When is the perirhinal cortex necessary for the performance of spatial memory tasks?

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Received 23 June 2004; revised 26 August 2004; accepted 26 August 2004

Abstract

The perirhinal cortex and hippocampus have close anatomical links and it has, therefore, been proposed that they have important, coordinated roles in memory. This review examines the relative role of these structures in spatial memory tasks that are known to be hippocampal-dependent. The published lesion data gives a mixed picture, as only some studies detect spatial deficits after perirhinal cortex lesions. The possible reasons for these inconsistencies are reviewed, along with electrophysiological data that indicate how perirhinal cortex lesions may alter neuronal activity in the hippocampus. Overall, the disruptive effects of perirhinal lesions on spatial memory performance are, when they occur, typically transient and never as severe as those seen after hippocampal lesions. It is argued that parallel cortical routes provide key, sensory data to the hippocampus such that in the absence of the perirhinal cortex alternative information is available. The deficits associated with perirhinal damage may then reflect difficulties that arise when task performance requires the use of ambiguous distal cues, for example, those containing overlapping visual features.

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Keywords: Perirhinal cortex; Parahippocampal gyrus; Hippocampus; Spatial memory

The perirhinal cortex (areas 35 and 36), which forms part of the parahippocampal region, has direct anatomical connections with the hippocampus (Fig. 1). It also has dense, reciprocal connections with the entorhinal cortex which, in turn, is connected to the hippocampus (Fig. 1). Through these direct and indirect links the perirhinal cortex can influence the hippocampus [1,2]. Both the perirhinal cortex and the hippocampus are regarded as key regions for aspects of memory, and by virtue of their interconnections these mnemonic roles are often seen as being tightly linked. The extent to which these two regions are involved in the same classes of memory has, however, become a contentious topic (for contrasting views see [3–5]).

The purpose of this review is to consider the importance of the perirhinal cortex for one aspect of memory, spatial memory. To be more specific, this review will examine those aspects of spatial memory that are dependent on an intact hippocampus. In view of their connections, the discovery that the perirhinal cortex is also necessary for spatial memory would provide an important confirmatory step in the notion of an interdependent perirhinal–hippocampal memory system. Although research with nonhuman primates will be described, this review will focus primarily on data from studies with rats. This is because the large majority of relevant studies have been carried out with this species. It is, therefore, important to appreciate that a similar pattern of anatomical relationships exists between the perirhinal cortex and the hippocampus in both the rodent and the primate brain [6].

This review was prompted by the fact that a glance at the relevant lesion data will show that they are contradictory, and that by carefully picking the right references it is possible to support almost any viewpoint. Thus, for a range of different spatial tasks that are consistently sensitive to hippocampal damage (Morris water maze, radial-arm maze, T-maze alternation, delayed nonmatching-to-position), some studies have found normal performance following

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doi:10.1016/j.neubiorev.2004.08.007
perirhinal lesions while an almost equal number have found impairments. Some studies have even found evidence for enhanced performance after perirhinal lesions. The uncertainty generated by these conflicting results is delaying progress in creating more formal models of the functional relationships between the perirhinal cortex, the hippocampus, and the remainder of the parahippocampal region [7,8].

Our strategy will be to consider first those general methodological features that might account for these differences in the effects of perirhinal lesions. This is followed by a detailed consideration of the findings for different types of spatial tasks. These tasks will be dealt with separately as they make varying demands on the animals. Unless it is specifically stated, the information refers to studies on the rat brain. The outcome of this initial review will then be placed in the context of other forms of evidence, in particular, single cell recording studies in normal rats and in rats with perirhinal lesions.

1. Lesion evidence

As outlined above, the effects of perirhinal lesions on tests of spatial memory are remarkable for their degree of inconsistency. Just as a large number of papers have reported no lesion induced deficits [9–18], so have an equally large number found impairments [19–29].

1.1. Extent of perirhinal damage

The perirhinal cortex lies in the rhinal sulcus and extends rostro-caudally for a distance of approximately 4.5 mm in the rat brain. In view of its shape and historical variation in the definition of its borders [1,6] it is not surprising that the extent of perirhinal surgeries has sometimes varied. This leads to perhaps the most obvious explanation for the inconsistent findings in the literature: those studies associated with lesion-induced deficits have a more complete removal of the perirhinal cortex. In fact, an examination of the published data rapidly shows that this is not the case.

