THE ROYAL SOCIETY

doi 10.1098/rstb.2001.0946

Neural systems underlying episodic memory: insights from animal research

John P. Aggleton* **and John M. Pearce**

School of Psychology, University of Cardiff, Cardiff CF10 3YG, UK

Two strategies used to uncover neural systems for episodic-like memory in animals are discussed: (i) an attribute of episodic memory (*what*? *when*? *where*?) is examined in order to reveal the neuronal interactions supporting that component of memory; and (ii) the connections of a structure thought to be central to episodic memory in humans are studied at a level of detail not feasible in humans. By focusing on spatial memory (*where*?) and the hippocampus, it has proved possible to bring the strategies together. A review of lesion, disconnection and immediate early-gene studies in animals reveals the importance of interactions between the hippocampus and specific nuclei in the diencephalon (most notably the anterior thalamic nuclei) for spatial memory. Other parts of this extended hippocampal system include the mammillary bodies and the posterior cingulate (retrosplenial) cortex. Furthermore, by combining lesion and immediate early-gene studies it is possible to show how the loss of one component structure or tract can influence the remaining regions in this group of structures. The validity of this convergent approach is supported by new findings showing that the same set of regions is implicated in anterograde amnesia in humans.

Keywords: configural learning; hippocampus; amnesia; spatial memory; recognition; immediate early genes

1. INTRODUCTION

The anterograde amnesic syndrome demonstrates that specific brain structures are necessary for episodic memory. Once these individual structures are identified, the next goal will be to identify neural systems that are necessary for this form of memory, as no brain structure operates in isolation. A potentially vital piece of information associated with both research goals is that pathology in either the medial temporal lobe or the medial diencephalon can lead to similar amnesic syndromes. This raises the possibility that structures in these regions form part of a common system that is compromised in amnesia, a proposal first made explicitly by Delay & Brion (1969) following their analyses of Korsakoff's syndrome (principally a form of diencephalic amnesia) and examples of medial temporal lobe amnesia.

There are, however, severe limitations in using clinical findings to identify neural systems for memory processes. A persistent problem is that the pathology in clinical cases of amnesia is almost never confined to a single structure, making it impossible to be definitive about the necessary and sufficient pathologies for anterograde amnesia. Furthermore, studying the effects of pathology in the medial temporal lobe will not reveal whether that region is functionally linked in a vital way with the diencephalon, or vice versa. While there is little doubt that functional imaging (e.g. functional magnetic resonance imaging) will offer more and more clues as to the circuitry of different functions (e.g. when combined with structural equation modelling), this approach is not without its drawbacks. Anatomical resolution remains a problem for many sites, and null results (i.e. the lack of an overall change in a measure of activity) are difficult to interpret. As a consequence, attempts to assess the interdependence of different brain structures remain problematic. More general limitations arise from the fact that in order to identify and specify the full extent of a functional system, it is necessary to have a comprehensive knowledge of the connectivity of the structures under investigation. As has been observed (Crick & Jones 1993), our knowledge of the connectivity of the human brain is in fact very poor. This is principally because axonal transport techniques, widely used with animals, are not applicable with humans.

Research with animals provides a way of overcoming some of these problems as it offers the opportunity for high anatomical precision set within a detailed background knowledge of not only the connections of the target area but also its physiological, pharmacological and molecular properties. Furthermore, by applying disconnection techniques it is possible to address the issue of functional connectivity in a way that is simply not possible in humans. Animal research is not, however, without its own limitations. The most obvious is that brains have been subject to evolution, and the consequent variability means that generalizing across species can be fraught with problems. A less obvious, but even more fundamental problem, is whether it is possible to assess episodic memory in animals. Memory for a particular episode assumes retrieval of information concerning what happened, when it happened, and where it happened. To

*Author for correspondence (aggleton@cf.ac.uk).

examine these combined facets of memory in a single behavioural task has required especially ingenious solutions (see Clayton 2001), and the practicality and generality of such tests for detailed neuroscientific examination remain to be determined. Even if it is possible to examine these combined aspects of memory, this will still fall short of demonstrating 'episodic memory' if inherent in the definition is a sense of conscious or active retrieval associated with mentally travelling back in time to recollect (Tulving 1983). By applying the principle of parsimony or Lloyd Morgan's canon (Morgan 1894), it is evident that the involvement of processes such as deliberate access rather than automatic access cannot be assumed in animals and, hence, episodic memory cannot be demonstrated.

This review examines two strategies used in animal research to address these problems. It then considers how the resultant information has helped to identify functional systems for the processing of episodic-like memory. In the first approach, a particular component of episodic memory that can be examined in animals is identified and the neural systems underlying that facet of episodic memory identified. Relevant to this approach is the acknowledgement that 'the presence or absence of episodic memory is no more an all-or-none matter between species than it is within them' (Tulving 1984, p. 258). Accordingly, it should be possible to break down episodic memory into a number of simpler components and examine them separately. Given that an event in episodic memory will characteristically contain information concerning *what*? *when*? and *where*? these components form obvious targets for animal research. These attributes can then be examined singly or even in pairs (Gaffan 1992). Of these attributes, the question *where*? is not only the most amenable to behavioural testing, but there are also theoretical grounds for believing that some forms of spatial memory are especially pertinent for the analysis of episodic-like memory (see § 2).

The second approach is to focus on a brain structure that clinical studies have implicated in episodic memory, and then to explore the functional connectivity of that structure in animals. In fact, if both approaches are valid then the two sets of findings should intersect. This prediction is supported by studies into the neural basis of spatial memory. While a number of brain regions are important for the acquisition of new spatial knowledge (the *where*? component of episodic memory), the hippocampal formation is thought to be pre-eminent (O'Keefe & Nadel 1978; Morris *et al.* 1982; Maguire *et al.* 1996; Riedel *et al.* 1999; Holdstock *et al.* 2000; Rosenbaum *et al.* 2000). At the same time, clinical research into temporal lobe amnesia has shown that hippocampal damage is not only necessary but is almost certainly sufficient to induce anterograde amnesia in humans. Thus, the hippocampus is necessary for episodic memory as well as spatial processing. This intersection of evidence may reflect specific features of spatial memory.

2. STIMULUS BINDING AND THE RELEVANCE OF SPATIAL MEMORY

There are conceptual reasons why the study of episodic-like memory in animals (and especially rodents) has focused on spatial memory (Gaffan 1991). The notion

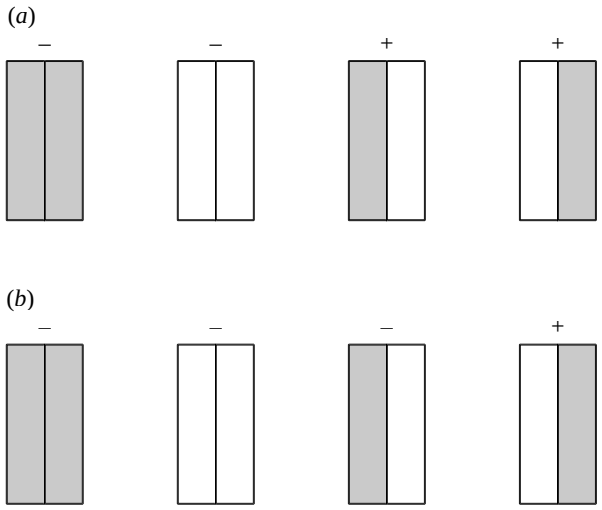

Figure 1. Design of a configural learning task (*a*) 'positive patterning', and (*b*) a 'structural learning' task. The grey and white bars depict elements of a discriminative stimulus that is always composed of two elements. The symbols + and − indicate which stimuli are associated with reward and non-reward, respectively. Neither discrimination can be solved by reference to a single element (white or grey) and, hence, are configural. The structural task has the added feature that the geometrical position of the cues is relevant.

that the episodic memory of an event can be regarded as a 'mental snapshot' (Tulving 1983; Gaffan 1992) underlines the importance of linking or binding elements that are in memory. Thus, to create a 'snapshot' it is not sufficient to encode just the component items, but it is also necessary to have them arranged in a unique, spatial array. In a similar way, the cues that are used for allocentric spatial processes have to be combined in a manner that involves not just the identity of the component cues but also their relative positions. (Allocentric processing refers to the use of the relative positions of distal cues to aid spatial location and navigation.) By this view, episodic memory entails a record not just of a list of items but of how those items are linked or bound together.

The possible relationship of episodic memory processes to the binding of cues in configural groups has been noted before (Sutherland & Rudy 1989; Rudy & Sutherland 1995; Gaffan 1998), and has led to numerous studies that have attempted to identify brain regions that are critical for the acquisition of configural tasks such as negative patterning, positive patterning, transverse patterning and biconditional discriminations. The diagnostic feature of these tasks is that they cannot be solved by merely learning about the significance of an individual cue or element, rather the animal must also learn about the significance of combinations of cues. In positive patterning, for example, an outcome occurs when two stimuli, A and B, are presented together but not when they are presented separately i.e. AB+, A−, B− (figure 1*a*). Such tasks have been used to test the importance of the hippocampus in configural memory, and while the data are not entirely consistent it is clear that rats with hippocampal or hippocampal system damage can still acquire many configural tasks (Gallagher & Holland 1992; Davidson *et al.* 1993; Rudy & Sutherland 1995; Bussey *et al.*

1998, 2001*b*). At first sight, this pattern of results would appear to contradict the premise described above, as hippocampal lesions consistently disrupt allocentric tasks yet are able to spare configural tasks. In fact, a key aspect of both 'snapshot' memories and 'allocentric' processing is that the elements have a structural component. That is, they have a specific spatial relationship to one another. This is not a demand of most configural tasks. It therefore appears that the closest parallel to mental snapshots may be found in a subclass of configural learning, known as 'structural' learning.

For a structural discrimination, the signals for reward and non-reward are composed of the same features, or elements, but they are assembled in different ways. Hence, a rat might be required to respond in one way when it is shown a black rectangle to the left of a white rectangle, and in a way different from the mirror image of this pattern (figure 1*b*). Animals can solve this type of problem (Wodinsky *et al.* 1952; George *et al.* 2001) and there are good reasons for believing that it might require processes additional to those normally considered necessary for the solution of other discriminations. According to a number of connectionist theories of discrimination learning (e.g. Gluck & Bower 1988; Pearce 1994) when a pattern of stimulation is presented to a network, it is decomposed into its components which then have the opportunity to enter either directly or indirectly into an association with the trial outcome. Because the two black and white patterns that have just been mentioned are composed of the same features, it follows that they will be indistinguishable to the network and a discrimination between them will not be possible. George *et al.* (2001) have argued that in order for the network to solve a structural discrimination, it must be extended to allow it to be sensitive to structural information—that is, information about the relationships among the features within a particular pattern of stimulation. Perhaps it is this aspect of discrimination learning that depends upon an intact hippocampus. If this is correct, then there would be no need for an intact hippocampus if animals are to solve a positive patterning discrimination. Although the same features are presented on both reinforced and non-reinforced trials, even a relatively simple network can solve a negative patterning discrimination because a different set of features is presented on each type of trial (Gluck 1991; Pearce 1994).

An ability to appreciate the structure among features to create unique scenes or snapshots would seem to be an important attribute of episodic memory. Suppose a rat must locate a goal that is hidden near one corner of a featureless, rectangular test arena. In order to find the goal the rat must appreciate that the rectangle is composed of long and short walls, and that the goal is, say, near one of the two corners where the short wall is to the left of the long wall. If animals were unable to respond on the basis of the relationship between the short and long wall they would be forced to search indiscriminately among all four corners. In fact, in a preliminary study, Good *et al.* (2001) have shown that rats can be trained to search preferentially in the correct corners in this task. Furthermore, they have shown that if the rats have received bilateral lesions to the hippocampus then they are no longer able to discriminate the correct from the incorrect corners. The implication of these results is that normal rats are able to appreciate the structure of the rectangular test arena, and that this appreciation depends upon an intact hippocampus. Of course, it is not just for finding goals in rectangular environments that an appreciation of structure might be beneficial. Orientation in many spatial tasks is likely to depend on this ability. If an animal is required to use two landmarks to identify the position of a goal, then the manner in which it searches for the goal will depend very much, say, on whether one landmark is to the left or right of the other landmark. It is thus quite possible that the disruptive effect of hippocampal damage on spatial tasks, such as the Morris swimming pool, is due to the effect it has on the ability of the animal to appreciate the way in which the many landmarks in the environment are positioned with respect to each other.

