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Dissociating prefrontal and hippocampal function in episodic memory encoding

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Human lesion data indicate that an intact left hippocampal formation is necessary for auditory–verbal memory¹. By contrast, functional neuroimaging has highlighted the role of the left prefrontal cortex^{2–4} but has generally failed to reveal the predicted left hippocampal activation. Here we describe an experiment involving learning category–exemplar word pairs (such as ‘dog...boxer’) in which we manipulate the novelty of either individual elements or the entire category–exemplar pairing.

We demonstrate both left medial temporal (including hippocampal) and left prefrontal activation and show that these activations are dissociable with respect to encoding demands. Left prefrontal activation is maximal with a change in category–exemplar pairings, whereas medial temporal activation is sensitive to the overall degree of novelty. Thus, left prefrontal cortex is sensitive to processes required to establish meaningful connections between a category and its exemplar, a process maximized when a previously formed connection is changed. Conversely, the left medial temporal activation reflects processes that register the overall novelty of the presented material. Our results provide striking evidence of functionally dissociable roles for the prefrontal cortex and hippocampal formation during learning of auditory–verbal material.

The role of medial temporal structures, including the hippocampal and parahippocampal formation, in episodic memory is well established, with homologous left- and right-sided structures mediating verbal and visual aspects of memory, respectively^{1,5,6}. In the monkey, lesions restricted to the hippocampus lead to striking memory impairment⁷. Memory processes can be fractionated into those relating to encoding (learning), consolidation (storage) and retrieval (recall). Functional neuroimaging, although failing to specify the role of the medial temporal cortex, has emphasized specific involvement of the left and right prefrontal cortices at encoding and retrieval respectively^{2–4}. In this experiment we sought to reconcile prefrontal and hippocampal involvement in encoding by showing that hippocampal activation reflects a response to the relative novelty of sensory data whereas prefrontal activation reflects an aspect of associative semantic processing. By novelty we refer to the relative familiarity of the verbal material in the context of the experiment; associative semantic processing refers to the formation of meaningful associations between verbal items.

The study material consisted of word-paired associates comprising a category (for example, dog) and an exemplar (for example, boxer) presented auditorily. Twelve separate perfusion scans were acquired in six male subjects while they were presented with sets of 12 paired associates. The scanning window was preceded by the presentation of two sets of 12 paired associates that created the context for the critical experimental manipulation during scanning (Fig. 1). We used a design in which category and exemplar were independent factors, with two levels related to whether an item was novel (that is, not previously presented) or old (previously presented). The study thus comprised four separate conditions representing two levels of novelty (new versus old) with respect to either category or exemplar (Fig. 1). So, for example, the initial presentations of a word pair (such as dog ... boxer) during the lead-in period might be followed, during the critical scanning period, with an entirely new pair (new–new condition: for example, food ... biscuit). Alternatively, it may be followed by a change in category (new–old condition, such as sportsman ... boxer) or a change in exemplar (old–new condition: for example, dog ... labrador). In the fourth condition, subjects heard repeat presentation of pairs presented during the lead in (old–old condition; that is, dog ... boxer). Thus, in the new–new condition, the relative emphasis is on novelty, whereas in the new–old and old–new conditions, the process emphasized is the making and breaking of semantic linkages.

Activation of the left dorsolateral prefrontal cortex (DLPFC) was sensitive to a manipulation of the association between category and exemplar or vice versa. Thus, maximal activation in this region was seen in the two conditions involving a change in category exemplar pairings. Figure 2a shows a statistical parametric map (SPM) of this activation for the contrast of the two conditions (new–old and old–new) in which there was a change in category–exemplar linkage with the condition where there was no change (old–old) ($P < 0.05$, corrected). These data are shown in Fig. 2b, where the mean adjusted activity in the left DLPFC is plotted for each of the four

experimental conditions. It can be seen that maximal activation is expressed in the two conditions involving a change in category–exemplar pairings compared to conditions in which there is no change with respect to previously established pairings. A further contrast of both conditions involving change in category exemplar pairings (new–old and old–new) with the two other conditions combined (new–new and old–old) again showed that the same left dorsolateral prefrontal cortex region is the most significant focus of activation. Additional significant activation foci were seen in the medial parietal cortex and left middle frontal gyrus. Examination of their activation profiles indicated that they represented relative decreases in the new–new condition. An activation in the left inferior parietal cortex was not predicted and does not survive correction. Table 1 lists the coordinates and associated z-scores for all of these contrasts.