An inspection of the extent of those lesions that were targeted at just the perirhinal cortex also fails to support the premise that lesion size is the key factor. Some of the most discrete lesions appear to be those by Wiig and Bilkey [19,28] where there is some sparing of the rostral perirhinal cortex. Nevertheless, in both studies the lesions produce
significant deficits on tests of spatial memory. Perhaps the sole example where lesion size may have been an important factor is a study in which the perirhinal lesions were described as subtotal, with approximately 75% of the region being spared [30]. In this study the lesions did not impair acquisition of a water maze task.

1.2. Lesion method and cell loss beyond the perirhinal cortex

Lesions of the perirhinal cortex have been made in a number of different ways. ‘Conventional’ methods include removing the region by aspiration [12,31,32] or damaging it with electrolytic lesions [19,20,22–24,27,30,32,36] or radiofrequency current [29]. Of these conventional methods the only evidence of a difference is the suggestion that electrolytic lesions may be more disruptive than aspiration lesions in tests of the postoperative retention of a location in the water maze [32,33] ‘Neurotoxic’ methods involve injecting NMDA [9–11,13–17,34,35] or ibotenic acid [18,23,25,26,34–37] at concentrations that act as an excitotoxin. The rationale for using neurotoxins reflects the goal of minimising damage to fibres of passage e.g. the white matter in the external capsule that lies immediately below the perirhinal cortex. There does, however, appear to be some trade-off with this latter method in terms of control over the location and extent of the lesion [38].

A few years ago it seemed that conventional lesions typically produced spatial impairments [19,20,28], while neurotoxic lesions had no apparent effect [9–11]. The implication was that the involvement of fibres of passage might be critical in producing a deficit. In fact, more recent studies have shown this interpretation to be incorrect. Thus, spatial deficits have been found in a series of studies using ibotenic acid [23,25,26]. Conversely, unimpaired performance has been reported in some studies after conventional lesions [12,31,33 Exp. 3]. Furthermore, direct comparisons have been made between conventional and neurotoxic lesions on T-maze alternation, with both techniques producing similar delay-dependent deficits [23]. Lastly, close inspection of the lesion sites in some of those studies with conventional surgeries associated with lesion-induced deficits appears to rule out the involvement of white matter deep to the perirhinal cortex (e.g. [19]). It, therefore, seems that the critical issue is not hidden damage to fibres of passage.

A related issue concerns the extent to which the perirhinal lesions extend into adjacent areas. Immediately ventral to much of the rostral perirhinal cortex is the pyriform cortex and, more caudally, the lateral entorhinal cortex. This is potentially relevant as combined lesions of the perirhinal and entorhinal cortices impair spatial tasks in the water maze [39] and radial-arm maze [40]. Inspection of those studies that have reported the most involvement of these regions shows that these include cases where there is no spatial deficit, e.g. [8,12–14]. Consistent with this conclusion is the report that the addition of damage to the lateral entorhinal cortex, that part of the entorhinal cortex adjacent to the perirhinal cortex, does not induce a spatial deficit in the water maze [18].

Of more obvious concern is the possible contribution from damage to the hippocampus proper. Parts of region CA1 are immediately medial to the fundus of the perirhinal cortex and are therefore especially vulnerable. Studies with conventional lesions typically report no direct damage to the hippocampus proper [19,20,22–24,27,28]. Involvement of CA1 does, however, appear to be more frequent with neurotoxic lesions. Restricted bilateral cell loss in CA1 was reported in a number of such studies [9,10,16,26]. In the first three of these studies [9,10,16] no deficit was found, however, on the various spatial tasks that were used. A very transient deficit was found by Burwell et al. [18], which was ascribed to CA1 involvement. Overall, there is no obvious relationship with study outcome and the minor involvement of regions outside the perirhinal cortex. It should also be added that in almost all of these experiments [9,10,16,26] the degree of hippocampal damage was typically very slight and, on the basis of other studies [41,42], might be expected to have little or no apparent effect given its locus and extent.

