case that memory for verbal events generally relies on bilateral cortical processes, then the domain of the material specific deficit hypothesis should be restricted to memory tasks other than episodic verbal tasks. Finally, the LI assumption suggests that separation of the medial temporal lobe memory systems (i.e. commissurotomy) should not result in memory impairment, provided the subject is allowed to respond with the hemisphere involved in the task. Given the ample evidence for significant memory impairment with commissurotomy, the latter proposition is doubtful (e.g. [20, 38]), although secondary epileptogenic or surgical damage to memory critical structures can not be definitively ruled out.

Although all of our patients groups were impaired, we do not mean to suggest that there are not differences in the severity of impairment, merely that in no case would any of the deficits be reasonably classified as mild or lateralized. Similarly, although Figs 3 and 4 suggest a slight advantage for the right versus left hippocampal patients in this experiment, we would contend that this is a difference in degree and not kind. The difference then, is viewed as material related, but not material specific (in the strong sense of the term) because both groups are severely impaired despite laterality of lesion site. The reason(s) for this remain uncertain. One could speculate that the performance of the unilateral groups was a function of the synaptic distance of the task relevant cortical representations from the functional medial temporal lobe system. Because free recall tasks place heavy requirements on reinstating spatiotemporal context, right hippocampal patients would be severely impaired, despite some ability to benefit from inter-item associations between exemplars encountered in the list. Furthermore, left hippocampal patients would be at an even greater disadvantage, because the verbal/semantic representations elicited during the list would not be bound, or be loosely bound to both the context and each other (see [23]). Note however, that this account does not explain why commissurotomy patients were superior to right hippocampal patients at immediate recall. If both the right medial temporal lobe and commissurotomy patients are relying on an intact left hemisphere to perform the tasks, their behavior should be similar. Furthermore, if commissurotomy patients had in fact suffered damage to the left medial temporal lobe due to epilepsy, their performance should be worse than the right medial temporal lobe patients. One could argue that the superior performance for commissurotomy patients was a result of spared callosal or hippocampal commissural fibers in some members of the group (see [38]). However, this argument is weakened somewhat because secondary memory scores were superior for every commissurotomy subject compared with right hippocampal patients. At this point, the reasons for the differences between these groups remain unknown. A final important result in the current study relates to the permanence of the subject
deficits observed. Table 1 clearly demonstrates that the observed deficits can be viewed as permanent. In the case of infarction patients there was a minimum of two years between vascular accident and testing, with the majority of spans considerably greater.

At a minimum, the current results of our unilateral lesion patients indicate that some, if not most, verbal episodic memory tasks require bilateral processes during encoding and/or retrieval. As such, the material specific hypothesis and LI assumption lack generality. Furthermore, the results from the commissurotomy patients implicate some degree of interdependence between the medial temporal lobe memory systems. We wish to emphasize that the results of the current study do not address whether or not visuospatial memory may be adequately explained within the material specific hypothesis, nor do they suggest that verbal memory performance will not be lateralized with some tasks. For example, Abrahams et al. [1] have demonstrated a unilateral deficit in allocentric spatial memory for locations, in both patients who have undergone right temporal lobectomy, those whose volumetric estimates suggest right hippocampal formation sclerosis. The current results merely emphasize the point that the finding of performance differences as a function of laterality of lesion for particular memory tasks, does not logically require independent underlying systems or processes (cf. [41]).

The neurological basis of the possible interdependence suggested above remains unknown; however, numerous neuroimaging studies have demonstrated prefrontal cerebral asymmetries during encoding and retrieval tasks in memory (for reviews see Nyberg et al. [33] and other authors [4, 34, 49]). Based on this group of findings alone, one could speculate that commissurotomy patients would be impaired on the free recall task employed simply because right activations associated with episodic retrieval would be isolated from the typically language dominant left hemisphere. Additionally, the observed asymmetries suggest that bilateral processing is often involved in verbal episodic memory. Notably, these prefrontal activations may not be critical for performance on some recall tasks. For example, Swick and Knight [46] demonstrated normal accuracy in right prefrontal lesion patients in a word stem cued recall task.

However, asymmetries in prefrontal activations do not address the impairment observed in the unilateral medial temporal lobe patients. With regard to this group, there are several developed theories (e.g. [12, 27, 45, 47]) which hold that episodic or declarative remembering is dependent on plasticity within structures of the hippocampal system–Brion circuit [13]. A review of these theories is outside the scope of this research. However, we wish to stress that none make strong assertions regarding the dependence of the bilateral memory systems posited.

In conclusion, we contend that unilateral damage to the medial temporal lobe memory system, as a result of posterior cerebral artery infarction, results in a severe and permanent deficit in verbal episodic memory on sufficiently demanding memory tasks, regardless of laterality of lesion site (cf. [28, 53]).

Given the small sample sizes, some may question the validity of these findings. Although systematic errors in sampling can never be definitively ruled out, we believe that patient selection on the basis of lesion site and not pre-observed task deficits helps reduce this risk (see Robertson et al. [40], for the logic underlying group lesion studies). Furthermore, when individual groups differ in sample size, and the numerically larger group has a greater variance, t-tests are in fact conservative with respect to type I error [17]. Thus any concerns regarding heterogeneity in post hoc tests between age-matched controls and patient groups are lessened.

The finding of sizable impairment in the commissurotomy group accords with previous studies which have documented memory deficits in this population (e.g. [20, 57, 58]) and suggest that the section of the dorsal hippocampal commissure may play a role in this deficit [38]. It would be valuable to contrast the performance of lobectomy patients, many of whom have spared posterior entorhinal cortex which gives rise to the dorsal hippocampal commissure, with that of the hippocampal and commissurotomy patients reported here. Based on the above considerations, we believe it is important to bring to bear current cognitive neuroscience techniques on questions regarding the possible roles of the dorsal hippocampal commissure, and callosal hemispheric interactions in episodic remembering. Finally, we wish to stress that without explicit consideration of the demands of the particular memory task involved as well as the type of material employed, characterizations of the degree or laterality of memory impairment in any population are not meaningful.

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