

RECOGNITION MEMORY: WHAT ARE THE ROLES OF THE PERIRHINAL CORTEX AND HIPPOCAMPUS?

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The hallmark of medial temporal lobe amnesia is a loss of episodic memory such that patients fail to remember new events that are set in an autobiographical context (an episode). A further symptom is a loss of recognition memory. The relationship between these two features has recently become contentious. Here, we focus on the central issue in this dispute — the relative contributions of the hippocampus and the perirhinal cortex to recognition memory. A resolution is vital not only for uncovering the neural substrates of these key aspects of memory, but also for understanding the processes disrupted in medial temporal lobe amnesia and the validity of animal models of this syndrome.

Since the seminal article by Scoville and Milner¹ in 1957, clinical investigations of medial temporal lobe amnesia have centred on the hippocampus as the critical locus of damage. A standard feature of this classical anterograde amnesic syndrome is a loss of recognition memory. However, recent animal work highlights a major role in recognition memory not for the hippocampus but for a subadjacent region, the perirhinal cortex. Thus, groups working with rats and monkeys all agree that the severity of impairment in standard tests of recognition memory in these species is greater after perirhinal lesions than after hippocampal lesions, even though there is still controversy about the magnitude of impairment after hippocampal lesions^{2–12}. Here, we seek to clarify this apparent conflict by considering potentially different roles in recognition memory for the hippocampus and perirhinal cortex, and by asking whether these potential roles can be dissociated. In short, can recognition memory be explained by a single-process model?

Recognition memory
Recognition memory is a fundamental facet of our ability to remember. It requires a capacity for both identification and judgement of the prior occurrence of what has been identified¹³. The most parsimonious model regards recognition memory as a unitary process directly linked

to other forms of explicit memory and hence dependent on the same systems^{14–16}. By this account, recognition memory is an integral component of the class of memory lost in amnesia. An alternative view is that there are different component processes within recognition memory^{13,17,18} and that only one of these processes maps directly onto the class of memory that is always lost in anterograde amnesia¹⁰.

For example, if you encounter a person in the street, you might recollect information about them such as where you previously met or their name. This will enable you to recognize that person as someone you have previously met. Alternatively, you might immediately know that the person is familiar but recollect no other information. By this analysis, it seems that, subjectively, it is possible to consider recognition memory as composed of at least two processes. The first is familiarity discrimination ('knowing' — I know I have seen you before but I do not remember a specific episode) and the second is recollective matching ('remembering' — I know I have seen you before because I can remember a specific episode), which automatically implies a successful familiarity judgement. Single-process models of recognition memory assume that 'knowing' reflects a weaker trace strength than 'remembering', and that these two processes differ only quantitatively. By contrast,

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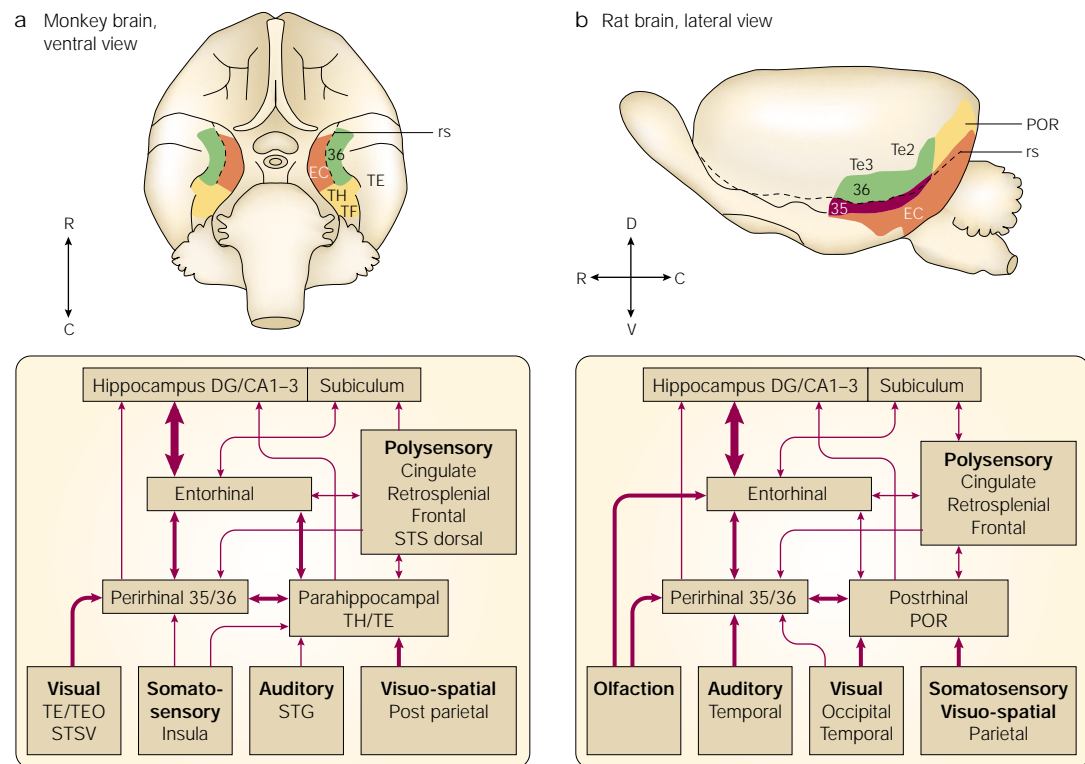