1.3. Gender and strain of rats

All studies have used male rats and so gender differences between studies can be discounted. As a variety of strains have been used this feature requires more careful consideration. Nearly all studies have used one of three strains, Dark Agouti, Long–Evans, or Sprague–Dawley. These strains differ in their abilities to learn both spatial and nonspatial tasks [43,44]. Inspection of perirhinal lesion studies reveals that those laboratories that use the pigmented Dark Agouti rat typically find no spatial deficits [9–11,13–16,31] while those using albino strains e.g. Sprague–Dawley [19–26,27] have reported deficits. An exception is the study by Ramos [17] in which no evidence of a deficit was found in albino (Wistar) rats on a spatial discrimination. A third strain, Long–Evans hooded rats, has also been used. Water maze studies using the Long–Evans strain have reported either no perirhinal lesion effect [8,12,18] or only a transient deficit [32,33 Exp. 2], while more persistent deficits were found on a radial-arm maze task [29]. In contrast, Hooded rats with perirhinal lesions acquired radial maze tasks at normal levels [34,35]. Taken overall, there appears to be a strong, but not perfect, association between the use of albino rats and the presence of a spatial deficit, while pigmented rats are associated with little or no deficit. It is important to add that for nonspatial tasks, e.g. tests of recognition memory, perirhinal lesion deficits are found in pigmented rat strains [9,45,46] suggesting that any association is restricted to spatial learning.

The first thing to appreciate is that an apparent association with strain type could be completely misleading. This is because different laboratories typically use only one strain, and so strain type will be confounded with
a multitude of other procedural factors. Furthermore, a strain effect does not, in itself, provide a full explanation but raises further questions about its cause. At present only one study [47] has examined this specific issue. Rats of the Dark Agouti and Sprague–Dawley strains, with or without neurotoxic perirhinal cortex lesions, were tested on a range of reference and working spatial memory tasks in the water-maze. Although there were strain differences among the control groups [47], perirhinal lesions did not affect acquisition or probe performance of the reference memory task in either strain. During initial training (10 sessions) on a working memory task in the water maze there were again no lesion effects for either strain, though the Dark Agouti rats with perirhinal lesions were now impaired when a delay of 180 s was placed between trials 1 and 2 (the most sensitive trials with which to test working memory). This deficit was, however, very restricted as no lesion effects were found on subsequent manipulations of the working memory task. It is also, perhaps, ironic that the only strain by lesion interaction was found because of poor performance by the Dark Agouti strain, the strain that on the basis of previous studies appeared to be least affected by perirhinal cortex lesions.

This preliminary study [47] supports the idea that strain by lesion site interactions could occur. For this reason it is helpful to consider why strain choice could be a factor. One possibility concerns the fact that different strains differ in their sensory capabilities. This has been examined for vision where it has been shown that the three strains most typically used for perirhinal lesion studies (Sprague–Dawley, Dark Agouti, Long–Evans) do not have the same levels of visual resolution [48]. The strain with relatively poor visual acuity (Sprague–Dawley 0.5 cycle/deg grating discrimination) is most often impaired, while those strains with better acuity (Dark Agouti, Long–Evans, both 1 cycle/deg) are often unimpaired after perirhinal lesions.

This difference in acuity could have direct effects on performance if it was necessary that rats actually discriminate one visual cue from another in order to solve the spatial task. This is classically assumed to be the case in allocentric processing where the arrangement of distal cues, which are typically visual, sets the animal’s current position. In fact, it can be argued that in many instances position can be determined without the animals having to discriminate individual cues from each other. For example, in situations if the number of cues varies from surface to surface, or when there are salient size differences in the cues. In contrast, the demand on cue discrimination becomes greatest when (1) no other cues (ideothetic or otherwise) are available to provide a reference orientation, and (2) visual cues are placed symmetrically about an axis in the environment. In fact, it would be most unusual to use symmetrically placed cues, and experimenters typically try to avoid cues that might be difficult to discriminate. For these reasons, a difference in levels of acuity might normally have little effect on most spatial mapping problems. Nevertheless, under certain conditions (e.g. low light levels, cues placed relatively far away, common cues in different locations) this acuity difference might bias particular rat strains to rely on different combinations of intramaze and extramaze cues to solve spatial tasks. This could, in turn, lead to different lesion effects.

1.4. Type of spatial task

In view of the rationale for understanding perirhinal–hippocampal interactions this review will only consider spatial tasks that are consistently sensitive to the effects of hippocampal damage. The review will start with tasks in the Morris water maze. The advantage of this apparatus is that with few exceptions (e.g. distance from side walls) local, intramaze cues are of limited assistance, and so accurate performance is reliant on distal cues.