By contrast, the left medial temporal cortex, including the hippocampus and parahippocampal region, showed a striking responsiveness to novelty in the presented material. Thus, maximal hippocampal activation was seen in the condition in which both category and exemplar were novel. This was significant when the condition involving a novel category and item was compared with each of the other conditions ($P < 0.001$, uncorrected). The data for the contrast of the condition where category and exemplar are new

compared to the condition when both are old is displayed as an SPM in Fig. 3a. The mean adjusted activity at the pixel of maximal significance, located in the hippocampus, for each separate condition is illustrated graphically in Fig. 3b. This shows a significant stepwise pattern of activation, with the highest values being expressed when category and exemplar are novel, intermediate when either category or exemplar are novel, and lowest when neither are novel. The associated foci of activation are shown in Table 1. To test the robustness of the left medial temporal activation further, we repeated this analysis of the hippocampal activation on each individual subject and found that in all cases, there was significant medial temporal activation ($P < 0.05$, uncorrected).

The crucial finding in this study is that there are functionally dissociable roles for the left medial temporal cortex and left prefrontal cortex during encoding of auditory–verbal material. This functional and anatomical dissociation implies that anatomically distinct brain regions have differential sensitivities to stimulus parameters and, by implication, processing requirements during encoding. These parameters may well reflect different stages in the encoding process⁸.

The importance of the human hippocampus and related medial temporal structures in auditory–verbal memory is exemplified by amnesic patients with selective lesions of this structure⁹. Activation

Lead-in list 1	Lead-in list 2	Scanning time
12 paired associates e.g. Game...Bridge Dog...Boxer	Identical to lead-in list 1	Condition 1 (New-New) New category/New exemplar e.g. Stone...Granite Cloth...Velvet Condition 2 (New-Old) New category/Old exemplar e.g. Structure...Bridge Sportsman...Boxer Condition 3 (Old-New) Old category/New exemplar e.g. Game...Football Dog...Dalmatian Condition 4 (Old-Old) Old category/Old exemplar e.g. Game...Bridge Dog...Boxer

Figure 1 The experimental design, which involved subjects hearing 12 word-paired associates while being scanned. Before scanning there was a lead-in, during which subjects had two presentations of 12 paired associates which provided the context for the experimental conditions presented during scanning. The paired associates consisted of a category and a semantically related exemplar presented at a rate of one per 4 s. There were four experimental conditions whose order was counterbalanced within and between subjects. The critical experimental conditions, each repeated three times, were defined by the degree of novelty of the category or exemplar as illustrated.

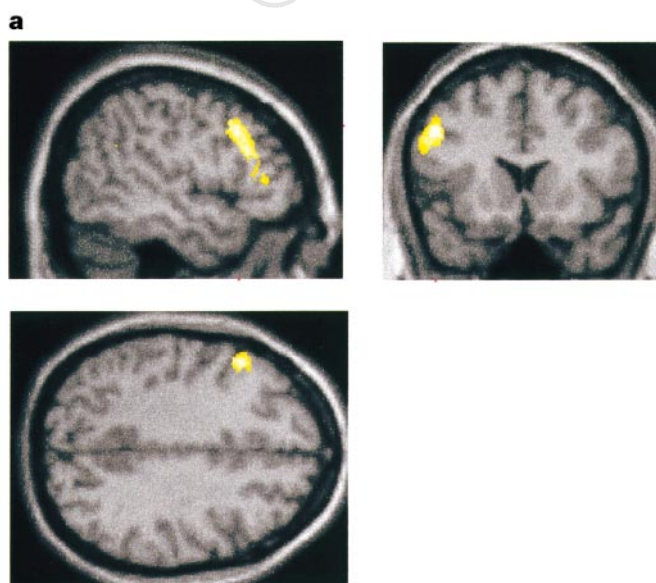
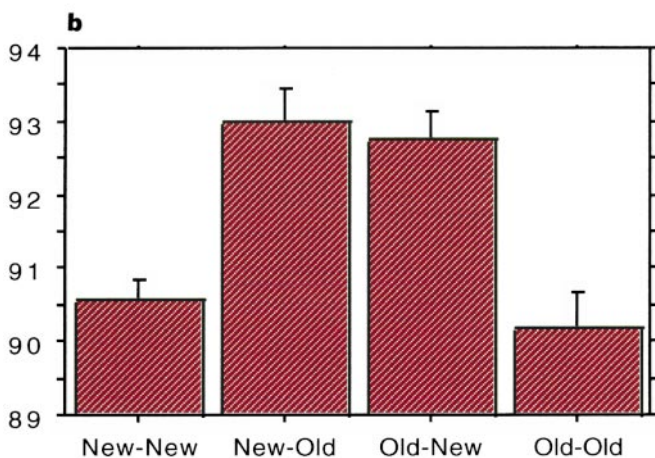