Figure 1 | **Multiple routes for sensory information reaching the hippocampus.** The positions of the perirhinal, entorhinal, parahippocampal and postrhinal cortices are shown in the monkey (macaque) brain (a) and rat brain (b). The perirhinal cortex, as defined here, includes Brodmann's areas 35 and 36 (REF. 146) and the hippocampus also refers to the dentate gyrus, subfields CA 1–3 of the hippocampus and the subicular complex. The connective diagrams show parallel routes by which sensory information reaches these cortical regions and from there reaches the hippocampus^{146–151}. The thickness of the arrows indicates the size of the projection. (DG, dentate gyrus; EC, entorhinal cortex; POR, postrhinal cortex; rs, rhinal sulcus; STG, superior temporal gyrus; STS, superior temporal sulcus; SUBIC, subicular complex.) (Adapted with permission from REF. 146 © (1989) Elsevier Science.)

dual-process models view these processes as qualitatively different modes of recognition memory. This article considers the evidence for two different modes of recognition memory and whether they can be mapped on to the perirhinal cortex and hippocampus. (The term 'hippocampus' is used to include the dentate gyrus and subicular complex as well as the hippocampus itself (FIG. 1).)

Evidence from neuronal recordings in animals
 Electrophysiological recordings^{19–24} from the medial temporal lobe of monkeys performing RECOGNITION MEMORY TASKS using large stimulus sets have repeatedly revealed that some neurons respond less to subsequent presentations of a visual stimulus that has been previously encountered^{25–31}. The reduction in neuronal response carries information about the prior occurrence of that stimulus and might signal either the relative familiarity or the relative recency of that stimulus^{20–22,24} (FIG. 2). Response enhancements following stimulus repetition occur much less often, except under specialized conditions^{22,24,32}. Response reductions occur commonly (~25% of recorded neurons) in the anterior inferior temporal cortex, notably in the perirhinal cortex, but are much less frequent (<~1%) in the hippocampus^{19,22–24,29,33–35}. Although such hippocampal

responses have been found at low levels in two studies^{33,35}, they were observed at no more than chance levels in two other studies^{24,34}.

Perirhinal cortex. The reduction in neural response to repeated stimuli that is observed in perirhinal and adjacent association cortex has many of the properties required for a substrate of a familiarity and recency discrimination system^{24,29}. That is, as a population, the responses show very rapid (~75 ms) and efficient familiarity and recency discrimination for individual visual stimuli^{22,24}. These responses also show single-trial learning, long-term storage (>24 h) of information and high information storage capacity. Furthermore, these response changes are endogenous and automatic: they do not require specific prior training and occur whether or not an animal is required to make behavioural use of the information. Neurons with these response properties have been described in the perirhinal cortex of rats as well as monkeys^{26,28,29,36}. By contrast, only a few hippocampal neurons have been found to change their response after the repetition of individual stimuli, and these response changes have much longer latencies than those of perirhinal neurons and do not persist for 24 h^{24,35}. Unfortunately, although neuronal responses that are related to the performance of a recognition

RECOGNITION MEMORY TASKS
 Tasks that rely on a judgement of prior occurrence for their solution.

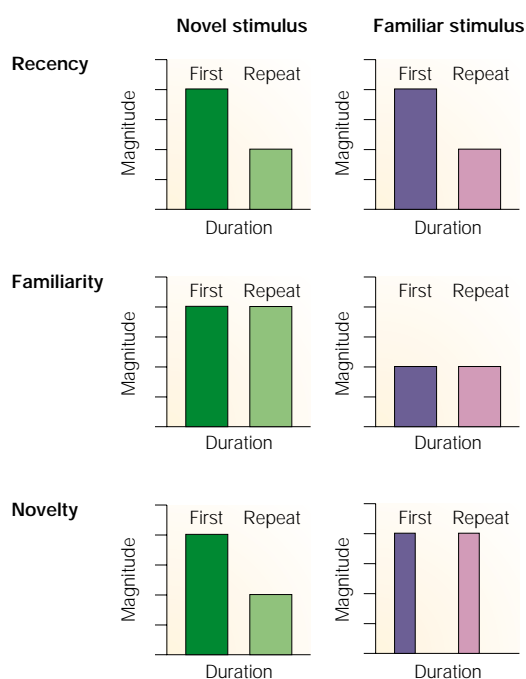


Figure 2 | Response decrements on stimulus repetition: separable encoding of recency and familiarity information. Three patterns of neuronal response reduction on repetition of visual stimuli have been found in the anterior inferior temporal cortex, including the perirhinal cortex²⁴. By repeating both novel and highly familiar stimuli, it can be shown that these responses separately encode recency and familiarity, so providing a potential substrate for our ability to know both whether an item is familiar or unfamiliar and whether it has been seen recently or not. As illustrated, neurons with ‘recency responses’ signal that a stimulus has been seen recently by a reduced response to that stimulus but do not signal whether it is unfamiliar or highly familiar, because the response to both types of stimulus is the same. ‘Familiarity responses’ signal that a stimulus is highly familiar (has been seen many times on previous days) by a reduced response to such a stimulus but do not signal that a stimulus has been seen recently (within the past several minutes), because the responses to its first and second occurrence are the same. ‘Novelty responses’ signal that the stimulus is being seen for the first time (or at least has not been seen for some weeks previously) by a vigorous response that is much weaker when the stimulus is repeated and much briefer (thinner bar) if the stimulus is highly familiar.