1.4.1. Morris water maze: reference memory

A total of 10 studies have examined the effects of perirhinal lesions in rats on learning to swim to a submerged platform in a constant position across sessions. Impairments were reported in five studies [19,22,26,27,32,33]. In one of these studies [33] a very mild deficit was observed on a preoperatively learnt place task (confined to trial 2, Exp. 2), but the acquisition of a new platform location was unimpaired (Exp. 3). Likewise, Glenn et al. [32] found that an impairment was present on just the first retention trial after surgery, and that thereafter performance appeared unaffected. The authors felt that this subtle impairment ‘may not be due to impaired spatial memory abilities’ [32].

Normal task acquisition and probe performance was reported in two studies [8,13] while one study, with subtotal lesions [30] found initial evidence of enhanced performance. Finally, in a series of four experiments lesions of the perirhinal cortex consistently failed to affect acquisition although transient deficits were found in the probe trials of one of these experiments [18].

At first it is difficult to determine any methodological differences that correlate with these findings. In all studies new start positions were used on every trial to preclude response-based cues, and although pool diameter varied between studies (1.37 m Glenn and Mumby [12,32,33], 1.5 m Bilkey and colleagues [19,22,26,27], 1.8 m Burwell [8,18], 2.0 m Aggleton and colleagues [8,13,16]) this factor does not predict the presence or absence of a deficit in a systematic way, i.e. deficits were not restricted to the largest pools. Another issue concerns the size of the room used in these studies as this will affect the proximity of allocentric cues. Room size (in m) varied from 4.8 by 5.2 [19,22,26,27] to 4.4 by 4.0 [13], 3×4 [16] and 3.3 by 4.5 m [12,32,33]. Although the studies where a lesion effect was observed occurred in the largest room, when the actual distances are compared, the differences are relatively minor. For example, the difference in distance from the pool edge to the room wall (where the distal cues were located) between the...
Liu and Bilkey studies (where an effect occurred [19,22,26, 27]) was approximately 1–2 m while in the Bussey et al. study [13] (where it did not) it was only around 0.5 m.

A factor that could potentially interact with room size is illumination level. It is interesting that the selection of illumination levels for the water maze tasks can be related to the choice of rat strain. Automated animal tracking systems function most successfully with a high contrast between the target and the background. As a result an albino rat is best tracked against a dark background with low light levels whereas a pigmented strain can be tracked against a well-lit light-coloured background. As a result, one marked difference between the studies of Liu and Bilkey [22,26,27] and Aggleton and colleagues [13,16] pertains to the lighting within the experimental rooms. Whereas the former studies were run with low light levels, for example, in a room lit by four 60 W bulbs (approximately 10–20 lux immediately above the water), the latter studies utilised four 500 W lights (approximately 365 lux). It would be the case, therefore, that the combination of low light levels and greater distance to cues would have further disadvantaged a strain of rats with poor visual acuity if determining cue identity was critical to solution of the task. This factor remains to be analysed systematically.

We will first consider the effects of perirhinal lesions on acquisition of the standard task, prior to considering probe performance or any other manipulations. The data show that when there is an acquisition deficit, it appears to be transient. That is, after a small number of training sessions performance of the perirhinal lesion animals catches up transient. That is, after a small number of training sessions when there is an acquisition deficit, it appears to be performance or any other manipulations. The data show that acquisition of the standard task, prior to considering probe analyses systematically.

1.4.2. Morris maze: working memory

Three studies have examined delayed matching-to-place (DMTP) in the water maze, a test of working memory. In this task the platform moves position from session to session [16,26], or from trial to trial within each session [12]. As a consequence the animal must repeatedly update its place learning. In two studies no evidence of a perirhinal lesion deficit was observed on task acquisition [12,16]. In both studies task difficulty was then increased by extending the retention delay between the sample and test trial to 300 s [12] or 30 min [16]. In neither study did this result in a delay dependent deficit. The outcome was not affected by whether the task was learnt prior to surgery or after surgery [12]. In both cases DMTP was the only water maze task used in the study.

A different pattern of results was reported by Liu and Bilkey [26]. While performance with retention delays of 30 s was normal, an impairment was found with delays of 180 s. There are several differences in procedure that may account for this effect. Unlike the other two studies [12,16], these animals had been trained immediately prior to the DMTP on the reference memory version of the water maze task, i.e. fixed platform position across sessions, immediately prior to the working memory version [26]. Although this sequence might be expected to have some negative transfer effects, as the animals must learn a new rule, it is difficult to see how this could produce the observed pattern of delay dependent deficits yet fail to affect performance on the sample phase of the procedure.
Another difference between working memory procedures is that Liu and Bilkey [26] started animals from different positions during the sample and test phase (trials 1 and 2) of the task. In contrast, other studies either used the same start position for the first two trials of each session [16], or the same start position for each pair of trials [12]. Although the repeat start position makes it possible to equate swim distance for the working memory comparison, the task might also become easier. Against this explanation is the fact that the study by Glenn and Mumby [12] used up four pairs of trials per session, i.e. four new locations to learn within each session, and still no perirhinal lesion deficit was observed. Other potential differences relate to strain effects, room size and levels of illumination. These differences have been discussed in Section 1.4.1, and could also affect the working memory task.

