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A pencil rescues impaired performance on a visual discrimination task in patients with medial temporal lobe lesions

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We tested proposals that medial temporal lobe (MTL) structures support not just memory but certain kinds of visual perception as well. Patients with hippocampal lesions or larger MTL lesions attempted to identify the unique object among twin pairs of objects that had a high degree of feature overlap. Patients were markedly impaired under the more difficult task conditions. However, the deficit was fully rescued when patients used a pencil to draw lines between the twin pairs, thereby eliminating the need to hold material in memory as they worked at each display. The perceptual demands of the task were presumably the same with or without this memory aid. Accordingly, the results suggest that the deficit on this and similar tasks, which involve comparisons across stimuli, are better understood in terms of impaired memory rather than impaired perception.

[Supplemental material is available for this article.]
Table 1. Characteristics of memory-impaired patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Education (years)</th>
<th>WAIS-III IQ</th>
<th>WMS-R Attention</th>
<th>WMS-R Verbal</th>
<th>WMS-R Visual</th>
<th>WMS-R General</th>
<th>WMS-R Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.A.</td>
<td>M</td>
<td>30</td>
<td>12</td>
<td>95</td>
<td>104</td>
<td>90</td>
<td>91</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>K.E.</td>
<td>M</td>
<td>71</td>
<td>13.5</td>
<td>108</td>
<td>114</td>
<td>64</td>
<td>84</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>L.J.</td>
<td>F</td>
<td>75</td>
<td>12</td>
<td>101</td>
<td>105</td>
<td>83</td>
<td>60</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>R.S.</td>
<td>M</td>
<td>56</td>
<td>12</td>
<td>99</td>
<td>99</td>
<td>85</td>
<td>81</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>G.W.</td>
<td>M</td>
<td>53</td>
<td>12</td>
<td>108</td>
<td>105</td>
<td>67</td>
<td>86</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>J.R.W.</td>
<td>M</td>
<td>49</td>
<td>12</td>
<td>90</td>
<td>87</td>
<td>65</td>
<td>95</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>G.P.</td>
<td>M</td>
<td>67</td>
<td>16</td>
<td>98</td>
<td>102</td>
<td>79</td>
<td>62</td>
<td>66</td>
<td>66</td>
</tr>
</tbody>
</table>

WAIS-III is the Wechsler Adult Intelligence Scale-III and the WMS-R is the Wechsler Memory Scale-Revised. The WMS-R does not provide numerical scores for individuals who score below 50. IQ scores for R.S. and J.R.W. are from the WAIS-Revised, and the IQ score for D.A. is from the WAIS-IV.

2005). D.A., K.E., L.J., R.S., G.W., and J.R.W. have an average bilateral reduction in hippocampal volume of 35, 49, 46, 48, and 44%, respectively (all values >2.9 SDs from the control mean). On the basis of two patients (L.M. and W.H.) with similar bilateral volume loss in the hippocampus for whom detailed post-mortem neurohistological information was obtained (Rempel-Clower et al. 1996), the degree of volume loss in these six patients likely reflects nearly complete loss of hippocampal neurons. The volume of the parahippocampal gyrus (temporopolar, perirhinal, entorhinal, and parahippocampal cortices) is reduced by –5%, 11%, –5%, 10%, 12%, and –17%, respectively (all values within 2 SDs of the control mean). The minus values indicate instances where the volume was larger for a patient than for controls. The volumes for parahippocampal gyrus differ a little from volumes reported previously for these patients (Knutson et al. 2012) and are based on newly published, more detailed guidelines for identifying the caudal border of the gyrus (Franko et al. 2012).

One patient (G.P.) has severe memory impairment resulting from viral encephalitis. G.P. has demonstrated virtually no new learning since the onset of his amnesia, and during repeated testing over many weeks he does not recognize that he has been tested before (Bayley et al. 2005). G.P. has a bilateral reduction in hippocampal volume of 96%. The volume of the parahippocampal gyrus is reduced by 94%. Eight coronal MR images from each patient, together with detailed descriptions of the lesions, can be found in Supplemental Material.