There is a parallel between the foregoing proposals and findings from research with humans. Kroll *et al.* (1996) presented subjects with a list of two-syllable words, and occasionally presented recognition test trials with new words composed of the syllables from previously shown words. Thus they might be presented with 'valley' and 'barter' and then asked if they had been shown 'barley'. Normal subjects made relatively few errors on this task, but those with damage to the left hippocampus showed a strong tendency to respond to the novel test words as if they had seen them previously. According to Kroll *et al.* (1996), the hippocampus is important for binding together information about pairs of syllables that occur in the same word. Damage to this structure disrupts this process and results in subjects classifying stimuli as familiar simply on the basis of whether or not they are composed of familiar syllables. Related data come from two studies of amnesic individuals with pathology thought to be largely confined to the hippocampus (Vargha-Khadem *et al.* 1997; Mayes *et al.* 1999; Mayes 2001). In both studies there was striking evidence of a sparing of recognition when individual items were used as stimuli. In contrast, more consistent deficits appeared when subjects were given tests of associative recognition, in which the component stimuli were familiar but their arrangements were novel (Vargha-Khadem *et al.* 1997; Mayes *et al.* 1999).

The starting point for this analysis was the notion of a mental snapshot, but this is not sufficient of itself. Not only is it necessary to bind items within a scene but it is also necessary to combine scenes in the correct temporal order. Unfortunately we lack appropriate ways of testing this process in rodents, although experiments with pigeons have formally demonstrated that animals can distinguish between sequences of stimuli in which the choice cannot be made on the basis of the final stimulus alone (Weisman *et al.* 1980). It would clearly be of great interest to know whether the hippocampus, or structures connected with the hippocampus, are critical for this function in rats.

3. LESION STUDIES OF ALLOCENTRIC SPATIAL PROCESSES

Although it is not yet possible to identify brain sites necessary for 'structural discriminations', we can identify

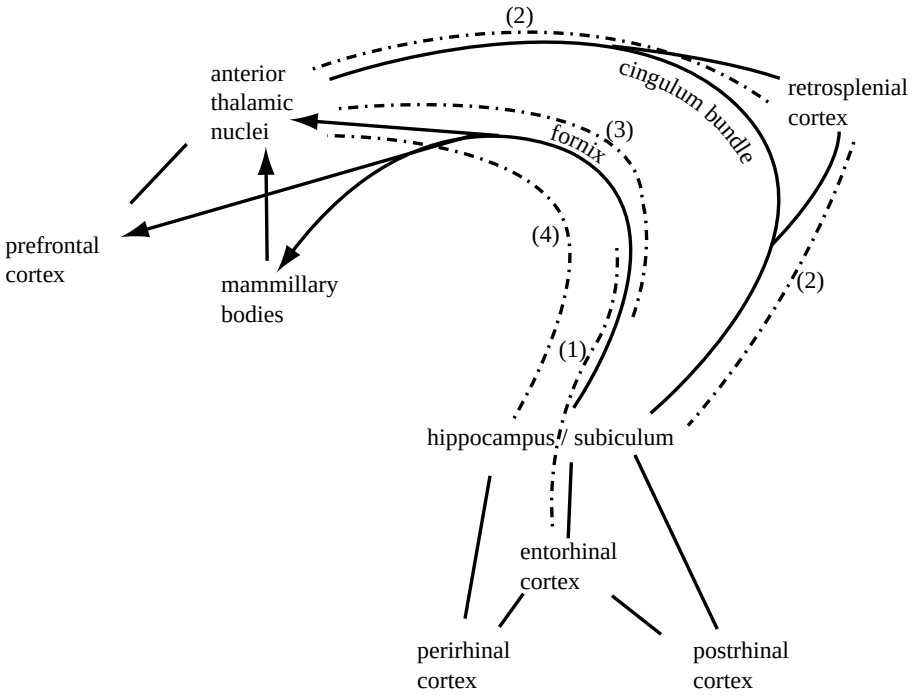

Figure 2. Schematic diagram showing the interconnections (solid lines) linking some of the key structures implicated in spatial memory in the rat. The dashed lines indicate where functional linkages have been established by disconnection studies, while the numbers refer to the relevant study ((1) Olton *et al*. 1982; (2) Sutherland & Hoesing 1993; (3) Warburton *et al*. 2000; (4) Warburton *et al*. 2001).

neural systems underlying spatial (allocentric) processing. Thus, in this section we will review evidence from lesion studies that have sought to identify the brain structures necessary for the acquisition and performance of allocentric spatial tasks. The resulting evidence reveals a group of interconnected structures that all have extensive links with the hippocampus. The final part of this section describes a number of disconnection studies that test whether these brain regions function in an interlinked way. These are of especial relevance as this class of task can be conducted experimentally in animals but will rarely, if ever, occur in clinical cases.

(a) *Hippocampus*

Studies with rats have shown that the hippocampus (dentate gyrus, CA1–4 and subiculum) is essential for allocentric spatial processing (O'Keefe & Nadel 1978; Morris *et al*. 1982, 1990). The involvement of this structure appears to occur at more than one stage of spatial learning and performance (Riedel *et al*. 1999; see Morris 2001) making it difficult to tease out individual component processes. Furthermore, both anatomical and electrophysiological evidence suggest that within the hippocampus there are functional changes along the longitudinal axis and, consistent with this, some lesion studies point to a greater contribution to spatial learning from the rat dorsal than the ventral hippocampus (Moser *et al*. 1995; Moser & Moser 1998).

Studies of spatial memory in non-human primates present a slightly more complex picture for several reasons. First, there are problems of task comparability as spatial tasks for monkeys typically involve little if any ambulation and so often differ from those given to rats (but see Murray *et al*. 1989). Second, the surgical approach used for aspiration lesions involves additional damage to subicular and parahippocampal regions, and this may contribute to the outcome of the study. Consistent with this, current data on selective neurotoxic hippocampal lesions in monkeys indicate that these may have more limited effects on tests of spatial memory (Murray & Mishkin 1998; Murray *et al*. 1998) than aspiration lesions (Jones & Mishkin 1972; Parkinson *et al*. 1988). Athough the cause of this discrepancy remains unproven, the most likely explanation is that conventional lesions disconnect the subicular, presubicular and parasubicular cortices. These regions are of especial significance as they provide hippocampal outputs to other regions implicated in spatial memory (Aggleton *et al*. 1986; Swanson *et al*. 1987; Naber *et al*. 2000).

(b) *Cortical regions*

The anatomical connections of the hippocampus can be used to guide assessments of the contribution made to spatial memory by additional brain structures (figure 2). The principal cortical input to the hippocampus comes from the entorhinal cortex, but there is also a complex pattern of both direct and indirect inputs from other parahippocampal cortices and from the retrosplenial cortex (Burwell *et al*. 1995; Witter *et al*. 1989). Careful anatomical studies in the rat have recently revealed that the perirhinal cortex preferentially projects to the lateral entorhinal cortex, while the postrhinal cortex projects to the medial entorhinal cortex (Witter *et al*. 1989). Furthermore, these two entorhinal divisions have different projection fields within the hippocampus (Witter *et al*. 2000), suggesting that there are at least two functional processing

streams, one via the perirhinal cortex and one via the postrhinal cortex. The functional nature of these streams and the ways in which they interact remain to be uncovered, but the visuospatial nature of the inputs to the postrhinal cortex (Burwell & Amaral 1998) suggest that this may be the more important for spatial processes.

Lesion studies have confirmed that entorhinal lesions can disrupt tests of spatial memory in rats, deficits being most consistent in studies using conventional lesions (Ramirez & Stein 1984; Hunt *et al.* 1994; Kirby & Higgins 1998). A common finding, however, is that the deficits are appreciably less severe than those observed after hippocampectomy. This is most evident in the case of cytotoxic lesions where studies have typically observed mild or even no apparent deficit on tasks sensitive to hippocampectomy (Bouffard & Jarrard 1988; Galani *et al.* 1998; Kesner & Giles 1998; Pouzet *et al.* 1999; Aggleton *et al.* 2000*b*). Thus although the entorhinal cortex is involved in spatial memory, it also appears that fibres passing through the entorhinal cortex have a contribution. This conclusion suggests that the remaining parahippocampal cortices (the perirhinal and postrhinal cortices in the rat) may have an additional role in spatial processes.

The consequences of perirhinal cortex lesions in rats have been varied. Removal of this area has been reported to have either no effect (Ennaceur *et al.* 1996; Ennaceur & Aggleton 1997; Mumby & Glenn 2000; Bussey *et al.* 2001*a*) or relatively mild, disruptive effects (Wiig & Bilkey 1994*a*,*b*; Liu & Bilkey 1998*a*,*b*; Mumby & Glenn 2000) on spatial tasks sensitive to hippocampal damage. What is consistent is that the deficits (when present), are considerably less severe than those following hippocampectomy. Fewer studies have examined the postrhinal cortex, but the removal of this region appears to have no effect on standard spatial tasks sensitive to hippocampectomy (Bussey *et al.* 1999, 2000). The conclusion to be drawn from these studies on the parahippocampal cortices is that while the entorhinal, perirhinal and postrhinal cortices may contribute to spatial memory processing, their involvement is poorly revealed by standard spatial memory tasks (Aggleton *et al.* 2000*b*). As an example of this, perirhinal lesions will impair a conditional task in which spatial information must be used to solve a visual discrimination, but more standard spatial tasks remain unaffected (Bussey *et al.* 2001*a*).

A third cortical region to be considered is the cingulate cortex, and in particular the retrosplenial cortex (in the rat there is no posterior cingulate cortex, area 23, but an extended retrosplenial cortex, area 29). This region projects directly to the parahippocampal cortices and parts of the subicular complex, and has extensive reciprocal connections with the anterior thalamic nuclei (Wyss & Van Groen 1992). Like the parahippocampal cortices, the effects of lesions in this region have been varied and when deficits are found they are more often associated with conventional rather than cytotoxic lesions (Sutherland *et al.* 1988; Sutherland & Hoesing 1993; Warburton *et al.* 1998; Aggleton *et al.* 2000*b*). The interpretation of cingulate lesion effects is complicated by the fact that the cingulum bundle passes immediately adjacent to much of the retrosplenial cortex and this tract is compromised by conventional lesions. Not only does the cingulum bundle provide connections for the retrosplenial cortex itself, but it also contains afferents to and from the hippocampal formation (Mufson & Pandya 1984). It is therefore not surprising that selective lesions of the cingulum bundle can produce mild, but significant, deficits on spatial tasks (Neave *et al.* 1996, 1997; Warburton *et al.* 1998). Furthermore, the lack of effect of cytotoxic retrosplenial lesions on spatial tasks would seem to suggest that the cingulum bundle deficit does not include the consequences of retrosplenial disconnection. In fact, recent evidence (S. D. Vann & J. P. Aggleton, unpublished data) shows that unusually complete cytotoxic lesions of the full length of the retrosplenial cortex, that spare the cingulum bundle, can produce clear deficits on a variety of tests that tax allocentric spatial memory (figure 3). It would therefore appear that the retrosplenial cortex does contribute to the performance of tasks that tax allocentric memory and that this accounts for some of the effects of cingulum bundle damage.

The hippocampus is also connected to parts of the frontal cortex, and in the rat these connections are principally with the prelimbic cortex in the medial prefrontal cortex (Jay & Witter 1991). While lesions of this medial prefrontal region produce deficits on tasks sensitive to hippocampal dysfunction, the impairments are qualitatively different. Thus prefrontal deficits are often independent of retention interval (Aggleton *et al.* 1995*b*), and can often be characterized as reflecting a tendency to perseverate with inefficient strategies (Chudasama & Muir 1997; Ragozzino *et al.* 1999; Kesner 2000; Dias & Aggleton 2000). In this regard, they clearly mirror some of the consequences of prefrontal cortex damage in primates (Passingham 1993). Thus although these prefrontal regions appear to have an important role in the execution of spatial tasks, presumably via an interaction with the hippocampal system, their contribution appears to be of a more general nature.