1.4.3. Radial-arm maze: working memory

Dry maze tasks (e.g. radial-arm maze and T-maze) suffer the problem that rats often have at their disposal a greater array of extramaze and intramaze cues with which to solve the task [50–53]. In addition, there is the potential to use egocentric or proprioceptive cues to guide choices. As rats are flexible in the way in which they use different cue types to solve spatial tasks [51–55] there is the potential for greater variability between studies. Furthermore, as rats are able to switch between cue types [50,52,53] a lesion induced deficit for one specific class of cue might be difficult to isolate. These caveats should be kept in mind when comparing the different studies.

The standard radial-arm maze task, and variants of it, have been used repeatedly to test the effects of perirhinal lesions. Acquisition deficits were found in four studies [24–27] while six other studies failed to find impairments [10,13,15,16,34,35]. In all cases, task acquisition involved starting with all arms baited. When deficits were observed the rats with perirhinal lesions required between four [26] and eight [24,25] sessions before their performance overlapped with that of the control groups. It has been suggested that a potentially important variable is the amount of habituation to the maze prior to training, and that with more extended habituation lesion effects might be masked [56]. This possibility was examined formally by Machin et al. [16] who found no evidence that a deficit appeared with restricted habituation sessions. The same study also looked at the effects of switching the rats to a novel room, where no habituation to the maze was required. Once again, there was no evidence that perirhinal lesions had a disruptive effect [16].

A slightly different procedure was used by Mair et al. [29] who used a continuous nonmatching-to-arm procedure. Each session involved retention delays from 1 to 25 s and lasted for 40 trials, so there was much greater proactive interference than in the standard task. Perirhinal lesions resulted in a delay independent deficit [29], although the lesions consistently extended into the postrhinal cortex and entorhinal cortex and this may have contributed to the pattern of results.

The standard radial-arm maze task can be made more difficult by adding delays after the animal has made a preselected number of different arm choices (either forced or free choice). In two studies deficits were found to reappear when delays of 10 min were placed after the first four arm choices [25,26]. By rotating and cleaning the maze during this period it was possible to remove intramaze cues that could assist performance. From this pattern of results it is tempting to conclude that perirhinal deficits are variable in acquisition but consistently appear when performance is taxed by longer retention delays. It is, however, the case that Bussey et al. [13] found no deficit in animals with combined perirhinal and postrhinal lesions after retention intervals of 30 min following the first four arm choices. Likewise, Moran and Dalrymple-Alford [34] found no perirhinal lesion deficit associated with delays of 20 s–40 min after the rat had visited the first six arms in a 12 arm maze. In spite of this apparent inconsistency there is again general agreement that when perirhinal lesions are disruptive the effects are typically much milder than those following hippocampal lesions [26,29,38]. Two studies have performed direct comparisons of the two surgeries. Liu and Bilkey [26] found that hippocampal lesions were significantly more disruptive on task acquisition, though there was an overlap of scores when a delay of 10 min was inserted. Very recently, however, Winters et al. [35] reported a clear dissociation between the two groups, where hippocampal lesioned rats were impaired relative to both controls and peri- plus postrhinal cortex lesioned animals in both the initial testing phase as well as probe trials. In these probe trials, in which there was a delay of 30 min following the first four arm choices, the animals with perirhinal lesions did not differ from their controls [35].

1.4.4. T-maze alternation: working memory

Just as for the radial-arm maze, consideration should be given to the range of cues that could be used to solve T-maze alternation tasks [50–55]. In addition to the intramaze and extramaze cues that can also support radial-arm maze performance, rats in the T-maze can also use positional cues to alternate [50,52]. That is, they can learn to turn East then West. This ability appears to depend on vestibular and not egocentric information. An appreciation of the range of potential cues is likely to be important when understanding the effects of perirhinal lesions upon alternation.