DELAYED-MATCHING-TO-SAMPLE TASKS

In such recognition memory tasks, presentation of a stimulus is followed by a delay, after which a choice is offered. In matching tasks, the originally presented stimulus must be chosen; in non-matching tasks, a new stimulus must be selected. With small stimulus sets, the stimuli are frequently repeated, thus becoming highly familiar. Hence, typically, such tasks are most readily solved by short-term or working memory rather than by long-term memory mechanisms.

‘TRIAL UNIQUE’ STIMULI

Stimuli that are used on only one trial, or at least very infrequently, in a delayed matching task.

memory task have been reported in the human hippocampus, it is not clear that these relate to mnemonic processing rather than other aspects of the task³⁷.

Importantly, the reduction in the firing rate of the perirhinal neurons occurs after a single exposure of an infrequently presented stimulus and is even observed when many stimuli must be remembered simultaneously. This indicates that the observed reduction in neural response must depend on long-term memory²⁹. Changes in firing rate are also observed in DELAYED-MATCHING TASKS that use small stimulus sets and, as a consequence, have frequently repeating stimuli. Typically, in these tasks, only one stimulus need be remembered at a time^{29,34} and response differences between stimuli presented on matching and non-matching trials occur in both the

hippocampus and the anterior temporal association cortex^{27,31,34,38–43}. However, these latter tasks chiefly rely on short-term memory mechanisms. Perirhinal lesions impair performance of the ‘TRIAL UNIQUE’ STIMULUS (long-term memory) variant of the delayed-matching task but not the variant in which the stimuli repeat frequently, where working memory is taxed⁴⁴. This, together with differences in the ease of training these tasks, suggests that they rely on different neural substrates⁴⁵. Although match–mismatch response differences are likely to be important in the solution of repetitive recency discrimination tasks (by signalling what was last presented), they do not signal the relative familiarity of a stimulus³⁴; accordingly, they cannot provide a general substrate for familiarity discrimination²⁹.

Two other types of activity that could be related to the prior occurrence of stimuli have been described in anterior inferior temporal cortex, including the perirhinal cortex, under conditions where the animal needs to remember only one stimulus at a time. First, under these conditions, neuronal activity related to a prior stimulus occurs in the delay before an animal must make a familiarity discrimination about that stimulus^{22,34,41,46}. Second, if an animal has been trained to expect rewards for repetitions of a target stimulus but not of non-target stimuli, responses to the target stimulus can be enhanced rather than reduced³². Such response enhancements have, however, only been observed when the animal has been so trained. Reduced responses to repetition of stimuli are, by contrast, found even when the prior occurrence of many different stimuli must be remembered at the same time, and whether or not the animal has received specific training^{24,29}. So, despite the number of recording studies in perirhinal and adjacent cortex, response reduction following stimulus repetition is the only known neuronal substrate within this cortex that has the properties required for a generalized recency and familiarity discrimination system for individual items²⁹.

Hence, there is strong a priori evidence from recording studies that neurons in perirhinal and adjacent visual association cortex (anterior area TE) are involved in discriminating the recency and familiarity of individual visual stimuli. Moreover, there is strong evidence that the crucial processing occurs in perirhinal and adjacent visual association cortex, independently of the hippocampus. Thus, the latency for discrimination of prior occurrence is (within current measurement) as fast as the latency for identification within monkey perirhinal cortex and anterior area TE^{22,24}. The rapidity of this response seems to exclude top-down input from the hippocampus (or prefrontal cortex). Indeed, the sparsity and long latency of any appropriate hippocampal responses accords with this lack of hippocampal dependency^{24,35}. These changes in the response properties of the neurons in anterior temporal cortical areas are not the passive reflections of changes occurring earlier in the visual pathway because these do not persist for more than a few seconds or a few intervening trials^{47–50}. This suggests that the response differences that are important for long-term memory are likely to be generated first within perirhinal and neighbouring visual association cortex^{24,29}.

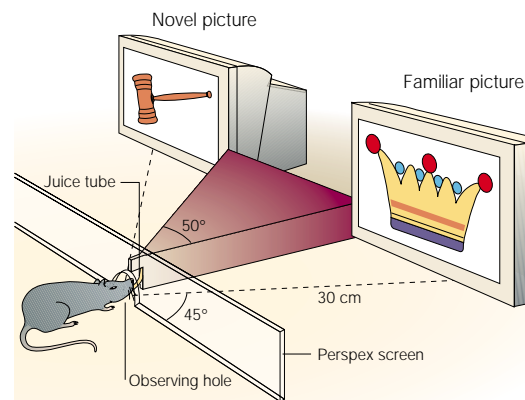


Figure 3 | The paired-viewing procedure for simultaneously presenting novel and familiar stimuli. In the paired-viewing procedure⁷², a rat views two pictures simultaneously, one novel and the other seen many times previously, while its head is in a hole in a perspex screen. A central partition ensures that each picture is seen by only one eye and is initially processed by the opposite cerebral hemisphere. In this way, novel and familiar stimuli can be shown under the same conditions of alertness and motivation, and with similar eye movements.