(c) *Subcortical areas*

The fornix provides the principal route for the subcortical connections of the hippocampus. As fornix lesions disrupt an array of spatial tasks in both rodents and primates (Mahut 1971, 1972; Olton *et al.* 1979; Murray *et al.* 1989), it has been assumed that subcortical regions linked to the hippocampus are involved. At the same time, fornix lesion deficits are sometimes not as severe as those associated with hippocampectomy (Eichenbaum *et al.* 1990; but see Whishaw & Jarrard 1995). For example, on reference memory tests in the Morris water maze, rats with fornix lesions are slower at learning than normal rats but they are still able to learn the approximate location of a hidden platform (Whishaw *et al.* 1995; Warburton & Aggleton 1999). In contrast, rats with hippocampal lesions require considerable overtraining to show a place preference in the Morris water maze (Morris *et al.* 1990).

Subcortical sites directly connected with the hippocampus via the fornix include the mammillary bodies, the anterior thalamic nuclei and the septum. All three have been implicated in supporting hippocampal function and, hence, supporting spatial processing. There are very close anatomical links between the mammillary bodies and the anterior thalamic nuclei, and it is not surprising

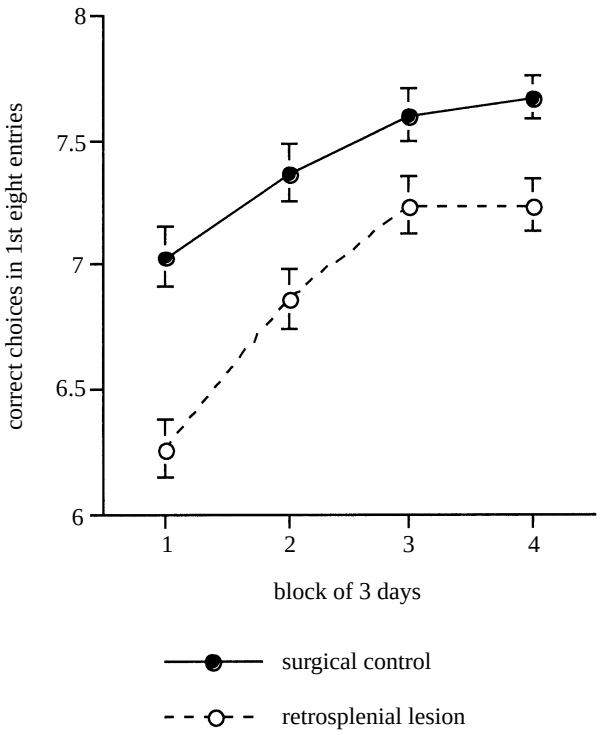

Figure 3. Performance of rats with complete neurotoxic lesions of the retrosplenial cortex on the eight arm radial arm maze task (S. D. Vann, unpublished data). The graph shows the significantly greater number of errors made by rats with retrosplenial lesions on this test of spatial working. Standard errors are shown by vertical bars.

that the effects of lesions in these two sites on tests of spatial memory are often similar (Sutherland & Rodriguez 1989; Aggleton *et al.* 1995*b*; Byatt & Dalrymple-Alford 1996). The effects of anterior thalamic lesions are, however, the more disruptive (Aggleton *et al.* 1995*b*; Warburton *et al.* 1997, 1999). This difference is consistent with their respective anatomical relationships with the hippocampus. While the mammillary bodies receive direct inputs from the hippocampus, the anterior thalamic nuclei receive both direct inputs from the hippocampus and indirect inputs via the mammillary bodies (figure 2). The anterior thalamic nuclei are composed of three major nuclei and all three appear to contribute to spatial processes (Aggleton *et al.* 1996; Byatt & Dalrymple-Alford 1996). A more caudal nucleus, the lateral dorsal nucleus is often added to this group as it has similar anatomical properties including direct connections with the hippocampus (Bentivoglio *et al.* 1993). Consistent with this, there is evidence that disruption of this nucleus exacerbates the effects of anterior thalamic damage (Mizumori *et al.* 1994; Warburton *et al.* 1997). Although the adjacent medial dorsal thalamic nucleus appears to modulate a range of tasks, including those taxing spatial memory, there is less direct evidence for a specific role in spatial memory (Hunt & Aggleton 1998*a*,*b*).

Other sites linked to the hippocampus, via the fornix, include the septum and the nucleus accumbens. Interpreting the consequences of septal damage has proved difficult as conventional lesions inevitably involve fornix fibres of passage. Nevertheless, studies using increasingly selective cytotoxic lesions of the region have found comparatively mild deficits on tasks in the Morris water maze (McAlonan *et al.* 1995; McMahan *et al.* 1997). Similarly, the effects of nucleus accumbens lesions on place learning in the water maze arm are very mild (Sutherland & Rodriguez 1989).

This review of the effects of selective lesions on tasks that tax spatial processing has provided a series of candidate regions that may function in an integrated manner with one another (figure 2). The hippocampus appears at the centre of this group, and associated with it are the anterior thalamic nuclei, the mammillary bodies, the septum, the retrosplenial cortex, and the entorhinal cortex. Of these, only removal of all of the anterior thalamic nuclei appears to produce deficits as severe as those associated with hippocampectomy (Warburton *et al.* 1997). Next it is necessary to test the extent to which these structures depend on each other. This will reveal whether these lesions studies have identified a number of disparate deficits or whether they reflect common components in an extended hippocampal system.

(d) *Disconnection studies*

Standard lesion approaches may reveal striking similarities between the effects of lesions in two or more sites, but this alone does not show that these sites are functionally interdependent. For this it is necessary to turn to disconnection studies. The rationale is that if area A is a critical source of inputs for area B, then a unilateral lesion in area A combined with a unilateral lesion in area B in the contralateral hemisphere will result in a disconnection of the spared half of area B (figure 4). The consequence will be an impairment that mimics the effect of bilateral loss of area B (and of area A). This prediction assumes that there are few, if any, crossed connections between areas A and B. Comparisons are then made with pairs of unilateral lesions, both lesions in the same (ipsilateral) hemisphere. In this latter group the total amount of tissue damage is the same as that in the disconnection case, but one hemisphere should remain functional. Thus the ipsilateral condition should have much milder disruptive effects.

The disconnection approach has been used with rats to identify interlinked systems necessary for the performance or acquisition of a number of spatial memory tests, all of which tax allocentric memory processes. These studies provide direct evidence for a link from the entorhinal cortex to the fornix (Olton *et al.* 1982), and from the fornix to the anterior thalamic nuclei (Warburton *et al.* 2000). In both cases, the hippocampal commissures had to be cut to induce a clear deficit, highlighting the involvement of interhippocampal transfer in normal performance. It should also be noted that the study by Olton *et al.* (1982) used conventional lesion methods and so it may be more accurate to say that it demonstrated a functional linkage between the parahippocampal cortex and fornix.

Other disconnection studies using the Morris water maze have provided evidence for a functional interaction between the hippocampus and anterior thalamic nuclei (Warburton *et al.* 2001), the anterior thalamic nuclei and the retrosplenial cortex (Sutherland & Hoesing 1993), and the hippocampus and retrosplenial cortex (Sutherland & Hoesing 1993). Once again, the retrosplenial lesions were

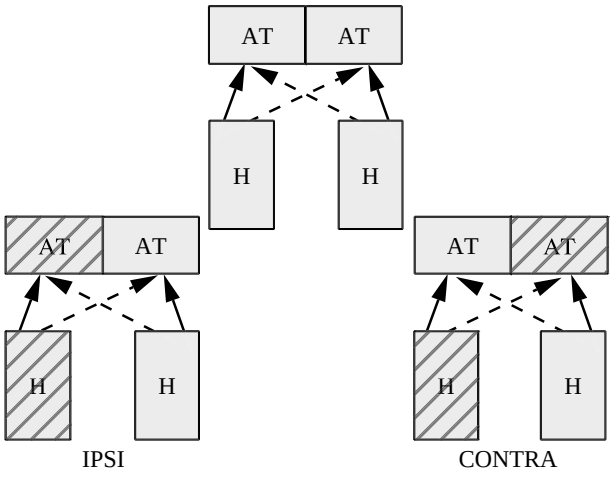

Figure 4. Pattern of ipsilateral (IPSI) and contralateral (CONTRA) lesions used in a disconnection study (Warburton *et al*. 2001) to examine whether the hippocampus (H) and anterior thalamic nuclei (AT) function in concert for the acquisition and performance of spatial memory tasks. For simplicity, the connections from the anterior thalamic nuclei to the hippocampus have not been added.

made by aspiration, raising the likelihood that damage to the cingulum bundle contributed to the deficits (Neave *et al*. 1996, 1997; Warburton *et al*. 1998). Nevertheless, when combined these disconnection studies provide direct evidence for a linked system that involves the parahippocampal (entorhinal) cortex, the hippocampus, the fornix, the anterior thalamic nuclei, and the retrosplenial cortex and cingulum bundle (figure 2). This system closely corresponds to the Papez (1937) circuit, which was originally regarded as a substrate for emotional interactions. The original ideas of Papez have long since been discarded, but his 'circuit' interlinks a set of regions (hippocampus, fornix, mammillary bodies, anterior thalamic nuclei, posterior cingulate cortex and retrosplenial cortex) via substantial tracts that are evident not only in rats, but also in monkeys and humans.

4. IMMEDIATE EARLY GENE (IEG) STUDIES

Lesion studies do not directly measure the contribution of a target region, rather they measure how the rest of the brain functions in its absence. As a consequence, there is a need to complement lesion data with those from techniques examining normal brain tissue. Measuring the activity of IEGs (Dragunow & Faull 1989; Herrera & Robertson 1996; Herdegen & Leah 1998) provides a novel form of functional imaging that permits activity in many sites to be compared in the same brain. Recent discoveries using this technique accord with the results of lesion studies, thus adding further support to the extended hippocampal system underlying spatial memory processes.

IEGs have low basal transcription rates, but they can be quite rapidly activated. This activation is, however, transient. Their gene product is thought to regulate the more long-term production of other proteins. Although there is evidence that IEGs may have an integral role in plastic processes that accompany learning (Tischmeyer & Grimm 1999), this remains unproven. There is more general agreement that IEGs can provide a more general measure of neuronal activity. As it is possible to compare the activity of multiple regions within the same brain this technique offers a form of functional mapping with exceptional anatomical resolution (down to the level of single neurons). There is, however, relatively low temporal resolution as IEG measurement occurs at the point of peak production either of mRNA or of the gene product itself. As this will be many minutes after the experimental (activating) event it is often impossible to tease apart component processes within a form of learning or performance.

(a) *c*-fos *imaging in normal animals*

In a series of experiments we have mapped the activity of an IEG, c-*fos*, during the performance of spatial memory tasks. Rats were tested in the radial arm maze (Olton *et al*. 1979), where they performed a test of spatial working memory that taxes allocentric spatial processing (Bussey *et al*. 1999) and is sensitive to hippocampal dysfunction. Comparisons with yoked control rats, matched for their perceptual, motor and reward experiences, have made it possible to identify a network of cortical and subcortical sites that show enhanced c-*fos* activity during such tests of spatial memory (Vann *et al*. 2000*a*,*b*). Evidence that the control procedure was appropriate came from the lack of difference in Fos levels in primary motor and sensory regions. In contrast, increased c-*fos* activity was found in all hippocampal and subicular subfields, the entorhinal cortex, postrhinal cortex, retrosplenial cortex, prelimbic cortex, septum, nucleus of the diagonal band, nucleus reuniens, and all three of the anterior thalamic nuclei (figure 5). This list includes many of the same sites revealed by lesion studies.