Six studies have examined the effects of perirhinal lesions on T-maze alternation. In all of these studies the animal first received a forced ‘sample’ run down one arm and then, after a variable retention interval, was given a free choice between the two arms. Selection of the arm not visited in the sample run was rewarded. No evidence of an impairment was found in four studies [9,11,14,31], in which retention delays of up to 60 s were used. Three of these studies [9,11,14] were in open T-mazes with salient
extramaze cues, while the fourth [31] was in low lighting with very limited extramaze visual cues. In the remaining studies, which both used longer retention intervals [20,23], deficits were observed. The study by Liu and Bilkey [23] found deficits for retention delays of 120 and 180 s, but not for 15 s retention delays, while Wiig and Bilkey [20] found deficits at 60–120 s but not for 15 s. This evidence for faster forgetting rates was found both for animals with electrolytic lesions and neurotoxic lesions [23].

An informative aspect of the study by Liu and Bilkey [23] was the use of different control conditions to help determine the cues that the animals were reliant upon to solve the alternation task. Animals were tested (1) with prominent extramaze cues removed from the curtain that surrounded the apparatus, (2) with a different experimenter and (3) with the choice point of the maze covered with a novel surface. All these tests were conducted at the 15 s delay, and none had an effect on the animals’ performance. This indicates that neither distal visual cues, inadvertent cues provided by an experimenter or stable local cues associated with the choice point are required for task solution. In a second manipulation, T-maze rotations were conducted between the sample and test phase of the task. A re-analysis of data from the 360° (zero) and 90° rotation conditions reveals that there was a significant effect of rotation (p < 0.0001) and a significant group by rotation interaction (p < 0.01), with lesion animals being less affected by the 90° rotation than were controls. This finding suggests that the perirhinal lesioned animals may have been utilising cues that were local to the T-maze to a greater extent than control animals or less able to use ‘positional’ cues. One form of cue that might be utilised in this way are local odour cues or odour trails [50,57]. It is possible, therefore, that the procedure of wiping the maze between the sample and test phase (e.g. [25]) would differentially impair perirhinal group performance. In the same vein, in the presence of these cues, the performance of lesion group animals might be no worse or even better than controls e.g. [14].

1.4.5. Automated delayed nonmatching-to-position: working memory (DNMTP)

Two studies have used this automated test of working memory to assess the effects of perirhinal cortex lesions. In this task a ‘sample’ lever protrudes from the test box and the animal must press it for the trial to continue. After a variable delay the sample and an alternative lever appear. In the nonmatching task the rat is rewarded for pressing the alternative lever. In one study rats were trained prior to surgery, received neurotoxic lesions, and were then retested with retention delays of up to 32 s [9]. No evidence of a deficit was observed. In contrast, Wiig and Burwell [21] reported that although perirhinal lesions did not affect acquisition of the task, deficits were observed with retention delays of 5–20 s. Once again, the deficit was found in albino rats [21] but not in pigmented rats [9].

A potential problem with this task is that rats are prone to using mediating responses to span the ‘retention’ delays [58, 59]. To reduce this problem, rats are often required to make an additional response during the retention delay. This is usually a nose poke at the front [9] or the back [21] of the chamber. It is, however, clear that nose poking at the front of the chamber does not eliminate this problem [58] and the effectiveness of requiring the rat to visit the back of the chamber still requires systematic study. Furthermore, although this task is sensitive to hippocampal system damage [9,60,61], it takes place within a confined space with impoverished cues. For these reasons it is probable that it does not tax allocentric processing. This conclusion is supported by lesion evidence of double dissociations between DNMTP and other spatial tasks [62].

1.4.6. Object-in-place/object-in-scene tasks

Evidence that perirhinal lesions can disrupt spatial memory comes from tasks in which learning about space is combined with learning about object identity. The first evidence came from studies by Gaffan who developed an ‘object-in-place’ task for monkeys in which learning a series of concurrent visual discriminations is thought to involve the monkey using the specific location and contextual setting of the visual stimuli on a touch screen [63]. Experiments using this task demonstrated that discrimination performance is not only sensitive to hippocampal system damage [63,64], but also to perirhinal cortex lesions [64] in monkeys. By using a disconnection technique evidence was found that the object-in-place task involves the interaction of the perirhinal cortex with the hippocampus [64].