Eight healthy individuals (five male) served as controls for the memory-impaired patients. Controls averaged 58.4 ± 6.1 yr of age (range = 23–76) and had 14.1 ± 0.5 yr of education. All procedures were approved by the Institutional Review Board at the University of California San Diego. Participants gave written informed consent prior to participation and were compensated.

The test consisted of 64 unique displays of five, seven, or nine nonsense objects, termed Fribbles, as used in earlier studies of object perception (Williams and Simons 2000; Barense et al. 2007). The Fribbles were computer generated using Bryce 5 software (Corel Corporation) and were composed of a main body and two or four appendages. Each display contained two, three, or four twin pairs plus one unique object that did not have a twin. The unique object could appear in any location in the display (Fig. 1).

The difficulty of each display was manipulated by varying the number of objects in each display (five, seven, or nine), the number of appendages on each object (two or four), the number of body colors in each display (two different body colors or only one body color), and the differences among the appendages (relatively salient or more subtle). Combinations of these components were used to create easier displays (difficulty levels 1–4, eight trials/difficulty level) and more difficult displays (difficulty levels 5–8, eight trials/difficulty level) (for details, see Knutson et al. 2012). At all difficulty levels, each appendage of the unique object always appeared on at least one of the twin pairs in the display. Accordingly, more than one appendage always needed to be considered to distinguish the unique object from the twin pairs. One of the eight displays at difficulty level 6 was identical to the display illustrated in an earlier study (Fig. 2c in Barense et al. 2007).

In the first condition, participants were told that they would see pictures of objects on a computer screen and that one object in each display did not have a twin pair. The task was to identify the unique object. The displays were presented in blocks of eight trials, beginning with difficulty level 1 and progressing to difficulty level 6. Difficulty levels 7 and 8 were presented in a subsequent testing session (with the exception of one hippocampal patient and one control participant who received difficulty levels 1–8 during one session). A printed reminder of the instructions was in view throughout testing. Performance was self-paced, and participants identified their choice by pointing to the computer screen. Accuracy and response times were recorded. The patients with hippocampal lesions and the controls were tested once. Patient G.P. with large MTL lesions was tested on two occasions separated by 1 mo.

In a second condition (scheduled up to 3 mo later), difficulty levels 5–8 (32 trials) from the standard test were presented on...
individual sheets of paper, and participants were instructed to use a pencil to draw lines between each twin pair as each pair was identified. The intention of this condition was to eliminate the need to hold any material in mind as participants worked at each display. All the participants used the pencil, and afterward some commented that, with the aid of the pencil, there was no need to keep track of which twin pairs they had already identified. The instructions were in view throughout testing, and performance was self-paced. The data to be presented were based on accuracy and response times for all trials (correct and incorrect). The patients with hippocampal lesions and controls were tested once. Patient G.P. with large MTL lesions was tested on two occasions separated by 8 mo. Performance for five of the six patients in the hippocampal group was reported previously for difficulty levels 1–6 (first condition only). Performance of this group in the second condition (with the pencil) is presented here for the first time. In addition, performance for G.P. was reported previously for the first condition and for one of the two tests in the second condition (Knutson et al. 2012). In total, G.P. was tested on four occasions extending across 1 yr.

At difficulty levels 1–4 all participants performed well (Fig. 2A). Controls scored 94.3% correct, patients with hippocampal lesions scored 89.6% correct, and patient G.P. with large MTL lesions scored 98.4% correct. Response times were similar as well (controls at difficulty levels 1–4 (Fig. 2A) but was impaired at difficulty levels 5–8 (8)). Brackets show SEM.

G.P. with large MTL lesions scored 87.5% correct. The memory aid did not significantly improve control performance (78.1% correct in Fig. 2B vs. 86.3% correct in Fig. 3, P > 0.10), but substantially improved the performance of both the hippocampal patients (by 28.7%, paired t-test, t<sub>12</sub> = 9.7, P < 0.01) and G.P. (by 26.6%). Response times were similar for controls, hippocampal patients, and patient G.P. (57.8 ± 6.6 sec, 51.7 ± 1.9 sec, and 63.0 sec, respectively).