The hippocampal area. Evidence linking the hippocampus to the signalling of the relative familiarity of an infrequently encountered individual stimulus is relatively weak^{19,24,27,33–36,51}. Many recording studies have established that hippocampal neuronal responses carry information, particularly spatial information, about an animal's environment. The extensive literature on place fields establishes that hippocampal neurons encode a rat's position in space, although there is also evidence that they signal information about other relationships between stimuli^{27,30,40,42,43,52–61}.

Significantly, neurons within the monkey and rat hippocampus have been shown to encode information about the relative familiarity of a visual stimulus occurring in a particular spatial position^{31,33,61}. This suggests that the hippocampus has a role in recognition memory when such memory involves information that has a spatial or associational component; that is, remembering that a particular stimulus occurred in a particular place^{31,62–65}. It also seems that hippocampal neurons might encode prior occurrence when a monkey has to decide in which of two lists a stimulus previously occurred (J. -Z. Xiang and M.W.B., unpublished observations). By contrast, perirhinal neurons seem to be much less involved in the encoding of allocentric spatial information⁶⁶. Finally, the entorhinal cortex might operate as a junctional region between the perirhinal cortex and the hippocampus (a view consistent with its anatomical relations): its neurons encode information about both stimulus familiarity and spatial information^{24,29,51,67,68}.

Therefore, much electrophysiological evidence indicates that reductions in the response of perirhinal neurons on stimulus repetition provide a potential substrate for familiarity discrimination for individual items. By contrast, the responses of hippocampal neurons provide

a potential substrate for recognition memory processes involving spatial and other associative information.

Evidence from immediate-early-gene imaging
The functional division between the hippocampus and the perirhinal cortex outlined above is supported by activation studies that image the activity of populations of neurons using IMMEDIATE EARLY GENES (IEGs). The IEG C-FOS is commonly expressed when neurons are active^{69,70}. In the present context, the Fos protein can be visualized and used to determine the anatomical distribution of neural responses to the presentation of an individual novel or familiar visual stimulus. More neurons are activated in rat perirhinal cortex (and adjacent temporal visual association cortex, area Te2) by novel stimuli than by familiar stimuli⁷¹, which is consistent with the electrophysiology results described above. However, similar changes were not observed in the hippocampus^{71,72}. This increase in perirhinal but not hippocampal neuronal activity for novel stimuli is found even when the behavioural design involves interhemispheric comparisons^{72,73} that ensure precise behavioural control of motivation and alertness (FIG. 3).

By contrast, Fos imaging studies reveal major hippocampal and postrhinal, but not perirhinal, involvement in situations in which the familiarity discrimination involves a spatial or associational component, such as an encounter with a new environment or a new spatial arrangement of familiar individual items^{74–77}. In this context, an environment can be regarded as a set of individual items in a particular spatial relation to each other. Recognition memory also encompasses the discrimination of the novelty or familiarity of a spatial arrangement of a set of equally familiar individual items (consider your reaction if the furniture in your room was rearranged). Again, the hippocampus and postrhinal, but not perirhinal, cortex are activated when a rat views novel rather than familiar spatial arrangements of a set of familiar objects⁷³.

So, Fos imaging demonstrates a double dissociation between the activation of perirhinal cortex and the hippocampus in processes related to recognition memory^{73,77}. Many neurons of the perirhinal cortex but not those of the hippocampus are activated differently by novel and familiar individual stimuli, whereas the hippocampus and POSTRHINAL CORTEX are activated differently by novel and familiar spatial arrangements of sets of stimuli.

Evidence from animal lesion studies

Both single-unit recordings and IEG studies point to a clear distinction between the involvement of the perirhinal cortex and hippocampus in recognition memory. This has been further explored in lesion studies that have examined recognition memory for individual visual objects and for spatial arrays of sets of stimuli. Surgical removal of the perirhinal cortex in monkeys and rats impairs recognition memory for individual objects^{3–5,7,8,78}; in the case of monkeys, this deficit is severe and seemingly permanent. The effects of entorhinal lesions are less severe and transitory^{3,79}, whereas lesions of parahippocampal areas TH and TF (FIG. 1) have no apparent effect

IMMEDIATE EARLY GENES
Immediate early genes control the transcription of other genes, and thereby provide the early stages in the control of the production of specific proteins.

C-FOS
An immediate early gene that is rapidly turned on when many types of neuron increase their activity. It can therefore be used to identify responsive neurons.

POSTRHINAL CORTEX
The region of rat cortex posterior to the perirhinal cortex, thought to be analogous to parts of the parahippocampal gyrus in primates.

on this ability in monkeys⁸⁰. It has also been shown that lesions including the perirhinal cortex will impair tactile and olfactory recognition memory^{4,81}, indicating that the recognition memory deficit is not confined to the visual modality, in parallel with human anterograde amnesia. This allays concerns that the effect of the perirhinal lesion on visual recognition memory arises from a perceptual component⁴⁴ (but see REF 82).