Evidence has also emerged that perirhinal lesions in rats also disrupt the ability to learn the location of a specific object. Using a spontaneous preference task it was first found that rats with combined perirhinal and postrhinal lesions appear unable to discriminate an object that had been relocated [14]. This was in contrast to the same animals’ ability to perform normally on T-maze alternation [14]. A failure to respond to objects that had switched position was also observed after just perirhinal lesions [26]. Lesions restricted to the perirhinal cortex were also found to impair the ability to learn a conditional task in which the solution to an object discrimination depends on the location of the animal [15]. Taking this evidence together it has been argued that these impairments reflect the importance of the perirhinal cortex for discriminating the object information that is required for the spatial component of the task [33,46]. As a consequence, these findings are thought to show how perirhinal activity may interact with the spatial processing being performed by the hippocampus, but they do not demonstrate a necessary role in spatial processing itself.

A more systematic analysis of this ability has been made possible with the development of an automated test of visual discrimination in which two-dimensional stimuli are displayed on monitors [65]. Rats with aspiration lesions of
the perirhinal cortex have been tested on visual discriminations in which the critical dimensions are either object position, object identity, or the combination of these two features (an ‘object-in-place’ task). Aspiration lesions of the perirhinal cortex [31] impaired object discriminations but not the position task. Surprisingly, the perirhinal lesions did not impair the object-in-place task [31]. This general pattern of results was repeated in a similar experiment, this time using radiofrequency perirhinal lesions [66]. The lack of a disruptive effect on the object—place configural version of the task is surprising given the difficulties with the object version. Perhaps even more surprising is the discovery that both anterior thalamic and fornix lesions can enhance performance of this condition [67] suggesting a need to understand more precisely how rats are solving this condition.

1.4.7. Reference memory in the plus maze, radial maze, and wisconsin general test apparatus

Three studies have investigated the effects of neurotoxic perirhinal lesions on reference memory performance in multi-armed mazes. Liu and Bilkey [26] reported that perirhinal-lesioned animals were not impaired during acquisition or during subsequent testing in a reference memory procedure conducted in the eight-arm radial maze. Furthermore, there was no lesion-induced deficit in a subsequent reversal procedure. Jarrard et al. [38] recently reported that rats with lesions including the perirhinal cortex were not impaired when learning to discriminate between four baited and four non-baited arms in an eight-arm maze. Ramos [17] also tested reference memory in a plus-maze and reported that the perirhinal-lesioned animals were unimpaired during both acquisition of the task and in a retention test conducted 24 days later. It is worth noting that the mazes were rotated between trials in two of these studies [17,26], to eliminate the possibility that animals might follow local cues, such as olfactory trails, to solve the task. Furthermore, in contrast to the lack of a perirhinal lesion effect in these tasks, in both of these studies animals with hippocampal lesions were impaired on the same tasks.

A similar dissociation was noted in a comparison of fornix lesions and perirhinal cortex lesions in monkeys [68]. While fornix lesions impaired the learning and subsequent reversal of simple spatial discrimination (e.g. always pick the right hand well), perirhinal lesions had no apparent effect. Using a similar task it was found that aspiration lesions of the perirhinal and entorhinal cortices in monkeys did not disrupt a place reversal or its subsequent reversals [69].

1.4.8. Contextual conditioning

A series of recent studies examined whether perirhinal cortex lesions can disrupt conditioning to a specific context. Contextual conditioning is of relevance to the present review as the animals learn about a location, although the task has no navigational demands.

In keeping with other tasks, the experimental findings are inconsistent. Four studies have examined conditioned freezing to a shock UCS in rats that have previously received perirhinal lesions. In one study, with Sprague–Dawley rats and large electrolytic lesions, no disruption of freezing was found to the context or an auditory signal [70]. In contrast, Bucci et al. [36] reported that both neurotoxic and electrolytic perirhinal lesions could disrupt the acquisition of a contextual, but not an auditory, conditioning task. In a follow-up study [37] it was argued that the failure to distinguish between the shock/no shock contexts reflected a configural learning deficit, although this interpretation was not fully tested as the two contexts still contained unique elements. Burwell et al. [18] recently demonstrated that rats with large excitotoxic lesions of the perirhinal cortex (including lateral entorhinal area) were impaired in the acquisition of a contextual fear discrimination task, showing a failure to learn the shock/no-shock context discrimination (which contained visual, tactile, and odour cues). This behaviour was, however, measured at an arbitrary stage of learning and it is not clear how permanent this deficit might be [18].