In a second experiment, rats were moved to a novel room for the final radial arm maze session, so requiring the animals to remap the external world in order to perform the task (Vann *et al*. 2000*a*,*b*). Comparisons were made with animals also performing the radial arm maze task, but in the same room that had always been used for training. The novel room manipulation should prove more demanding since the animal has to learn new distal room cues, in addition to maintaining its memory of which arms had been entered. This remapping is of especial interest as it is presumably allocentric and so is likely to tax aspects of structural learning. Increased c-*fos* activity was found in fewer sites, but these were always labelled in Experiment 1. Thus structures showing increased Fos production in both conditions included nearly all of the hippocampal subfields, the dorsal and caudal subiculum, postsubiculum, presubiculum, and parasubiculum, the prelimbic cortex, entorhinal cortex, postrhinal cortex, lateral septum, supramamillary nuclei, the three anterior thalamic nuclei, and nucleus reuniens (figure 5). Among the regions showing a Fos increase in Experiment 1 but not in Experiment 2 were the cingulate and retrosplenial cortices. The implication is that these latter regions contribute to radial arm maze task performance, but not to the creation and use of new cognitive maps. Two notable regions that did not show increased Fos levels in either condition were the perirhinal cortex and nucleus accumbens. This is of interest as both have

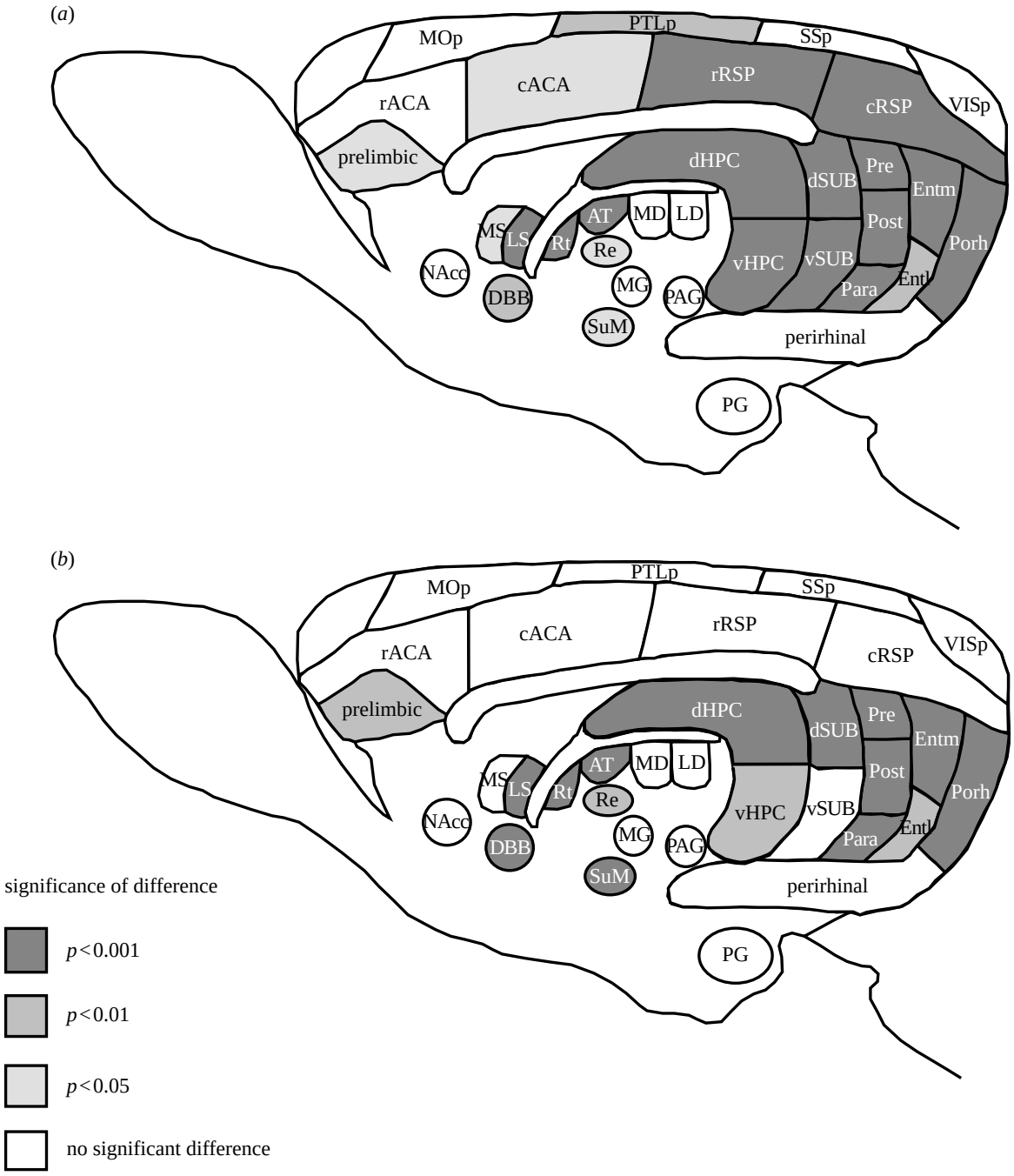

Figure 5. Summary of results from two c-*fos* experiments, depicting sites that show a significant increase in activity (Vann *et al.* 2000*a*,*b*). Experiment 1 (*a*) shows Fos increases following the performance of the radial arm maze task (compared with running up and down just one arm of the same maze). Experiment 2 (*b*) shows Fos increases when the radial arm maze task is performed in a novel room (compared with animals in a familiar room). Abbreviations: AT, anterior thalamic nuclei; cACA, caudal anterior cingulate cortex; cRSP, caudal retrosplenial cortex; DBB, diagonal band of Broca; dHPC, dorsal hippocampus; dSUB, dorsal subiculum; Entl, lateral entorhinal cortex; Entm, medial entorhinal cortex; LD, lateral dorsal thalamic nucleus; LS, lateral septum; MD, medial dorsal thalamic nucleus; MG, medial geniculate; MOp, primary motor cortex; MS, medial septum; NAcc, nucleus accumbens; PAG, periaqueductal grey; Para, parasubiculum; PG, pontine grey; Porh, postrhinal cortex; Post, postsubiculum; Pre, presubiculum; PTLp, parietal cortex; rACA, rostral anterior cingulate cortex; Re, nucleus reunions; rRSP, rostral retrosplenial cortex; Rt, rostral reticular thalamic nucleus; SSp, primary somatosensory cortex; SuM, supramammillary nucleus; vHPC, ventral hippocampus; VISp, primary visual cortex; vSUB, ventral subiculum.

strong anatomical links with the hippocampus, yet there is uncertain lesion evidence over their involvement in spatial learning (see § 3). While the present IEG data indicate that the perirhinal cortex is not directly involved in spatial mapping tasks, the adjacent postrhinal cortex did show increased Fos production in both experiments. Although loss of the postrhinal cortex does not appear to affect radial arm performance (Bussey *et al.* 1999), there are good grounds for believing that this region is normally involved in spatial processing. Most notably, it

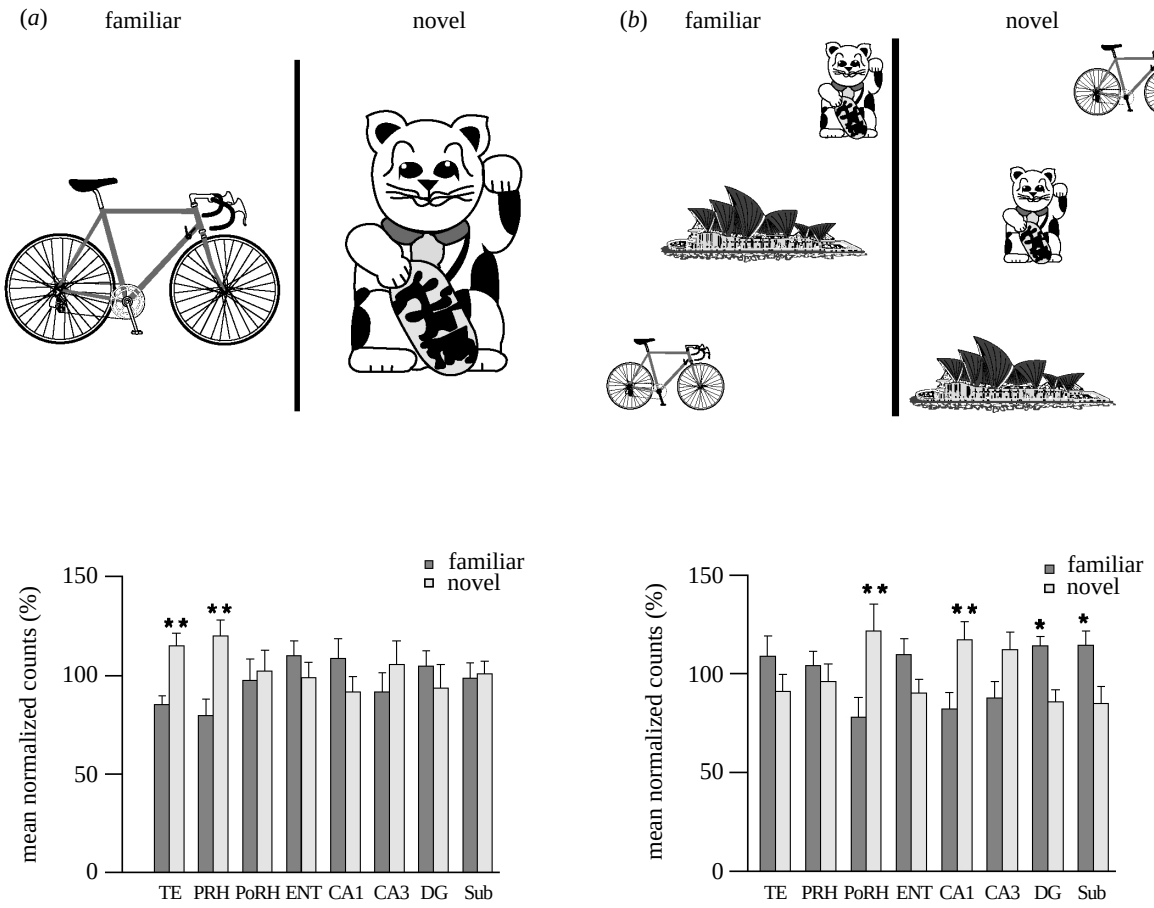

Figure 6. Paired-viewing study (Wan *et al*. 1999) that compared Fos activity in the two hemispheres following the presentation of a novel single stimulus (left) or the presentation of a novel arrangement of familiar individual stimuli (right). Note the different regions showing significant activations in the two versions of the task ($^{*}p < 0.05$, $^{**}p < 0.01$). The item to the left of the vertical line can be regarded as the familiar stimulus (seen by the left eye only), while the item to the right of the vertical line is novel and only seen by the right eye. Fos levels are then compared across hemispheres in the same animal. Fos counts have been normalized so that that equal counts in the two hemispheres would be 100%. Abbreviations: CA, hippocampal fields CA1 and CA3; DG, dentate gyrus; ENT, entorhinal cortex; PoRH, postrhinal cortex; PRH, perirhinal cortex; Sub, subiculum; TE, area TE. Standard errors are indicated by the vertical lines.

is the postrhinal cortex rather than the perirhinal cortex that receives the majority of sensory inputs associated with spatial information in the rat (Burwell *et al*. 1995).

A further manipulation provides an even more direct examination of the processes likely to be involved in structural discriminations (Wan *et al*. 1999). In this task rats were shown a series of visual stimuli, each composed of three objects in a specific location. These compound 'scenes' were shown simultaneously to the left and right eyes of the rat over a series of successive sessions, so that they could become familiar. On the final test day the stimuli shown to one eye remained unchanged, while those shown to the other eye were rearranged so that for each scene the component objects were the same but their locations were swapped, i.e. novel (figure 6). Levels of Fos were then measured and compared between the two hemispheres. Fos increases were found in the postrhinal cortex and in parts of the hippocampus in the hemisphere that first received visual inputs from the eye viewing the rearranged objects (Wan *et al*. 1999). No increases were found in the perirhinal cortex. In contrast, a comparison condition that involved showing novel versus familiar single objects (i.e. no structural component) led to increased activation in the perirhinal cortex, but not in the hippocampus or postrhinal cortex (Wan *et al*. 1999). These data implicate the hippocampus and postrhinal cortex in structural learning, i.e. learning about the way in which objects are located with respect to each other. They also provide a further parallel with studies of allocentric learning and c-*fos* imaging (Vann *et al*. 2000*b*).

(b) *c*-fos *imaging in animals with lesions*

In order to understand how a lesion in one structure can have detrimental effects on other sites, we have extended the c-*fos* procedure to examine how damage to a specific part of the circuit revealed by lesion studies can affect other putative members of that system. The first study measured the consequences of a unilateral fornix lesion upon c-*fos* activation during radial arm maze performance (Vann *et al*. 2000*c*). This tract was chosen since (i) clinical studies have increasingly indicated that damage to the fornix may be sufficient to induce anterograde amnesia (Aggleton *et al*. 2000*a*), and (ii) the fornix lies at the heart of connections between temporal and diencephalic regions implicated in spatial memory processes in rats. The radio-frequency lesion led to

decreased Fos production in an array of sites including all of the hippocampal subfields, most of the subicular complex, the entorhinal cortex, anterior cingulate cortex, retrosplenial cortex and postrhinal cortex. Subcortical regions showing decreased Fos included the anterior thalamic nuclei, the supramamillary nucleus, the lateral septum and diagonal band of Broca. Not only are many of these same sites implicated in spatial memory processes from electrophysiological and lesion data, but there is also striking overlap between those regions that show increased Fos production in the intact brain following performance of a spatial memory task (Vann *et al.* 2000*a*,*b*) and those that show abnormal production following fornix damage (Vann *et al.* 2000*c*). It is evident that fornix transection has widespread consequences that extend far beyond the hippocampus, and these will need to be considered when trying to understand why fornix lesions can impair memory processes (Gaffan & Gaffan 1991; Gaffan *et al.* 1991; Aggleton *et al.* 2000*a*).