To summarize, on tests of visual discrimination, patients performed well at the easier difficulty levels (1–4), but were impaired at difficulty levels 5–8. Three points deserve emphasis. First, patients were impaired only in the more difficult conditions (difficulty levels 5–8), even though at every difficulty level the task required discriminating among objects with overlapping features. This finding suggests that some other component of the task (besides the requirement to make perceptual discriminations) accounts for impaired performance. Second, the finding of an impairment in patients with circumscribed hippocampal lesions (not only patients with lesions that include the perirhinal cortex) suggests that the impairment is attributable to factors common to both brain areas, not to factors specific to perirhinal cortex. Inasmuch as the hippocampus has not been linked to object discrimination, the impairment after hippocampal lesions suggests that the impairment may be related to the importance of the hippocampus for long-term memory. Third, the impairment in patients was rescued by using a memory aid, a condition intended to reduce the burden on working memory. Specifically, there were 28 occasions when performance was tested with the memory aid (seven patients × difficulty levels 5–8). Performance improved with the memory aid on 22 of these 28 occasions and remained the same on six occasions. Because the perceptual demands of the task were presumably the same with or without the memory aid, this finding provides particularly strong evidence that the deficit should be understood in terms of impaired memory rather than impaired perception.

Our results support earlier suggestions that memory likely plays a role in many of the tasks used to investigate the MTL’s proposed role in visual perception (Hampton 2005; Suzuki 2009). Further studies of this issue will benefit from task designs that reduce the role of memory in task performance (e.g., Lee and Rudebeck 2010; Barense et al. 2012b). Last, in all studies of MTL function, there is the important issue of establishing the locus

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**Figure 2.** Accuracy at identifying the unique object for controls (CON, n = 8), patients with hippocampal lesions (H, n = 6), and a patient with large medial temporal lobe lesions (MTL, n = 1) across eight levels of difficulty (eight trials/difficulty level). Patient performance was similar to that of controls at difficulty levels 1–4 (A) but was impaired at difficulty levels 5–8 (B). Brackets show SEM.

**Figure 3.** Accuracy scores for controls (CON, n = 8), patients with hippocampal lesions (H, n = 6), and a patient with large medial temporal lobe lesions (MTL, n = 1) across difficulty levels 5–8. In this condition, participants used a pencil to draw lines between the twin pairs, thereby eliminating the need to hold material in mind as they worked through each display. With this aid, patients performed as well as controls. Brackets show SEM.
and extent of brain damage within patient groups and the possibility that direct or indirect damage lateral to the MTL might contribute to the deficits that are identified (Knutson et al. 2012; Insausti et al. 2013).

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References

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Series of eight T1-weighted coronal images of six patients are illustrated with limited hippocampal lesions (DA, GW, JRW, KE, LJ, and RS), one patient with extensive medial temporal lobe damage (GP), and one control (CON). The sections proceed posteriorly in 7mm intervals from the temporopolar (TP) cortex in the top section. The left side of the brain is on the right side of each image.

As described by Insausti et al. (1998), TP cortex extends medially from the inferotemporal sulcus (ITS) to the fundus of the TP sulcus. TP cortex extends rostrally from the tip of the temporal pole caudally to the limen insula (LI), which approximates the border between the TP cortex and perirhinal cortex (PRC). Caudal to TP cortex, the collateral sulcus (CS) is the most important structure for the identification of medial temporal lobe cortices. At its most rostral extent, the CS is surrounded entirely by PRC. Caudally, entorhinal cortex (EC) extends from the midpoint of the medial bank of the CS to the subiculum, while PRC extends laterally from the midpoint of the medial bank of the CS to the inferotemporal cortex. Two millimeters caudal to the disappearance of the gyrus intralimbicus of the hippocampus (H), the CS is surrounded by parahippocampal cortex (PHC). The caudal border of the posterior PHC is defined as lying 1.5mm posterior to the crus of the fornix at the point where the fimbria turns upwards to continue as the posterior pillars of the fornix and posterior to the pulvinar nucleus of the thalamus (Franko et al., 2012).