Figure 2 a, A statistical parametric map (SPM)²⁹ of a comparison between the combined 'new-old' and 'old-new' and the 'old-old' conditions, which shows greater activation in the left dorsolateral prefrontal cortex. The SPM has been rendered into standard stereotaxic space and superimposed on to orthogonal sections, at voxel coordinates (x, y, z were -46, 16, 32, respectively; z score, 4.7) of a magnetic resonance image (MRI) which is itself in standard space. **b**, Regional



cerebral blood flow (rCBF) equivalents (together with standard error bars) from the most significantly activated voxel in the left DLPFC, from the comparison in **a** for each experimental condition. This voxel has identical coordinates to that in **a**. It can be seen that activation is significantly greater for the conditions involving a change in category–exemplar pairings than either of the two other conditions.

of this region has been demonstrated in an auditory-verbal paradigm that confounded encoding and retrieval¹⁰. We are aware of a single previous report of hippocampal activation in an auditory task that compared item with location encoding¹¹. Although this activation was unexpected, it suggests that processing demands at encoding other than novelty may engage the hippocampus. This is in accord with our theory that encoding involves a number of different processes that are anatomically dissociable.

In our study, when both category and exemplar are presented for the first time, the critical processing emphasized is novelty of material (with respect to the overall experimental setting) and, as predicted, robust left medial temporal activation was elicited relative to all other conditions. The involvement of medial temporal structures in novelty encoding was indicated by results from electrophysiological studies in humans and by single-cell recordings from animals¹²⁻¹⁴. Neuropsychological data also indicate the absence of a characteristic electrophysiological response to novelty

in patients with hippocampal lesions¹⁵. A sensitivity to novelty is also implicit in the suggestion that hippocampal-dependent circuits maintain a template of the recent past for comparison with incoming stimuli¹⁶. Previous functional imaging studies have shown activation of the hippocampal formation during encoding of novel visual stimuli, pictures or faces^{8,17,18}. In our study, the material presented (words) was familiar, but a manipulation of the relative novelty of these words, within the experimental context engendered hippocampal activation. Note that the magnitude of hippocampal activation reflected the overall degree of novelty of the material. Our data thus support the view that the human hippocampus and related medial temporal structures are sensitive to novelty that extends beyond item novelty to include contextual novelty. This finding may explain the absence of reproducible medial temporal activation in previous functional imaging studies in that even baseline tasks that include novel material may engender hippocampal activation.

Table 1 Coordinates and z scores for activations in all reported comparisons

Comparison	Region	Coordinates	z score
New-New versus Old-Old	Left hippocampal and parahippocampal region	-16, -14, -12	3.5
		-28, -26, -20	3.8
		-42, -10, -24	3.9
New-Old + Old-New versus Old-Old	Left dorsolateral PFC	-46, 16, 32	4.6
		-46, 26, 24	4.0
New-Old + Old-New versus Old-Old + New-New	Left dorsolateral PFC	-46, 20, 30	5.3
		-46, 26, 24	4.7
	Medial parietal region (BA7)	0, -68, 50	5.8
	Left middle frontal gyrus (BA10)	-32, 58, 0	4.3
	Left inferior parietal cortex	-58, -48, 34	4.0