By comparison, standard tests of object recognition memory are more mildly impaired by hippocampal lesions than by perirhinal lesions¹⁰. Whereas one study of monkeys found normal levels of performance even after lengthy retention delays⁹, others have reported variable degrees of impairment that are most apparent at longer retention delays^{6,11,12,83}. A similar pattern is found in lesion studies with rats, in which hippocampectomy either has no apparent effect or produces very small deficits^{5,84–86}. Hippocampal system damage has more reliable effects on tasks in which the stimuli involve common elements that are rearranged within a scene⁶⁵. Similarly, neurotoxic hippocampal lesions in rats produce abnormal orientation responses to novel re-pairings of individually familiar stimuli⁸⁷. These findings point to a role in recognition memory that emerges more consistently when the familiarity judgement depends on associations between items rather than on the individual items themselves. Although these associations will often be spatial, associations involving non-spatial attributes might also prove to involve the hippocampus^{31,63} (although it is the perirhinal cortex that has been implicated in the temporal relationship between stimuli established by paired associate learning^{88,89}).

Removal of the hippocampus in rats produces devastating impairments on spatial navigation tasks and on tests of spatial working memory that rely on the animal being able to make recency discriminations about locations it has visited^{84,90–92}. In contrast to its effects on recognition memory, removal of the perirhinal cortex in rats often has no apparent effect on spatial tasks^{7,93,94}. Even when deficits are observed, they are less severe than those after hippocampectomy^{91,92}. So, when recognition memory judgements involve spatial information, the hippocampus and not the perirhinal cortex is the critical structure.

Although these findings have dissociated the perirhinal cortex from the hippocampus, these two regions also have functional interactions. This is to be expected from the anatomical interconnections between the two regions²⁴ and, indeed, behavioural evidence for such interactions is found in situations in which information about a particular object and a particular location are used or recognized⁹⁵. Such tasks are impaired by combined perirhinal and postrhinal removal, although standard spatial tasks seem to be unaffected by the same cortical lesions. Furthermore, by using CROSSED LESIONS in monkeys, evidence has emerged that the perirhinal cortex and fornix (the main pathway interconnecting the hippocampal formation with subcortical structures) cooperate in memory tasks in which the linking of a specific object to a specific place within a scene aids performance⁹⁶.

This result relates closely to recent Fos imaging studies that indicate that the hippocampus is activated differently when the particular spatial locations of specific items are essential to judgement of prior occurrence⁷³. Although these findings are consistent with the idea that the perirhinal cortex supplies object-based information to hippocampus-based associational processes, there is no evidence that this object-based process depends on the perirhinal familiarity-detection mechanism. Indeed, the mismatches between hippocampal and perirhinal lesion effects suggest otherwise. There is no a priori reason why the involvement of the perirhinal cortex in familiarity discrimination excludes it from contributing to other important perceptual and mnemonic functions (for example, object perception^{96,97} and paired associate learning^{88,89}). The fact that only a proportion of perirhinal neurons are involved in familiarity discrimination (as shown by neuronal recording²⁹) makes this feasible.

Evidence from clinical studies

If there are at least two forms of recognition memory and they have different anatomical bases, it would be predicted that, whereas focal hippocampal lesions in humans might induce anterograde amnesia for episodic information, certain types of recognition memory tasks should be relatively spared. This sparing should be most evident for tests that can be solved by discriminating the familiarity or recency of discrete items. By contrast, tests that can only be solved by using spatial or associative information should be more impaired, even when task difficulty is equated. Given that many temporal lobe amnesics suffer damage to both hippocampal and perirhinal regions, it can also be expected that the typical finding will be of dense impairments across different types of recognition memory test, so that specific dissociations might be rare.

In fact, a dissociation known to exist in amnesia concerns repetition priming (perceptual fluency), and this would seem to offer the most obvious account of a spared familiarity signal. Repetition priming refers to the way that the processing (for example, identification) of a stimulus is aided by prior exposure to that stimulus even though there is no explicit recall of the pre-exposure event. Despite this, clinical studies show that the putative familiarity signal cannot be the same as repetition priming⁹⁸. Many amnesics show normal levels of repetition priming but have very poor recognition memory^{99,100}. This difference is most strikingly demonstrated by a patient who, following herpes encephalitis, has extensive medial temporal lobe damage that bilaterally involves both the hippocampus and the perirhinal cortex¹⁰⁰. His recognition performance remains at chance for a wide variety of tasks, even for the same information for which he has shown priming¹⁰¹. Conversely, cortical damage in other regions can disrupt priming but leave recognition memory intact¹⁰². These data establish that the neural substrates of priming and familiarity discrimination differ, but they do not exclude the possibility that initial processes underlying these separable forms of memory might share a common mechanism²⁹. Finally, recent studies have helped to show that

CROSSED LESIONS

Unilateral lesions in two different sites in opposite hemispheres. Behavioural impairment following such lesions establishes that the regions are functionally dependent on each other.

the recognition memory deficit in temporal lobe amnesics with perirhinal damage is not simply perceptual^{103,104}.

Are there any convincing cases of spared recognition memory in amnesia, irrespective of site of pathology? A small number of group studies of amnesics clearly suggest spared recognition memory (see also REFS 105–107) but these studies are limited by their failure to explore task difficulty in a comprehensive manner. Although it is rare, a number of single-case studies clearly show that recognition memory can be spared and that this is not simply a confound of task difficulty or severity of amnesia^{108–110}. The case described by Parkin *et al.*¹⁰⁹ is of special interest because the preserved recognition memory seemed to rely on familiarity judgements, although the pathology (from an aneurysm of the anterior communicating artery) did not directly involve the hippocampus or its outputs.