The same approach, i.e. lesioning a specific site and then measuring the disruption of c-*fos* activity throughout the brain, has also been applied to the anterior thalamic nuclei. Bilateral neurotoxic lesions of the anterior thalamus resulted in hypoactivity in the hippocampus, as well as in the retrosplenial cortex and prelimbic cortex (Dias *et al.* 2000). This finding not only suggests that anterior thalamic damage might affect memory via its disruptive consequences on the hippocampus and other limbic regions, but also helps to explain why medial temporal lobe and medial diencephalic lesions might have similar consequences on memory.

5. OBJECT RECOGNITION MEMORY

A quite different approach to the study of episodic-like memory has come from the study of recognition memory in animals. This approach has been very influential (Mishkin 1978; Squire & Zola-Morgan 1991) and is intuitively extremely attractive. Recognition memory is often closely equated with episodic memory (Squire & Knowlton 1995; LePage *et al.* 2000; but see Yonelinas 2001) and, consistent with this, amnesic individuals almost always show a recognition memory deficit. As a consequence, it is quite common to see clinical deficits of recognition simply described as episodic memory impairments (e.g. Collie & Maruff 2000). Thus the testing of object recognition should provide an unusually direct means of testing episodic-like memory in animals. Furthermore, one might expect to discover that systems linked to the hippocampus that are important for spatial memory are also important for recognition memory. In fact, a surprisingly different set of key structures emerge when recognition memory is analysed in animals.

Before considering recognition in animals it is helpful to consider recognition by humans. If, in order to recognize an item as having previously been presented, a subject must mentally travel back in time in an active fashion, then tests of recognition memory can indeed be thought to test episodic memory. There is, however, considerable controversy over the nature of human recognition memory. The principal area of debate is whether it comprises a single process directly linked to other forms of episodic recall or whether it is a dual process in which recognition can stem from two (or more) independent processes (see Gardiner (2001) and Yonelinas 2001). While one of these processes does indeed appear to be episodic, as it involves actively remembering the repeated event, the other simply involves the detection of familiarity (Mandler 1980). This dichotomy helps to highlight a fundamental problem for tests of recognition memory in animals.

This problem can best be considered in the light of Lloyd Morgan's 'canon' (Morgan 1894). The most parsimonious account of recognition by animals is that objects are distinguished on the basis of their relative familiarity, rather than to suppose that the animal is actively engaged in recalling the event when one of the test objects was previously presented. This of course assumes that animals do have access to a signal that permits a judgement based on familiarity. Direct evidence that a familiarity signal exists comes from single unit recording studies in both monkeys and rats. Such studies have uncovered cells, most typically in the perirhinal cortex, that show differential responding to novel versus previously exposed visual stimuli (Brown *et al.* 1987; Zhu *et al.* 1995*a*; Brown & Aggleton 2001). Furthermore, lesion experiments have confirmed the critical importance of the same brain region for behavioural tests of recognition (Murray & Mishkin 1986; Zola-Morgan *et al.* 1989*b*; Murray 1996). The perirhinal cortex also shows increased c-*fos* activation when novel stimuli are presented (Zhu *et al.* 1995*b*, 1996). This convergence of data makes it increasingly likely that these electrophysiological signals do have an important role in the judgement of novelty (Brown & Aggleton 2001).

It is necessary to consider next the ways in which recognition is tested behaviourally in animals. Although there is a surprising range of potential tests (Steckler *et al.* 1998), two classes of task have had the most impact. The first is delayed non-matching-to-sample (DNMS). For this, the animal receives a food reward for selecting the novel item when offered a choice between a novel and a familiar item. Thus the animal must make a choice based on prior information (the familiarity of the item that had already been presented). Although this may superficially look like a test of recall, there is no demand on the animal to recall the episode of first seeing the now familiar stimulus. While it is the case that human amnesics are typically impaired on recognition tasks that have deliberately been made comparable with the animal DNMS task (Aggleton *et al.* 1988; Squire *et al.* 1988; but see Holdstock *et al.* 1995), this does not show that the task taxes episodic memory in animals. If judgements based on relative familiarity can effectively solve DNMS problems (which they presumably can), then the mere performance of this task does not demonstrate episodic memory in animals.

The second class of task involves tests of spontaneous exploration or viewing of novel versus familiar items (Zola-Morgan *et al.* 1983; Ennaceur & Delacour 1988; Bachevalier *et al.* 1993). This form of paired comparison task takes advantage of the fact that many animals show a spontaneous preference for novel objects or locations. The behavioural measure is not a single choice, but the difference in time spent examining the items within the pair of objects. The advantage of this task is that it

requires no pretraining, making it arguably a purer test of recognition, while the absence of a specific reward removes a potential source of variance. Disadvantages include the fact that it is disrupted by any manipulation that affects levels or patterns of exploration, while the final choice measure is dependent on rates of habituation. This latter factor presents a problem for testing hippocampal lesions as these can disrupt habituation (Honey & Good 2000). Although, human amnesics are impaired on analogues of the visual paired comparison task (McKee & Squire 1993), for the same reasons as noted above this does not show that the task taxes the recall of prior episodes by animals.

In view of these concerns, it is instructive to compare what is known about brain systems underlying object recognition and spatial learning. Lesions studies in animals have pointed to three principal regions associated with recognition deficits: the perirhinal cortex, the medial dorsal nucleus of the thalamus and the prefrontal cortex (Aggleton & Mishkin 1983; Zola-Morgan & Squire 1985; Murray & Mishkin 1986; Zola-Morgan *et al.* 1989*b*; Bachevalier & Mishkin 1986; Mumby & Pinel 1994; Murray 1996). In contrast, lesions of the fornix or mammillary bodies have little or no effect on tests of object recognition (Aggleton & Mishkin 1985; Bachevalier *et al.* 1985; Zola-Morgan *et al.* 1989*a*; Shaw & Aggleton 1993). There has, however, been much debate over the consequences of hippocampal damage on tests such as DNMS, but a recent meta-analysis helps to show that the effects are typically mild and consistently less severe than those observed after perirhinal cortex lesions (Baxter & Murray 2001).

The group of regions that appear most critical for object recognition (perirhinal cortex, prefrontal cortex, medial dorsal thalamic nucleus) are directly linked anatomically. Furthermore, by using disconnection procedures it has been possible to show that both the medial dorsal thalamus and the perirhinal cortex interact with the frontal cortex for the performance of recognition tasks by monkeys (Parker & Gaffan 1998). At the same time, these regions provide surprisingly little overlap with the key regions required for allocentric spatial memory processes, with the hippocampus providing a potential point of overlap. Nevertheless, comparisons between the perirhinal cortex and the hippocampus provide a series of double dissociations when the magnitude of lesion effects on DNMS and spatial learning are considered in rats (Brown & Aggleton 2001). Similar double dissociations are found for c-*fos* activation studies (Aggleton & Brown 1999).

While it is self-evident that tests of object recognition and spatial memory should not tax precisely the same neural substrates, the lack of overlap is surprising if both provide insights into episodic memory. One possibility is that standard tests of recognition as performed by animals assess familiarity judgements and, hence, do not depend on any episodic-like component of recognition memory. This explanation accounts for the different distribution of key structures for recognition and spatial memory, and accords with evidence that familiarity information is available in the perirhinal cortex. A second possibility is that, as in humans, there are dual processes for recognition and that one of these is familiarity-based while the other is a form of episodic memory. While it is the case that ingenious new behavioural tasks have shown that birds have access to memory functions that can be described as episodic-like (Clayton *et al.* 2001) and it is quite conceivable that this form of memory can help animals solve behavioural tests of recognition, there is no *a priori* case for assuming that animals do use this more complex form of memory when performing standard versions of tasks such as DNMS. To do this it will be necessary to derive independent measures that distinguish between these processes. This has proved extremely difficult in humans, and is likely to be even more challenging for research with animals.

A quite different way of thinking about object recognition is to assume that by monitoring object familiarity the same system is also able to provide information concerning item identity i.e. the *what*? element of episodic memory. This provides a more constructive way to consider the anatomical links between the perirhinal cortex and hippocampus, namely that they enable *what*? and *where*? information to be combined (Gaffan 1998). This view is supported by lesion data (Gaffan & Parker 1996; Bussey *et al.* 1999, 2001*a*), and helps to highlight the importance of the functional interactions between the hippocampus and parahippocampal cortices in both humans and animals (Squire & Zola-Morgan 1991; Eichenbaum 2000). At the same time, the analyses of spatial memory strongly suggest that these interactions are not sufficient and that connections with diencephalic sites are also required in order to combine these classes of information (Parker & Gaffan 1997).

6. CONCLUSIONS AND CAVEATS

In spite of the logical problems of assessing episodic memory in animals, it is possible to examine the neural basis of the key aspects of this form of memory, namely the *what*? *where*? and *when*? of an event. Furthermore, research with animals can determine how structures function in an integrated manner to support each of these attributes, e.g. by disconnection techniques. Using these approaches in rodents it has been possible to uncover an interlinked group of cortical and subcortical structures for spatial learning. The hippocampus is central to this group and, at the same time, is dependent upon other regions within it. It has also been proposed that aspects of spatial memory make it especially pertinent for the study of episodic-like processes. This is because a particular type of processing described as 'structural learning' may provide a precursor to the creation of 'mental snapshots'. As allocentric processing can be seen as a form of structural learning, the study of this aspect of spatial memory should be of especial value.

In order to examine the neural basis of spatial learning we have described how selective lesions can disrupt the performance of tasks that tax allocentric processing. Care must be taken, however, to exclude deficits that are not spatial but reflect more general disruptions of behaviour such as hyperactivity or response perseveration (Chudasama & Muir 1997). A more challenging problem is the fact that animals have multiple strategies to aid performance in tasks taxing allocentric processing. As a consequence, other structures may

provide quite different forms of spatial information that also promote successful navigation. Examples include 'egocentric information' (mapping external space with respect to your own body position, e.g. to the right or to the left) and 'path integration' (using self-movement cues such as motor and vestibular information to track a path through space). Of these, path integration is likely to be of particular relevance as there is growing evidence that the hippocampus is involved in this form of spatial tracking as well as allocentric mapping (Whishaw *et al.* 1995; Whishaw 1998). Note, however, that it is very difficult to understand how successful performance in spatial tasks such as the Morris pool can be explained solely by reference to path integration. Likewise, the similar effects on scene discrimination learning in rats following lesions of the fornix, anterior thalamic nuclei or mammillary bodies (Gaffan *et al.* 2001) cannot be interpreted as a deficit in path integration.

Disentangling systems for path integration and allocentric processing is likely to prove demanding as the same region might be involved in both spatial mechanisms. Examples include not only the hippocampus but also the retrosplenial cortex (Whishaw *et al.* 2001). Similarly, inputs in the rat from the anterior thalamic nuclei to the hippocampal formation provide head direction information (Taube 1995; Goodridge & Taube 1997), and this may prove to be relevant for both allocentric processing and path integration (Sharp 1999). At the same time, head direction information arises from only specific subregions within the anterior thalamic nuclei, yet both lesion and IEG data show that all of these nuclei contribute to spatial activity (Aggleton *et al.* 1996; Byatt & Dalrymple-Alford 1996; Vann *et al.* 2000*a*). Thus the anterior thalamic nuclei appear to have an additional, as yet unknown, contribution to the extended hippcampal system. Similarly, while the lateral mammillary nuclei are involved in providing head direction information for the anterior thalamic nuclei (Blair *et al.* 1999), the medial mammillary nuclei have a different function that also remains to be determined. Thus the 'extended hippocampal system' in the rat cannot be regarded as having a unitary function, even as regards spatial processing. There appears to be a much finer degree of anatomical specificity within the component structures as regards different functions. Furthermore, these different forms of spatial information need to be integrated so that they can be used in the most effective manner. Indeed, it has been argued that it is this process of integration, which enables an animal to monitor and remember its movements in space, that should be regarded as a more direct precursor of episodic memory in primates (Wise & Murray 1999).