The top section (1) shows the TP cortex and the ITS in the control brain. None of the patients with limited hippocampal lesions have damage evident at this level. For GP, the TP cortex is missing. The ITS is visible bilaterally at this level for patients GW, JRW, KE, and RS. For LJ, only the right ITS is visible. For DA, the ITS is not visible on either side at this level. The second section (2) shows TP cortex and the ITS in the control brain. The ITS and TP cortex is evident in all patients with limited hippocampal lesions at this level. None of the patients with limited hippocampal lesions has damage evident at this level. For GP, note that the portion of the temporal lobe missing corresponds to TP cortex and involves the lateral temporal lobe to a minimal extent (~10%). The CS is visible, indicating the beginning of PRC, in patients KE and RS (right side only). The third section (3) shows the CS and surrounding PRC and EC in the control brain. None of the patients with limited hippocampal lesions have damage evident at this level with the exception of KE, who has damage in the basal ganglia secondary to toxic shock syndrome (and to a lesser extent in section 4). For patient DA, the CS is not evident at this level and PRC is evident.
For patients GW, KE, and LJ, the PRC is evident on the left side, bounded by the LI and CS. On the right side, both EC and PRC are evident. For patients JRW and RS, both EC and PRC are evident bilaterally. For GP, no CS or surrounding tissue is evident. The fourth section (4) shows the anterior hippocampus and the adjacent PRC and EC in the control brain. At this level hippocampal damage is evident in patient DA. The hippocampus is not yet visible at this level in any of the other patients with limited hippocampal lesions. For DA, bilateral damage to the globus pallidus is evident at this level, presumably secondary to heroin overdose. No damage to the PRC or EC is evident for any of the patients at this level, except for GP who has no medial temporal lobe tissue at this level. The fifth section (5) shows the hippocampus and the adjacent PRC and EC in the control brain. The CS and the surrounding PRC and EC appear normal in all patients at this level with the exception of GP, who has no medial temporal lobe tissue at this level. Damage is evident in the hippocampal region of all patients. The sixth section (6) shows the hippocampus and the adjacent PRC and EC in the control brain. Damage is evident in the hippocampal region for all patients at this level. The surrounding PRC and EC appear normal in all patients except GP, who has little normal medial temporal lobe tissue in either hemisphere. Both the PRC and EC are visible in all hippocampal patients bilaterally, with the exception of JRW for whom only PRC is visible on the left side, indicated by the disappearance of the gyrus intralimbicus 2 mm rostral to the sixth section (not shown). The seventh section (7) shows the hippocampus and the CS, surrounded by PHC in the control brain. Damage to the hippocampus is evident in all patients at this level. In all patients with damage limited to the hippocampus, the PHC is evident, but in patient DA the PRC is still visible on the right side. Patient GP has little normal medial temporal lobe tissue in either hemisphere. Both the PRC and EC are visible in all hippocampal patients bilaterally, with the exception of JRW for whom only PRC is visible on the left side, indicated by the disappearance of the gyrus intralimbicus 2 mm rostral to the sixth section (not shown). The seventh section (7) shows the hippocampus and the CS, surrounded by PHC in the control brain. Damage to the hippocampus is evident in all patients at this level. In all patients with damage limited to the hippocampus, the PHC is evident, but in patient DA the PRC is still visible on the right side. Patient GP has little normal medial temporal lobe tissue in either hemisphere. The eighth section (8) shows the hippocampus in the control brain. Bilateral hippocampal damage is evident in patients DA, GW, KE, and GP at this level. Patient LJ shows hippocampal damage only on the left side, and no damage is evident in patient RS. At this level, the hippocampus is no longer evident in patient JRW. PHC is no longer evident at this level in patients DA, JRW, KE, LJ, or RS and PHC appears normal in patient GW. Patient GP has some spared PHC on the right at this level. The warping artifact in the right lateral temporal lobe of GW on this section did not interfere with the assessment of his damage. Posterior to this level, GP exhibits hippocampal damage and damage to the PHC. No damage is evident posterior to this level for any of the other patients.

References