A more direct test of the models considered in this article is whether selective hippocampal pathology can spare recognition memory, as tested by familiarity discrimination, and yet severely disrupt recall (recollection). Again, there is evidence from single cases that this can occur^{111,112}; there is also supportive evidence from cases of fornix damage^{106,113}. Of special relevance is a case^{112,114} with bilateral shrinkage of the hippocampus but apparent preservation of adjacent regions. This subject shows a persistent deficit in episodic memory but has strikingly preserved recognition memory, particularly in tests that can be solved by judging the prior occurrence of individual items. When recognition memory deficits are observed, they are most evident in associative recognition memory tasks (such as recognizing that item A has been paired with item B but not with item C, in contrast to recognizing the prior occurrence of individual items A, B or C). Similar selective deficits for associative recognition memory following early hippocampal damage have been reported by Vargha-Khadem and colleagues¹¹¹.

The assertion that selective hippocampal damage can cause a relative sparing of recognition memory has been challenged, and a series of cases with hippocampal pathology following hypoxia supports the alternative view, as all cases were significantly impaired on a wide variety of recognition memory tests^{115,116}. In fact, both single- and dual-process models predict that hippocampal pathology will impair recognition memory; the critical issue is whether the deficit is largely confined to recollection-based (associative) recognition memory. To begin to address this issue, dual-process models of recognition memory are being applied to amnesia. For instance, Yonelinas and co-workers¹¹⁷ have developed tests that distinguish familiarity and recollective aspects of recognition memory in normal subjects.

In amnesics with extensive pathology, there is typically a loss of both putative components of recognition memory¹¹⁸ (but see REF. 119). The critical test, however, concerns cases with more selective pathology. In one study, the proportion of recognition memory ascribed to familiarity or recall (determined subjectively) was analysed in a group of amnesics with pathology centred in the hippocampus^{99,120}. These subjects were impaired in both components of recognition memory. Although the

full extent of their temporal-lobe pathology cannot be confirmed until after death, these data seem to be more supportive of a single-process model of recognition memory. So, although clinical studies have been of immense value in isolating the contribution of repetition priming and in showing that recognition memory can be spared relative to recall, they have yet to provide a resolution of the debate about single- or dual-process models of recognition memory.

Evidence from human imaging studies

Imaging techniques might ultimately provide the strongest test of whether there are anatomical distinctions between subjectively different components of human recognition memory and hence of whether these processes are qualitatively different. Findings from EVENT-RELATED POTENTIALS (ERPs) and functional magnetic resonance imaging (fMRI) support the idea of multiple forms of recognition memory. In an informative ERP study, memory for encoding words was manipulated by subjects performing either a 'shallow' or a 'deep' DEPTH OF PROCESSING task¹²¹. During a subsequent word-recognition task, previously exposed words produced ERP activity in three different anatomical populations that were functionally dissociable¹²¹. One population (parietal) was insensitive to accuracy of recognition and depth of processing, and was therefore assumed to reflect implicit memory (priming). A second population (above the left parietal cortex from 500 ms after stimulus onset) was sensitive to depth of processing and was thought to correspond closely to conscious recollection. The third pattern (maximal over the frontal scalp 300–500 ms after stimulus onset) was thought to reflect item 'familiarity' as it was only found for recognized old items and was insensitive to depth of processing¹²¹. Similar distinctions between a recollective parietal (P600) effect at 400–800 ms and an earlier frontal (FN400) effect at 300–500 ms thought to reflect familiarity have since been made in studies using different types of stimulus to distinguish these forms of response^{122,123}.

The convergent results show that there are qualitatively different populations of neuronal activity involved because these occur in different locations and also have different properties, reflecting the likelihood of using recollection or familiarity to distinguish target items. Consistent with these distinctions, ERP studies have revealed different responses for items recognized with or without associated contextual information¹²⁴. Finally, ERP differences have been evaluated using the distinction between 'REMEMBER' (R; recollect the specific encoding experience) and 'KNOW' (K; feels familiar) judgements¹²⁵. Enhanced ERPs for R compared with K judgements were found over left parietotemporal and bilateral frontal electrode sites¹²⁵. Although the study suffered from low signal/noise ratio, the parietal recollective response is a common feature of these ERP studies¹²³. Taken together, ERP studies provide strong evidence that dissociable brain processes underlie recognition memory, although they do not establish the anatomical basis of these processes with any great precision owing to the low spatial resolution of the technique.

EVENT-RELATED POTENTIAL
Neural recordings made on the scalp in which activity changes in populations rather than specific neurons can be temporally linked to an event.

DEPTH OF PROCESSING
As the processing of information moves from perception-based features ('shallow') to semantic features ('deep'), subsequent recall is aided even though priming is little affected.

REMEMBER-KNOW PARADIGM
A subjective decision is made about whether the previous occurrence of a recognized stimulus is linked with the retrieval of the learning episode ('remembered') or whether there is merely a feeling of familiarity ('knowing').

As the ERP technique with scalp electrodes is relatively insensitive to changes in the inferior temporal lobe, a study that used electrodes within the temporal lobe is of special interest¹²⁶. With these electrodes, ERP differences that predicted whether words would subsequently be recalled or forgotten occurred at 310 ms in the anterior parahippocampal gyrus and at 500 ms in the hippocampus. Although the time difference is consistent with a faster perirhinal system and a slower hippocampal system, the results do not show whether this reflects a single, serial system or a dual, parallel system.