Although it is increasingly evident that the Papez circuit has multiple influences on spatial learning, we have argued that this circuit is important because it allows animals to appreciate the structure of complex stimuli, a fundamental component of episodic memory. By highlighting the role of 'structural learning' we have provided a new starting point that incorporates the contribution of configural learning within a more specific framework. This now requires testing, and a vital step will be the development of formal tests of structural learning by animals. At a more general level, it is possible to assess the validity of the approach adopted in this review by considering the pathologies responsible for anterograde amnesia in humans. This immediately shows that there is a very clear concordance between sites responsible for anterograde amnesia and those critical for tests of spatial memory in animals. In both cases the hippocampus is the most prominent site. Although clinical studies have persistently suffered from a lack of cases with circumscribed pathology, there is considerable evidence indicating that hippocampal damage is sufficient to induce amnesia (e.g. Penfield & Mathieson 1974; Squire 1992; Rempel-Clower *et al.* 1996). Of especial relevance is evidence that hippocampal damage in humans can result not only in amnesia, but also in a loss of spatial memory that is selective for allocentric memory (Holdstock *et al.* 2000). Establishing the importance of other single structures for anterograde amnesia has been more difficult, but a number of recent group studies have provided convincing evidence for the importance of the fornix, the mammillothalamic tract (and thus the mammillary bodies), and the anterior thalamic nuclei (Aggleton & Brown 1999; Aggleton *et al.* 2000*a*; Harding *et al.* 2000; Van der Werf *et al.* 2000). Similarly there is growing evidence that damage to the retrosplenial region can disrupt episodic memory (Valenstein *et al.* 1987; Maguire 2001), and this is supported by recent brain imaging data (Maguire 2001). These results highlight the same extended hippocampal system for spatial processing in rats and for episodic memory in humans. This concordance strongly supports the general approach outlined in this review.

The authors thank L. Awcock, N. Thomas and S. Vann (Cardiff University) for assistance, as well as the support of the UK Medical Research Council.

REFERENCES

Aggleton, J. P. & Brown, M. W. 1999 Episodic memory, amnesia and the hippocampal–anterior thalamic axis. *Behav. Brain Sci.* **22**, 425–444.

Aggleton, J. P. & Mishkin, M. 1983 Memory impairments following restricted medial thalamic lesions in monkeys. *Exp. Brain Res.* **52**, 199–209.

Aggleton, J. P. & Mishkin, M. 1985 Mamillary-body lesions and visual recognition in monkeys. *Exp. Brain Res.* **58**, 190–197.

Aggleton, J. P., Desimone, R. & Mishkin, M. 1986 The origin, course, and termination of the hippocampo–thalamic projections in the macaque. *J. Comp. Neurol.* **243**, 409–422.

Aggleton, J. P., Nicol, R. M., Huston, A. E. & Fairbairn, A. F. 1988 The performance of amnesic subjects on tests of experimental amnesia in animals: delayed matching-to-sample and concurrent learning. *Neuropsychologia* **26**, 265–272.

Aggleton, J. P., Neave, N., Nagle, S. & Hunt, P. R. 1995*a* A comparison of the effects of anterior thalamic, mamillary body and fornix lesions on reinforced spatial alternation. *Behav. Brain Res.* **68**, 91–101.

Aggleton, J. P., Neave, N., Nagle, S. & Sahgal, A. 1995*b* A comparison of the effects of medial prefrontal, cingulate cortex, and cingulum bundle lesions on tests of spatial memory: evidence of a double dissociation between frontal and cingulum bundle contributions. *J. Neurosci.* **15**, 7270–7281.

Aggleton, J. P., Hunt, P. R., Nagle, S. & Neave, N. 1996 The effects of selective lesions within the anterior thalamic nuclei on spatial memory in the rat. *Behav. Brain Res.* **81**, 189–198.

Aggleton, J. P., McMackin, D., Carpenter, K., Hornak, J., Kapur, N., Halpin, S., Wiles, C. M., Kamel, H., Brennan, P. & Gaffan, D. 2000*a* Differential effects of colloid cysts in the third ventricle that spare or compromise the fornix. *Brain* **123**, 800–815.

Aggleton, J. P., Vann, S. D., Oswald, C. J. P. & Good, M. 2000*b* Identifying cortical inputs to the hippocampus that subserve allocentric spatial processes: a simple question with a complex answer. *Hippocampus* **10**, 466–474.

Bachevalier, J. & Mishkin, M. 1986 Visual recognition impairment follows ventromedial but not dorsolateral prefrontal lesions in monkeys. *Behav. Brain Res.* **20**, 249–261.

Bachevalier, J., Saunders, R. C. & Mishkin, M. 1985 Visual recognition in monkeys; effects of transection of fornix. *Exp. Brain Res.* **57**, 547–553.

Bachevalier, J., Brickson, M. & Hagger, C. 1993 Limbic-dependent recognition in monkeys develops early in infancy. *Learn. Mem.* **4**, 77–80.

Baxter, M. G. & Murray, E. A. 2001 Opposite relationship of hippocampal and rhinal cortex damage to delayed nonmatching-to-sample deficits in monkeys. *Hippocampus* **11**, 61–71.

Bentivoglio, M., Kultas-Ilinsky, K. & Ilinsky, I. 1993 Limbic thalamus: structure, intrinsic organisation and connections. In *Neurobiology of cingulate cortex and limbic thalamus* (ed. B. A. Vogt & M. Gabriel), pp. 71–122. Boston, MA: Birkhäuser.

Blair, H. T., Cho, J. & Sharp, P. E. 1999 The anterior thalamic head direction signal is abolished by bilateral but not unilateral lesions of the lateral mammillary nucleus. *J. Neurosci.* **19**, 6673–6683.

Bouffard, J. P. & Jarrard, L. E. 1988 Acquisition of a complex place task in rats with selective ibotenate lesions of hippocampal formation: combined lesions of subiculum and entorhinal cortex versus hippocampus. *Behav. Neurosci.* **102**, 828–834.

Brown, M. W. & Aggleton, J. P. 2001 Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nature Rev. Neurosci.* **2**, 51–61.

Brown, M. W., Wilson, F. A. W. & Riches, P. 1987 Neuronal evidence that inferomedial temporal cortex is more important than hippocampus in certain processes underlying recognition memory. *Brain Res.* **409**, 158–162.

Burwell, R. D. & Amaral, D. G. 1998 Cortical afferents of the perirhinal, postrhinal, and entorhinal cortices of the rat. *J. Comp. Neurol.* **398**, 179–205.

Burwell, R. D., Witter, M. P. & Amaral, D. G. 1995 Perirhinal and postrhinal cortices of the rat: a review of the neuroanatomical literature and comparison with findings from the monkey brain. *Hippocampus* **5**, 390–408.

Bussey, T. J., Warburton, E. C., Aggleton, J. P. & Muir, J. L. 1998 Fornix lesions can facilitate acquisition of the transverse patterning task: a challenge for 'configural' theories of hippocampal function. *J. Neurosci.* **18**, 1622–1631.

Bussey, T. J., Muir, J. L. & Aggleton, J. P. 1999 Functionally dissociating aspects of event memory: the effects of combined perirhinal and postrhinal lesions on object and place memory in the rat. *J. Neurosci.* **19**, 495–503.

Bussey, T. J., Duck, J. D., Muir, J. L. & Aggleton, J. P. 2000 Distinct patterns of behavioural impairments resulting from fornix transection or neurotoxic lesions of the perirhinal and postrhinal cortices in the rat. *Behav. Brain Res.* **111**, 187–202.

Bussey, T. J., Dias, R., Amin, E., Muir, J. L. & Aggleton, J. P. 2001*a* Perirhinal cortex and place-object conditional learning. *Behav. Neurosci.* (In the press.)

Bussey, T. J., Dias, R., Redhead, E. S., Pearce, J. M., Muir, J. L. & Aggleton, J. P. 2001*b* Intact negative patterning in rats with fornix or combined perirhinal and postrhinal cortex lesions. *Exp. Brain Res.* (In the press.)

Byatt, G. & Dalrymple-Alford, J. C. 1996 Both anteromedial and anteroventral thalamic lesions impair radial-maze learning in rats. *Behav. Neurosci.* **110**, 1335–1348.

Chudasama, Y. & Muir, J. L. 1997 A behavioural analysis of the delayed non-matching to position task: the effects of scopolamine, lesions of the fornix and of the prelimbic region on mediating behaviours by rats. *Psychopharmacology* **134**, 73–82.

Clayton, N. S., Griffiths, D. P., Emery, N. J. & Dickinson, A. 2001 Elements of episodic-like memory in animals. *Phil. Trans. R. Soc. Lond.* B **356**, 1483–1491.

Collie, A. & Maruff, P. 2000 The neuropsychology of preclinical Alzheimer's disease and mild cognitive impairment. *Neurosci. Biobehav. Rev.* **24**, 365–374.

Crick, F. & Jones, E. 1993 The backwardness of human neuroanatomy. *Nature* **361**, 109–110.

Davidson, T. L., McKernan, M. G. & Jarrard, L. E. 1993 Hippocampal lesions do not impair negative patterning: a challenge to configural association theory. *Behav. Neurosci.* **107**, 227–234.

Delay, J. & Brion, S. 1969 *Le syndrome de Korsakoff*. Paris: Masson.

Dias, R. & Aggleton, J. P. 2000 Effects of excitotoxic prefrontal lesions on acquisition of nonmatching- and matching-to-place in the T-maze: evidence for intact spatial working memory but differential involvement of the prelimbic–infralimbic and anterior cingulate cortices in providing behavioural flexibility. *Eur. J. Neurosci.* **12**, 1–12.

Dias, R., Morgan, A., Brown, M. W. & Aggleton, J. P. 2000 Anterior thalamic lesions disrupt hippocampal activity measured by c-*fos* imaging: implications for temporal lobe memory processes and amnesia. *Eur. J. Neurosci.* **12** (Suppl. 11), 42.2.

Dragunow M. & Faull R. 1989 The use of c-*fos* as a metabolic marker in neuronal pathway tracing. *J. Neurosci. Meth.* **29**, 261–265.

Eichenbaum, H. 2000 A cortical-hippocampal system for declarative memory. *Nature Rev. Neurosci.* **1**, 41–50.

Eichenbaum, H., Stewart, C. & Morris, R. G. M. 1990 Hippocampal representation in place learning. *J. Neurosci.* **10**, 3531–3542.

Ennaceur, A. & Aggleton, J. P. 1997 The effects of neurotoxic lesions of the perirhinal cortex combined to fornix transection on object recognition memory in the rat. *Behav. Brain Res.* **88**, 181–193.

Ennaceur, A. & Delacour J. 1988 A new one-trial test for neurobiological studies of memory in rats. I Behavioural data. *Behav. Brain Res.* **31**, 47–59.

Ennaceur, A., Neave, N. & Aggleton, J. P. 1996 Neurotoxic lesions of the perirhinal cortex do not mimic the behavioural effects of fornix transection in the rat. *Behav. Brain Res.* **80**, 9–25.

Gaffan, D. 1991 Spatial organization of episodic memory. *Hippocampus* **1**, 262–264.

Gaffan, D. 1992 The role of the hippocampus–fornix–mammillary system in episodic memory. In *Neuropsychology of memory*, 2nd edn (ed. L. R. Squire & N. Butters). New York: Guilford Press.

Gaffan, D. 1998 Idiothetic input into object-place configuration as the contribution to memory of the monkey and human hippocampus: a review. *Exp. Brain Res.* **123**, 201–209.

Gaffan, D. & Gaffan, E. A. 1991 Amnesia in man following transection of the fornix. *Brain* **114**, 2611–2618.

Gaffan, D. & Parker, A. 1996 Interaction of perirhinal cortex with the fornix-fimbria: memory for objects and 'object-in-place' memory. *J. Neurosci.* **16**, 5864–5869.

Gaffan, E. A., Gaffan, D. & Hodges, J. R. 1991 Amnesia following damage to the left fornix and to other sites. *Brain* **114**, 1297–1313.