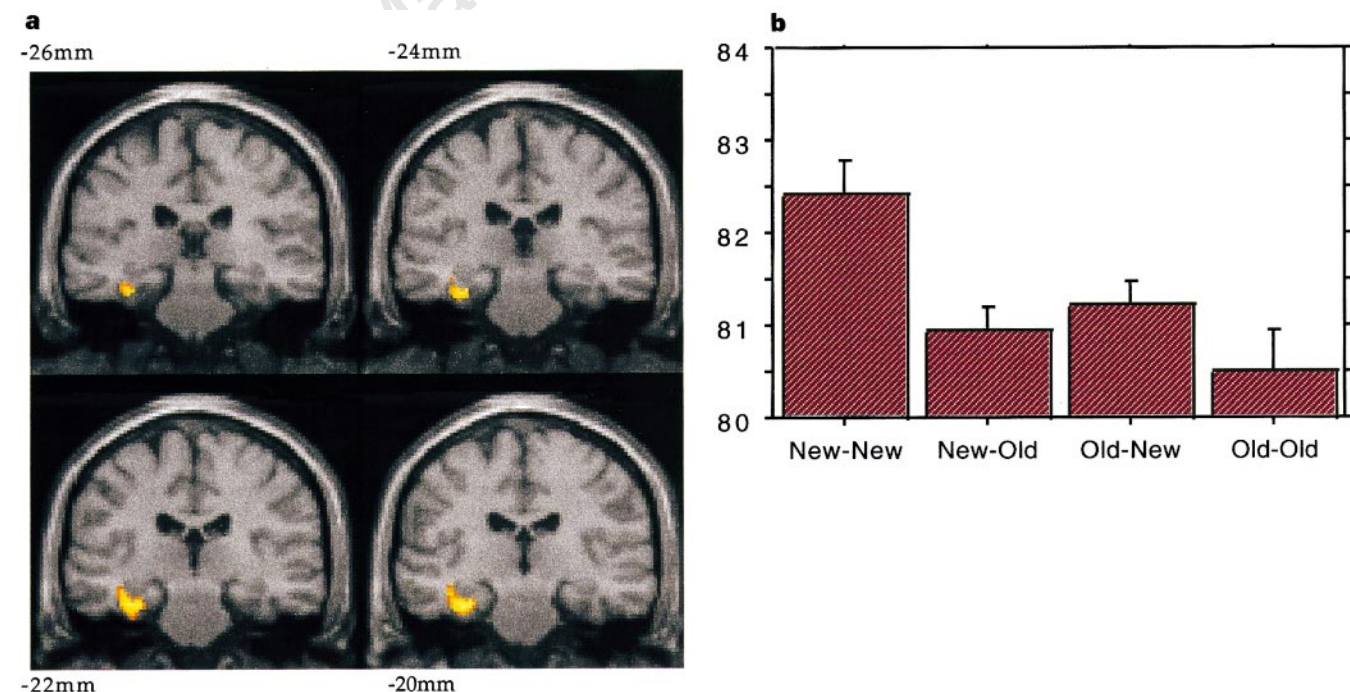


Figure 3 a, An SPM of the comparison between the 'new-new' and the 'old-old' conditions, showing significantly greater activation in the former centred on the left medial temporal cortex that incorporates the left hippocampus. The SPM has been superimposed onto 4 consecutive coronal MRI sections in the y-axis, progressing in 2-mm increments from 24 mm (top left section) to 18 mm (bottom right section) posterior to the anterior commissure. **b**, Regional cerebral blood flow equivalents (together with standard error bars) from one of the two most

significantly activated voxels (x, y, z were $-16, -14, -12$; z score, 3.5) in the left medial temporal cortex in the comparisons in **a**. The other significant voxel (x, y, z values, $-28, -26, -20$, respectively). Data from this voxel are shown for each experimental condition and indicate a stepwise pattern of activation which reflects the relative degree of novelty in the four experimental conditions: that is, the contrast of new-old and old-new activations in left medial temporal cortex were also significant ($P < 0.01$) with respect to the old-old values.