The processes underlying recognition memory have also been examined with fMRI. In an elegant EVENT-RELATED fMRI task, different bilateral medial temporal lobe activations were found during encoding. These activations predicted not only whether visual scenes would be successfully recognized on subsequent presentation but also whether they would be remembered rather than merely described as feeling familiar; that is, whether they would be R (larger activations) or K (smaller activations)¹²⁷. As this pattern can be accommodated by both single- and dual-process models, two other event-related studies compared retrieval activity associated with R or K responses^{128,129}. Both studies found evidence for a dissociation between components of recognition memory for words. One study¹²⁸ found that R and K responses produced different activations in frontal cortex, along with an increased response in the left posterior hippocampus for 'remember' compared with 'not remember' responses¹²⁸. The second study was even more striking, having used a slightly different technique to aid R and K judgements in a word-recognition task¹²⁹. A clear, qualitative difference within recognition memory was observed, with activity in the hippocampus only increasing when retrieval was accompanied by conscious recollection (R) of the learning episode¹²⁹. Critically, familiar (K) responses did not produce a weaker version of the R response; instead, the hippocampal activity for K responses could not be distinguished from that for correct rejections or misses (failure to recognize the sample).

Other pertinent findings come from an fMRI study of both encoding and retrieval¹³⁰ in which the signal from the parahippocampal region decreased as pictures of scenes became familiar. Such decreases in response to familiar compared with novel stimuli have also been reported in other studies in inferior temporal cortex^{131–134} and perirhinal cortex¹³⁵, and are in accord with the electrophysiological and immunohistochemical data from experiments with animals. By contrast, recognition memory for the names of previously studied drawings increased hippocampal responses^{130,136}. The nature of this second task might be relevant because the stimuli used in the recognition memory test (words) had strong associations with the stimuli shown at acquisition (pictures) but were not the actual sample stimuli themselves^{130,136}. Under such circumstances, the process of recognition memory is likely to require recollection or associative recall of the encoding event, and so provide optimal conditions to detect hippocampal activation. Recent studies have, in fact,

shown that this associative condition is not necessary to see increased fMRI activity in the hippocampus during retrieval success in a recognition test¹³⁷. However, as predicted by dual-process models, the condition that encourages more associative processing does produce more hippocampal activity. The critical test is whether hippocampal activation still occurs under conditions that preclude the recollective or associative aspects of recognition memory.

Why have two recognition memory systems? Studies of human visual recognition memory have demonstrated its speed, accuracy and huge capacity^{138,139}. Moreover, under a variety of controlled conditions (under which task instructions do not require decisions about recollection to be provided first), familiarity (K) decisions are made faster than recollect (R) decisions^{139–141}. Intriguingly, this latency difference parallels the temporal ERP differences that are thought to reflect familiarity and recall¹²³. Clearly, fast familiarity discrimination leads to rapid and accurate detection and hence to a rapid reaction to novelty, and this should provide an evolutionary advantage. However, modelling suggests that, to be optimally fast, such a system might not be able to provide associative recollection^{142,143}.

A neural network model based on biologically plausible parameters and Hebbian learning rules indicates that it is indeed possible to construct a system that achieves very fast and accurate familiarity discrimination^{142,143}. The model uses learning rules based on long-term depression and long-term potentiation, forms of plasticity that are found in perirhinal cortex as well as other brain areas^{144,145}. Given these rules and appropriate connectivity, the theoretical neurons of the model have responses that mimic the types of neuronal response found in perirhinal cortex²⁴. Moreover, the theoretical network performs familiarity discrimination with great efficiency compared with systems that rely on associative learning, in terms of both the relatively small number of neurons required and the speed of decision making. Furthermore, the possession of a specific familiarity discrimination system has another advantage: it removes the need for perceptual categorization networks to permanently register the prior occurrence of stimuli^{24,29}.

In this scheme, categorization networks are freed from the necessity of making long-term changes to their synaptic connections each time a novel stimulus is encountered. The novel stimulus can be perceived and identified by the unique pattern of activation that it evokes within the categorization network; its occurrence can be registered and stored, and its novelty or familiarity judged by a separate familiarity discrimination network. However, categorization networks will need to be modified if associations of the stimulus are to be remembered, or if a new category needs to be formed: the familiarity discrimination network as envisaged does not perform these functions. Indeed, a second associative (hippocampal) system will be required to perform this function and so to allow associative or recollective aspects of recognition memory.

EVENT-RELATED fMRI
Functional magnetic resonance imaging (fMRI) in which it is possible to detect signal changes after single events.