Gaffan, E. A., Bannerman, D. M., Warburton, E. C. & Aggleton, J. P. 2001 Rat's processing of visual scenes: effects of lesions to fornix, anterior thalamus, mamillary nuclei or the retrohippocampal region. *Behav. Brain Res.* **121**, 103–117.

Galani, R., Weiss, I., Cassel, J. C. & Kelche C. 1998 Spatial memory, habituation, and reactions to spatial and nonspatial changes in rats with selective lesions of the hippocampus, the entorhinal cortex or the subiculum. *Behav. Brain Res.* **96**, 1–12.

Gallagher, M. & Holland, P. 1992 Preserved configural learning and spatial learning impairments in rats with hippocampal damage. *Hippocampus* **2**, 81–88.

Gardiner, J. M. 2001 Episodic memory and autonoietic consciousness: a first-person approach. *Phil. Trans. R. Soc. Lond.* B **356**, 1351–1361.

George, D., Ward-Robinson, J. & Pearce, J. M. P. 2001 The discrimination of structure. I Implications for connectionist theories of discrimination learning. *J. Exp. Psychol. Anim. Behav. Process.* **27**, 206–218.

Gluck, M. A. 1991 Stimulus generalization and representation in adaptive network models of category learning. *Psychol. Sci.* **2**, 50–55.

Gluck, M. A. & Bower, G. H. 1988 From conditioning to category learning: an adaptive network model. *J. Exp. Psychol. Gen.* **117**, 225–244.

Good, M. A., Haywood, A., McGregor, A., Muir, J. L. & Pearce, J. M. A unique role for shape in spatial navigation in the watermaze: evidence from overshadowing manipulation and hippocampal lesion. *Soc. Neurosci. Abstracts* 2001.

Goodridge, J. P. & Taube, J. S. 1997 Interaction between the postsubiculum and anterior thalamus in the generation of head direction cell activity. *J. Neurosci.* **17**, 9315–9330.

Harding, A., Halliday, G., Caine, D. & Kril, J. 2000 Degeneration of anterior thalamic nuclei differentiates alcoholics with amnesia. *Brain* **123**, 141–154.

Herdegen, T. & Leah, J. D. 1998 Inducible and constitutive transcription factors in the mammalian nervous system: control of gene expression by Jun, Fos and Krox, and CREB/ATF proteins. *Brain Res. Rev.* **28**, 379–490.

Herrera, D. G. & Robertson, H. A. 1996 Activation of c-*fos* in the brain. *Prog. Neurobiol.* **50**, 83–107.

Holdstock, J. S., Shaw, C. & Aggleton, J. P. 1995 The performance of amnesic subjects on tests of delayed matching-to-sample and delayed matching-to-position. *Neuropsychologia* **33**, 1583–1596.

Holdstock, J. S., Mayes, A. R., Cezayirli, E., Isaac, C. L., Aggleton, J. P. & Roberts, J. N. 2000 A comparison of egocentric and allocentric spatial memory in a patient with selective hippocampal damage. *Neuropsychologia* **38**, 410–425.

Honey, R. C. & Good, M. 2000 Associative modulation of the orientating response: distinct effects revealed by hippocampal lesions. *J. Exp. Psychol. Anim. Behav. Process.* **26**, 3–14.

Hunt, M. E., Kesner, R. P. & Evans, R. B. 1994 Memory for spatial location: functional dissociation of entorhinal cortex and hippocampus. *Psychobiology* **22**, 186–194.

Hunt, P. R. & Aggleton, J. P. 1998*a* An examination of the spatial working memory deficit following neurotoxic medial dorsal thalamic lesions in rats. *Behav. Brain Res.* **97**, 129–141.

Hunt, P. R. & Aggleton, J. P. 1998*b* Neurotoxic lesions of the dorsomedial thalamus impair the acquisition but not the performance of delayed matching to place by rats: a deficit in shifting response rules. *J. Neurosci.* **18**, 10 045–10 052.

Jay, T. M. & Witter, M. P. 1991 Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of *Phaeolus vulgaris* leucoagglutinin. *J. Comp. Neurol.* **313**, 574–586.

Jones, B. & Mishkin, M. 1972 Limbic lesions and the problem of stimulus-reinforcement associations. *Exp. Neurol.* **36**, 362–377.

Kesner, R. P. 2000 Subregional analysis of mnemonic functions of the prefrontal cortex in the rat. *Psychobiology* **28**, 219–228.

Kesner, R. P. & Giles, R. 1998 Neural circuit analysis of spatial working memory: role of pre- and parasubiculum, medial and lateral entorhinal cortex. *Hippocampus* **8**, 416–423.

Kirby, D. L. & Higgins, G. A. 1998 Characterization of perforant path lesions in rodent models of memory and attention. *Eur. J. Neurosci.* **10**, 823–838.

Kroll, N. E. A., Knight, R. T., Metcalfe, J., Wolf, E. S. & Tulving, E. 1996 Cohesion failure as a source of memory illusions. *J. Mem. Lang.* **35**, 176–196.

Lepage, M., Ghaffar, O., Nyberg, L. & Tulving, E. 2000 Prefrontal cortex and episodic memory retrieval mode. *Proc. Natl Acad. Sci. USA* **97**, 506–511.

Liu, P. & Bilkey, D. K. 1998*a* Lesions of perirhinal cortex produce spatial memory deficits in the radial maze. *Hippocampus* **8**, 114–121.

Liu, P. & Bilkey, D. K. 1998*b* Perirhinal cortex contributes to performance in the Morris water maze. *Behav. Neurosci.* **112**, 304–315.

McAlonan, G. M., Dawson, G. R., Wilkinson, L. O., Robbins, T. W. & Everitt, B. J. 1995 The effects of AMPA-induced lesions of the medial septum and vertical limb nucleus of the diagonal band of Broca on spatial delayed non-matching to sample and spatial learning in the water maze. *Eur. J. Neurosci.* **7**, 1034–1049.

McKee, R. D. & Squire, L. R. 1993 On the development of declarative memory. *J. Exp. Psychol. Learn. Mem. Cogn.* **19**, 397–404.

McMahan, R. W., Sobel, T. J. & Baxter, M. G. 1997 Selective immunolesions of hippocampal cholinergic input fail to impair spatial working memory. *Hippocampus* **7**, 130–136.

Maguire, E. A. 2001 The retrosplenial contribution to human navigation: a review of lesion and neuroimaging findings. *Scand. J. Psychol* **42**, 225–238.

Maguire, E. A., Frackowiak, R. S. J. & Frith, C. D. 1996 Learning to find your way: a role for the human hippocampal formation. *Proc. R. Soc. Lond.* B **263**, 1745–1750.

Mahut, H. 1971 Spatial and object reversal learning in monkeys with partial temporal lobe ablations. *Neuropsychologia* 9, 409–424.

Mahut, H. 1972 A selective spatial deficit in monkeys after transection of the fornix. *Neuropsychologia* **10**, 65–74.

Mandler, G. 1980 Recognizing: the judgment of previous occurrence. *Psychol. Rev.* **87**, 252–271.

Mayes, A. R., Van Eijk, R., Gooding, P. A., Isaac, C. L. & Holdstock, J. S. 1999 What are the functional deficits produced by hippocampal and perirhinal lesions? *Behav. Brain Sci.* **22**, 460–461.

Mayes, A. R. & Roberts, N. 2001 Theories of episodic memory. *Phil. Trans. R. Soc. Lond.* B **356**, 1395–1408.

Mishkin, M. 1978 Memory in monkeys severely impaired by combined, but not by separate removal of amygdala and hippocampus. *Nature* **273**, 297–298.

Mizumori, S. J. Y., Miya, D. Y. & Ward, K. E. 1994 Reversible inactivation of the lateral dorsal thalamus disrupts hippocampal place representation and impairs spatial learning. *Brain Res.* **644**, 168–174.

Morgan, C. L. 1894 *An introduction to comparative psychology.* London: Scott.

Morris, R. G. M. 2001 Episodic-like memory in animals: psychological criteria, neural mechanisms and the value of episodic-like tasks to investigate animal models of neurodegenerative disease. *Phil. Trans. R. Soc. Lond.* B **356**, 1453–1465.

Morris, R. G. M., Garrud, P., Rawlins, J. N. P. & O'Keefe, J. 1982 Place navigation impaired in rats with hippocampal lesions. *Nature* **297**, 681–683.

Morris, R. G. M, Schenk, F., Tweedie, F. & Jarrard, L. E. 1990 Ibotenate lesions of hippocampus and/or subiculum: dissociating components of allocentric spatial learning. *Eur. J. Neurosci.* **2**, 1016–1028.

Moser, M.-B. & Moser, E. I. 1998 Functional differentiation in the hippocampus. *Hippocampus* **8**, 608–619.

Moser, M.-B., Moser, E. I., Forrest, E., Andersen, P. & Morris, R. G. M. 1995 Spatial learning with a minislab in the dorsal hippocampus. *Proc. Natl Acad. Sci. USA* **92**, 9697–9701.

Mufson, E. J. & Pandya, D. N. 1984 Some observations on the course and composition of the cingulum bundle in the rhesus monkey. *J. Comp. Neurol.* **225**, 31–43.

Mumby, D. G. & Glenn, M. J. 2000 Anterograde and retrograde memory for object discriminations and places in rats with perirhinal cortex lesions. *Behav. Brain Res.* **114**, 119–134.

Mumby, D. G. & Pinel, J. P. J. 1994 Rhinal cortex lesions and object recognition in rats. *Behav. Neurosci.* **108**, 1–8.

Murray, E. A. 1996 What have ablation studies told us about the neural substrates of stimulus memory? *Semin. Neurosci.* **8**, 13–22.

Murray, E. A. & Mishkin, M. 1986 Visual recognition in monkeys following rhinal cortical ablations combined with either amygdalectomy or hippocampectomy. *J. Neurosci.* **7**, 1991–2003.

Murray, E. A. & Mishkin, M. 1998 Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. *J. Neurosci.* **18**, 6568–6582.

Murray, E. A., Davidson, M., Gaffan, D., Olton, D. S. & Suomi, S. 1989 Effects of fornix transection and cingulate coritical ablation on spatial memory in rhesus monkeys. *Exp. Brain Res.* **74**, 173–186.

Murray, E. A., Baxter, M. G. & Gaffan, D. 1998 Monkeys with rhinal cortex damage or neurotoxic hippocampal lesions are impaired on spatial scene learning and object reversals. *Behav. Neurosci.* **112**, 1291–1303.

Naber, P. A., Witter, M. P. & Lopes da Silva, F. H. 2000 Networks of the hippocampal memory system of the rat. The pivotal role of the subiculum. *Ann. NY Acad. Sci.* **911**, 392–403.

Neave, N., Nagle, S., Sahgal, A. & Aggleton, J. P. 1996 The effects of discrete cingulum bundle lesions in the rat on the acquisition and performance of two tests of spatial working memory. *Behav. Brain Res.* **80**, 75–85.

Neave, N., Nagle, S. & Aggleton, J. P. 1997 Evidence for the involvement of the mamillary bodies and cingulum bundle in allocentric spatial processing by rats. *Eur. J. Neurosci.* **9**, 101–115.

O'Keefe, J. & Nadel, L. 1978 *The Hippocampus as a cognitive map*. Oxford University Press.

Olton, D. S., Becker, J. T. & Handelman, G. E. 1979 Hippocampus, space, and memory. *Behav. Brain Sci.* **2**, 313–365.

Olton, D. S., Walker, J. A. & Woolf, W. A. 1982 A disconnection analysis of hippocampal function. *Brain Res.* **233**, 241–253.

Papez, J. W. 1937 A proposed mechanism of emotion. *Arch. Neurol. Psychiatry* **38**, 725–743.

Parker, A. & Gaffan, D. 1997 The effects of anterior thalamic and cingulate cortex lesions on 'object-in-place' memory in monkeys. *Neuropsychologia* **35**, 1093–1102.

Parker, A. & Gaffan, D. 1998 Interaction of frontal and perirhinal cortices in visual object recognition memory in monkeys. *Eur. J. Neurosci.* **10**, 3044–3057.

Parkinson, J. K., Murray, E. A. & Mishkin, M. 1988 A selective mnemonic role for the hippocampus in monkeys: memory for the location of objects. *J. Neurosci.* **8**, 4159–4167.

Passingham, R. E. 1993 *The frontal lobes and voluntary action*. Oxford University Press.