By contrast, left dorsolateral prefrontal cortex activation was maximal when either category or exemplar were novel, resulting in a new category–exemplar pairing. Activation of left prefrontal cortex is reported in a wide range of neuroimaging studies of episodic encoding^{2–4}. The foci of our activation are more dorsal than these previous reports, but the spread of activation indicates a considerable overlap. One interpretation of this activation is that it reflects retrieval of previously learned associates, but this is unlikely as cued retrieval of previously learned associates should be greatest in the contrasted old–old condition. Furthermore, retrieval of paired associates is strongly associated with right prefrontal activation⁵. Neuropsychological studies have indicated functional specialization in the prefrontal cortex for source, temporal sequence and strategic organizational requirements in memory^{19–22}. We found that maximal left prefrontal activation was elicited under conditions in which the critical emphasis was semantic processing necessary for the formation of new category–exemplar associations. This manipulation must elicit a degree of interference from previously encoded pairings, a phenomenon known as proactive interference. Proactive interference is a semantically mediated process and, strikingly, patients with prefrontal lesions show increased susceptibility to proactive interference^{23,24}, whereas isolated left prefrontal lesions result in an absent encoding advantage with semantic processing²⁵.

Retrieval-related prefrontal and hippocampal activations have been ascribed to effort and conscious recollection, respectively²⁶. Although we demonstrate dissociable prefrontal and hippocampal activations at encoding, we emphasize the relative nature of these differences. A hippocampal role in learning associational relations and a prefrontal sensitivity to aspects of novelty have been reported^{27,28}. Therefore, we assume that prefrontal and medial temporal activations reflect differential processing demands elicited by the experimental manipulations. In our study, prefrontal activation reflects a relative emphasis on associative semantic processing necessary in establishing and maintaining new semantic linkages in the context of already established linkages. Conversely, hippocampal activation reflects relative novelty in the study material that may engage processes that include a global integration of the sensory stimuli with the current cognitive context¹². Our data thus extend theories of hemispheric specialization for encoding by suggesting process-specific prefrontal and medial temporal activation and provide striking confirmation of the ‘novelty/encoding’ hypothesis and its predicted involvement of medial temporal structures⁸. □

Methods

Functional imaging. Six healthy male right-handed volunteers were studied using a Siemens/CPS ECAT exact HR+ (model 962) PET scanner in three-dimensional mode with a 15-cm axial field of view. Relative regional cerebral blood flow (rCBF) was measured from the distribution of radioactivity after a slow, bolus intravenous (i.v.) injection of H215O (8 mCi per scan, each lasting 90 s). Attenuation-corrected data were reconstructed into 63 image planes, with a resulting resolution of 6 mm at full-width-half-maximum (FWHM). For each subject, structural magnetic resonance (MR) images were obtained with a 2 T Magnetom Vision (Siemens, Germany).

Psychological tasks. Twelve rCBF measurements were made during the following four conditions: (1) novel category and novel word; (2) novel category and old word; (3) old category and novel word; (4) old category and old word. For each condition, subjects were scanned three times. While they lay with eyes closed in a quiet darkened room, stimuli were presented in an auditory verbal mode at a rate of one pair every four seconds. During the critical scanning window, subjects were presented with 12 individual word-paired associates (Fig. 1). Each of the critical experimental conditions was preceded by a run-in period in which subjects heard 2 presentations of 12 paired associates which provided the context for the presentations. Thus for example, word-paired associates might be presented twice in the run-in, whereas in the third presentation, during scanning, new exemplars might be

provided with previously presented categories as in condition (3). The order of presentation of experimental conditions was counterbalanced both within and across subjects. Subjects were instructed to attend to and memorize all the presented study material for later recall. Subjects were not informed as to when scanning occurred in relation to the presentation of the lists to ensure active attention to all the material presented. During the interscan interval, recall performance was assessed using the category as cues. For the old–new condition, subjects were asked to recall both exemplars heard at study. For the new–old condition, subjects were cued with the categories presented during the scan. These data showed recall was 95% for new–new, 83% for new–old, 73% for old–new and 93% for old–old.

Data analysis. Statistical parametric mapping (SPM96) software was used for image realignment, transformation into standard stereotactic space, smoothing and statistical analysis²⁹. All measurements per condition were averaged across subjects. State-dependent differences in global flow were co-varied out using ANCOVA. Main effects and interactions were assessed with contrasts of the adjusted task means, using *t* statistic subsequently transformed into normally distributed *z* statistic. The resulting set of *z* values constituted a statistical parametric map (SPM{*z*}), which was then thresholded at *P* < 0.001.

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