Table 1 | Perirhinal and hippocampal temporal lobe systems: summary of putative differences

	Perirhinal system	Hippocampal system
Properties	Rapid Automatic Non-effortful Single trial Single item Familiarity and recency discrimination components of recognition memory 'Knowing' rather than 'remembering' prior occurrence Probably economical in number of neurons required	Slower Associational Multi-item Spatial Episodes/events Recollective aspects of recognition memory 'Remembering' rather than 'knowing' prior occurrence Much richer and more powerful in capabilities and correspondingly likely to require the involvement of far more neurons
Neuronal responses	Many neurons with responses that signal information about the novelty, recency or familiarity of individual items Previously encountered items typically evoke reduced neuronal responses Other neurons signal item information regardless of prior occurrence Influence of spatial information relatively unexplored Some neurons signal certain types of associational information	Few neurons signal the prior occurrence of individual items Many neurons signal information about spatial position, associations of places, or associations between items Evidence of signalling of novelty or familiarity of items occurring in particular places (familiarity discrimination for combined object and place information)
Immunohistochemical imaging (Fos)	Different staining produced by novel and familiar individual visual pictures Different staining produced by novel and familiar arrangements of familiar items in postrhinal but not perirhinal cortex	Relatively few stained neurons (different or not) after showing novel or familiar individual pictures Different staining produced by novel and familiar arrangements of familiar items, and by radial-maze performance, in novel and familiar environments
Animal lesions	Impairment of single-item visual, tactile and olfactory recognition memory Spatial memory tasks relatively unimpaired Impairment of object-in-place tasks	Relatively less impaired single-item visual, tactile and olfactory recognition memory Impairment of spatial memory tasks Impairment of object-in-place tasks
Clinical findings	Lack of selective lesions Uncertainty about the location and extent of the human equivalent of the monkey perirhinal cortex makes the interpretation of current evidence difficult	In rare cases, relative sparing of recognition memory involving familiarity discrimination for individual items, with impairment of episodic (recollective) memory and associational recognition memory
Human event-related potentials (ERPs)	ERPs for 'know' recognition responses are fast Qualitative differences between ERPs for 'remember' and 'know' responses, but the anatomical substrates are uncertain	ERPs for 'remember' recognition responses are slower Different effects on 'remember' and 'know' responses in recognition memory have yet to be extensively examined in relation to their anatomical substrates
Human functional imaging	Some studies find reduced activation with stimulus repetition	Evidence for greater activation for recollective and associative recognition memory processes than for familiarity discrimination

Are the differences qualitative or quantitative? Much of the evidence from studies of activity in the intact brain favours a qualitative difference between the roles of the hippocampus and perirhinal cortex in recognition memory processes. Moreover, where the differences seem to be quantitative, they go in opposite directions for different functions. So, in animals, a difference in the response of neurons to novel and to familiar but infrequently encountered individual stimuli in the perirhinal cortex is so common, and typically so large, that it can be determined using population measures such as Fos imaging. In the hippocampus, neuronal response differences to such stimuli are found rarely and have not been shown to persist over very long intervals. By contrast, the responses of many hippocampal neurons carry spatial or associational informa-

tion, whereas perirhinal neurons do not seem to be so important in these processes. Such a double dissociation cannot simply be explained by a difference in unitary trace strength. In addition, fMRI studies indicate dissociations between hippocampal and perirhinal (parahippocampal) involvement in processes related to recognition memory. Furthermore, ERP studies have established qualitative differences between brain potentials related to recollection and familiarity discrimination, although these studies do not establish their precise anatomical substrates.

Dissociations in behaviour produced by lesions of the rat or monkey brain seem to be largely quantitative rather than qualitative. The deficit in familiarity discrimination is greater, and that in spatial tasks smaller, following perirhinal than hippocampal lesions but, at

least in some studies, both lesions produce measurable deficits in both types of task. However, again, the dissociation is double for recognition memory involving spatial information compared with that involving individual items. By contrast, the evidence of dissociation from human amnesic patients is equivocal. It remains possible that the failure to establish dissociations in humans arises both from the difficulty of determining the particular recognition memory processes being used and from the rare availability of subjects with critical, precisely determined pathology. So, although there is convincing evidence for a qualitative difference in hippocampal and perirhinal contributions to recognition memory, the behavioural case for dissociation remains to be proved.

Conclusions

Although the hippocampus and the perirhinal cortex will often function as interacting components of an integrated recognition memory system, as argued above, there are increasing indications that their contributions are different and can be dissociated (TABLE 1). Importantly, evidence from animal studies indicates that a system centring on the perirhinal cortex is concerned with discriminating the familiarity and recency of occurrence of individual stimulus items, whereas a system centring on the hippocampus is concerned with judging the prior occurrence of constellations of stimuli. The evidence relating to the hippocampus from animal studies is strongest for spatial arrangements of

stimuli but, notably, events normally include spatial information (the place where they occur), so that recognition memory for episodes would correspondingly be expected to be affected by hippocampal lesions.

Convincing clinical tests of these ideas must involve the assessment of patients in whom circumscribed pathology has been established. Here, there is a further difficulty in the extent of the region of human cortex that performs the equivalent function in recognition memory compared with that ascribed to the perirhinal and adjacent cortex in animals. Moreover, in future clinical patient and imaging studies, the mental processes that the subjects are using to solve the task must be under more precise control to determine whether they involve associative recollection or associative discrimination as well as simple familiarity discrimination. Equally, it should not be assumed in animal studies that a more complex psychological process (associative recollection) will be used in tasks that can be solved using a simpler process (familiarity/recency discrimination). So, future animal studies that aim to model human amnesia need to consider how well any task parallels those used in humans, and which aspects of recognition memory are being taxed.

Links

ENCYCLOPEDIA OF LIFE SCIENCES **Amnesia** | **Learning and memory** | **Neural activity and the development of brain circuits** | **Neural networks and behaviour** | **Long-term potentiation**

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