Pearce, J. M. 1994 Similarity and discrimination: a selective review and a connectionist model. *Psychol. Rev.* **101**, 587–607.

Penfield, W. & Mathieson, G. 1974 Memory: autopsy findings and comments on the role of the hippocampus in experiential recall. *Arch. Neurol.* **31**, 145–154.

Pouzet, B., Welzl, H., Gubler, M. K., Broersen, L., Veenman, C., Feldon, J., Rawlins, J. N. P. & Yee, B. K. 1999 The effects of NMDA-induced retrohippocampal lesions on performance of four spatial memory tasks known to be sensitive to hippocampal damage in the rat. *Eur. J. Neurosci.* **11**, 123–140.

Ragozzino, M. E., Detrick, S. & Kesner, R. P. 1999 Involvement of the prelimbic–infralimbic areas of the rodent prefrontal cortex in behavioral flexibility for place and response learning. *J. Neurosci.* **19**, 4585–4594.

Ramirez, J. J. & Stein, D. G. 1984 Sparing and recovery of spatial alternation performance after entrohinal cortex lesions in rats. *Behav. Brain Res.* **13**, 53–61.

Rempel-Clower, N. L., Zola, S. M., Squire, L. R. & Amaral, D. G. 1996 Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *J. Neurosci.* **16**, 5233–5255.

Riedel, G., Micheau, J., Lam, A. G. M., Roloff, E. V. L., Martin, S. J., Bridge, H., de Hoz, L., Poeschel, B., McCulloch, J. & Morris, R. G. M. 1999 Reversible neural inactivation reveals hippocampal participation in several memory processes. *Nature Neurosci.* **2**, 898–905.

Rosenbaum, R. S., Priselac, S., Kohler, S., Black, S. E., Gao, F., Nadel, L. & Moscovitch, M. 2000 Remote spatial memory in an amnesic person with extensive bilateral hippocampal lesions. *Nature Neurosci.* **3**, 1044–1048.

Rudy, J. W. & Sutherland, R. J. 1995 Configural association theory and the hippocampal formation: an appraisal and reconfiguration. *Hippocampus* **5**, 375–389.

Sharp, P. E. 1999 Complimentary roles for hippocampal versus subicular/entorhinal place cells in coding place, context, and events. *Hippocampus* **9**, 432–443.

Shaw, C. & Aggleton, J. P. 1993 The effects of fornix and medial prefrontal lesions on delaying nonmatching-to-sample by rats. *Behav. Brain Res.* **54**, 91–102.

Squire, L. R. 1992 Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* **99**, 195–231.

Squire, L. R. & Knowlton, B. J. 1995 Memory, hippocampus, and brain systems. In *The cognitive neurosciences* (ed. M. Gazzinaga), pp. 825–835. Cambridge, MA: MIT Press.

Squire, L. R. & Zola-Morgan, S. 1991 The medial temporal lobe memory system. *Science* **253**, 1380–1386.

Squire, L. R., Zola-Morgan, S. & Chen, K. S. 1988 Human amnesia and animal models of amnesia: performance of amnesic patients on tests designed for the monkey. *Behav. Neurosci.* **102**, 210–221.

Steckler, T., Drinkenburg, W. H. I. M., Sahgal, A. & Aggleton, J. P. 1998 Recognition memory in rats. I Concepts and classification. *Prog. Neurobiol.* **54**, 289–311.

Sutherland, R. J. & Hoesing, J. M. 1993 Posterior cingulate cortex and spatial memory: a microlimnology analysis. In *Neurobiology of cingulate cortex and limbic thalamus* (ed. B. A. Vogt & M. Gabriel), pp. 461–477. Boston, MA: Birkhäuser.

Sutherland, R. J. & Rodriguez, A. J. 1989 The role of the fornix/fimbria and some related subcortical structures in place learning and memory. *Behav. Brain Res.* **32**, 265–277.

Sutherland, R. J. & Rudy, J. W. 1989 Configural association theory: the role of the hippocampal formation in learning, memory, and amnesia. *Psychobiology* **17**, 129–144.

Sutherland, R. J., Whishaw, I. Q. & Kolb, B. 1988 Contributions of cingulate cortex to two forms of spatial learning and memory. *J. Neurosci.* **8**, 1863–1872.

Swanson, L. W., Kohler, C. & Bjorklund, A. 1987 The limbic region. I The septohippocampal system. In *Handbook of chemical neuroanatomy, vol. 5: integrated systems of the CNS*, part 1

(ed. A. Bjorklund, T. Hokfelt & L. W. Swanson), pp. 125–277. New York: Elsevier.

Taube, J. S. 1995 Head direction cells recorded in the anterior thalamic nuclei of freely moving rats. *J. Neurosci.* **15**, 70–86.

Tischmeyer, W. & Grimm, R. 1999 Activation of immediate early genes and memory formation. *Cell. Mol. Life Sci.* **55**, 564–574.

Tulving, E. 1983 *Elements of episodic memory.* New York: Oxford University Press.

Tulving, E. 1984 Precis of *Elements of episodic memory. Behav. Brain Sci.* **7**, 223–268.

Valenstein, E., Bowers, D., Verfaellie, M., Heilman, K. M., Day, A. & Watson, R. T. 1987 Retrosplenial amnesia. *Brain* **110**, 1631–1646.

Van der Werf, Y. D., Witter, M. P., Uijlings, H. B. M. & Jolles, J. 2000 Neuropsychology of infarctions in the thalamus: a meta-analysis. *Neuropsychologia* **38**, 613–627.

Vann, S. D., Brown, M. W. & Aggleton, J. P. 2000*a* Fos expression in the rostral thalamic nuclei and associated cortical regions in response to different spatial memory tasks. *Neuroscience* **101**, 983–991.

Vann, S. D., Brown, M. W., Erichsen, J. T. & Aggleton, J. P. 2000*b* Fos imaging reveals differential patterns of hippocampal and parahippocampal subfield activity in response to different spatial memory tasks. *J. Neurosci.* **20**, 2711–2718.

Vann, S. D., Brown, M. W., Erichsen, J. T. & Aggleton, J. P. 2000*c* Using Fos imaging in the rat to reveal the anatomical extent of the disruptive effects of fornix lesions. *J. Neurosci.* **20**, 8144–8152.

Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., Van Paesschen, W. & Mishkin, M. 1997 Differential effects of early hippocampal pathology on episodic and semantic memory. *Science* **277**, 376–380.

Wan, H., Aggleton, J. P. & Brown, M. W. 1999 Different contributions of the hippocampus and perirhinal cortex to recognition memory. *J. Neurosci.* **19**, 1142–1148.

Warburton, E. C. & Aggleton, J. P. 1999 Differential effects in the Morris water maze following cytotoxic lesions of the anterior thalamus and fornix transection. *Behav. Brain Res.* **98**, 27–38.

Warburton, E. C., Baird, A. L. & Aggleton, J. P. 1997 Assessing the magnitude of the allocentric spatial deficit associated with complete loss of the anterior thalamic nuclei in rats. *Behav. Brain Res.* **87**, 223–232.

Warburton, E. C., Aggleton, J. P. & Muir, J. L. 1998 Comparing the effects of selective cingulate cortex and cingulum bundle lesions on a spatial navigation task. *Eur. J. Neurosci.* **10**, 622–634.

Warburton, E. C., Morgan, A., Baird, A. L., Muir, J. L. & Aggleton, J. P. 1999 Does pretraining spare the spatial deficit associated with anterior thalamic damage in rats? *Behav. Neurosci.* **113**, 956–967.

Warburton, E. C., Baird, A. L., Morgan, A., Muir, J. L. & Aggleton, J. P. 2000 Disconnecting hippocampal projections to the anterior thalamus produces deficits on tests of spatial memory in rats. *Eur. J. Neurosci.* **12**, 1714–1726.

Warburton, E. C., Morgan, A., Baird, A., Muir, J. L. & Aggleton, J. P. 2001 The importance of the anterior thalamic nuclei for hippocampal function: evidence from a disconnection study in rats. *J. Neurosci.* (In the press.)

Weisman, R. G., Wasserman, E. A., Dodd, P. W. D. & Larew, M. B. 1980 Representation and retention of two event sequences in pigeons. *J. Exp. Psychol. Anim. Behav. Process.* **6**, 312–325.

Whishaw, I. Q. 1998 Place learning in hippocampal rats and the path integration hypothesis. *Neurosci. Biobehav. Rev.* **22**, 209–220.

Whishaw, I. Q. & Jarrard, L. E. 1995 Similarities vs. differences in place learning and circadian activity in rats after fimbria-fornix section or ibotenate removal of hippocampal cells. *Hippocampus* **5**, 595–604.

Whishaw, I. Q., Cassel, J-C. & Jarrard, L. E. 1995 Rats with fimbria-fornix lesions display a place response in a swimming pool: a dissociation between getting there and knowing where. *J. Neurosci.* **15**, 5779–5788.

Whishaw, I. Q., Maaswinkel, H., Gonzalez, C. L. R. & Kolb, B. 2001 Deficits in allothetic and idiothetic spatial behavior in rats with posterior cingulate cortex lesions. *Behav. Brain Res.* **118**, 67–76.

Wiig, K. A. & Bilkey, D. K. 1994*a* Perirhinal cortex lesions in rats disrupt performance in a spatial DNMS task. *NeuroReport* **5**, 1405–1408.

Wiig, K. A. & Bilkey, D. K. 1994*b* The effects of perirhinal cortical lesions on spatial reference memory in the rat. *Behav. Brain Res.* **63**, 101–109.

Wise, S. P. & Murray, E. A. 1999 Role of the hippocampal system in conditional motor learning: mapping antecedents to action. *Hippocampus* **9**, 101–117.

Witter, M. P., Groenewegen, H. J., Lopes da Silva, F. H. & Lohman, A. H. M. 1989 Functional organization of the extrinsic and intrinsic circuitry of the parahippocampal region. *Prog. Neurobiol.* **33**, 161–253.

Witter, M. P., Naber, P. A., Van Haeften, T., Machielsen, W. C. M., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P. & Lopes da Silva, F. H. 2000 Cortico–hippocampal communication by way of parallel parahippocampal–subicular pathways. *Hippocampus* **10**, 398–410.

Wodinsky, J., Varley, M. A. & Bitterman, M. E. 1952 Situational determinants of the relative difficulty of simultaneous and successive discriminations. *J. Comp. Physiol. Psychol.* **47**, 337–340.

Wyss, J. M. & Van Groen, T. 1992 Connections between the retrosplenial cortex and the hippocampal formation in the rat: a review. *Hippocampus* **2**, 1–12.

Yonelinas, A. P. 2001 Components of episodic memory: the contribution of recollection and familiarity *Phil. Trans. Roy. Soc. Lond.* B **356**, 1363–1374.

Zhu, X. O., Brown, M. W. & Aggleton, J. P. 1995*a* Neuronal signalling of information important to visual recognition memory in rat rhinal and neighbouring cortices. *Eur. J. Neurosci.* **7**, 753–765.

Zhu, X. O., Brown, M. W., McCabe, B. J. & Aggleton, J. P. 1995*b* Effects of the novelty or familiarity of visual stimuli on the expression of the intermediate early gene c-*fos* in the rat brain. *Neuroscience* **69**, 821–829.

Zhu, X. O., McCabe, B. J., Aggleton, J. P. & Brown, M. W. 1996 Mapping recognition memory through the differential expression of the immediate early gene c-*fos* induced by novel or familiar visual stimulation. *NeuroReport* **7**, 1871–1875.

Zola-Morgan, S. & Squire, L. R. 1985 Amnesia in monkeys after lesions of the mediodorsal nucleus of the thalamus. *Ann. Neurol.* **17**, 558–564.

Zola-Morgan, S., Dabrowska, J., Moss, M. & Mahut, H. 1983 Enhanced preference for perceptual novelty in the monkey after section of the fornix but not after ablation of the hippocampus. *Neuropsychologia* **21**, 433–454.

Zola-Morgan, S., Squire, L. R. & Amaral, D. G. 1989*a* Lesions of the hippocampal formation but not lesions of the fornix or the mammillary nuclei produce long-lasting memory impairments in monkeys. *J. Neurosci.* **9**, 898–913.

Zola-Morgan, S., Squire, L. R., Amaral, D. G. & Suzuki, W. A. 1989*b* Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. *J. Neurosci.* **9**, 4355–4370.