Using a different procedure, Sacchetti et al. [71] found that reversible lesions of the perirhinal cortex after conditioning could disrupt both auditory and contextual fear conditioning. Finally, evidence was found that perirhinal cortex lesions can disrupt the avoidance of a context associated with LICl, even though the same animals could learn a discrimination between two different contexts [72].

1.4.8.1. Studies where perirhinal lesions ‘improve’ spatial performance. A very surprising feature of a number of studies has been the finding that perirhinal lesions (or perirhinal plus postrhinal lesions) can occasionally lead to significantly superior levels of performance on spatial tasks. Given the number of experiments that have been conducted it might be expected that this should happen by chance, yet the fact that this has been reported in six studies suggests that a real lesion effect might be occurring.

In five studies this enhancement effect was found for tests in a ‘dry’ maze. Fewer errors on radial-arm maze acquisition were reported by Bussey et al. [13], while Machin et al. [16] found that the perirhinal lesioned rats made significantly fewer errors when they were switched to performing two consecutive trials per session (so increasing proactive interference). Liu and Bilkey [26] reported superior performance when there was a delay of 30 s after four initial forced choices in the radial-arm maze, but the same animals were significantly worse than the controls when the delay was increased to 600 s. Again in the radial-arm maze, Moran and Dalrymple-Alford [32] found that rats with perirhinal lesions significantly outperformed control rats during the initial set of sessions when a 20 s delay was imposed after the rats had visited the first six arms of a 12 arm maze. A fifth study [14] found that rats with combined
perirhinal plus postrhinal lesions significantly outperformed control animals on T-maze alternation when challenged with 60 s retention intervals (the longest used).

It may well be relevant that all of these examples relate to tests in ‘dry’ mazes where, as noted above, animals are more likely to have a wider choice of cues to help solve the task. For this reason the cases of enhanced performance may, in fact, reflect an aberrant focussing on some cue types that under specific circumstances are beneficial to performance, e.g., there is less ambiguity or less proactive interference. The sole exception to this account is a study that found perirhinal lesions could lead to significantly shorter escape latencies during acquisition of a water maze (reference memory) task [30]. The perirhinal lesions in this instance were, however, subtotal as they spared approximately 75% of the cortex. Furthermore, in view of evidence that these same rats showed heightened levels of exploration [30] it is possible that this difference reflects a greater willingness to swim out into the centre of the pool at the start of training. Consistent with this account, differences were observed from the first session but the rates of learning of the perirhinal and control groups were very similar.

2. Electrophysiological evidence

Few studies have examined the spatial firing properties of perirhinal cortex neurons. In each of these studies, however, it has been shown that perirhinal neurons are only weakly modulated by the position of the animal [73–75]. This finding contrasts with the results of similar recordings made in the hippocampus, where ‘place cells’ that fire when the animal is in a restricted region of the environment (the cell’s place field) are commonplace [76]. Not only do fewer perirhinal neurons show spatial selectivity as compared to hippocampal neurons, there is also less evidence that perirhinal neurons are controlled by the manipulation of distal cues [73].

Bearing in mind the connectivity between the perirhinal cortex and hippocampus, researchers have looked at the effects of perirhinal lesions on the electrophysiological properties of hippocampal units. In one study, the firing characteristics of dorsal CA1 place cells were examined in rats with bilateral ibotenic acid lesions centered on the perirhinal cortex or control surgeries as they foraged freely in a recording arena [77]. The effect of the lesions on the localisation of place firing was also observed after the animals were removed from the arena for a delay period of either 2 min, or 1 or 24 h. It was determined that the place fields of individual cells recorded from these animals were more likely to shift position during the delay period than control animals. These data indicate that although the initial formation of place fields in the hippocampus is not dependent on perirhinal cortex, the maintenance of this stability over time is disrupted by perirhinal lesions.

There are at least two possible explanations for this effect. One is that this instability may represent an erroneous ‘re-mapping’ of the environment caused by a loss of memory for some aspect of spatial location. An alternative explanation is that the place cells of perirhinal lesioned animals tended to respond more to local cues such as odours rather than distal visual cues. While these cues would have been relatively stable within a recording session, they would have been unstable across the delay period (particularly so because the arena was wiped between recording sessions). The finding that cells from lesioned animals were more likely to maintain position relative to the arena (but not the visual cue) compared to control cells is consistent this latter explanation. A more recent study has shown that the size of hippocampal complex-spike cell place fields is decreased in animals with perirhinal cortex lesions that are foraging freely [78]. It is possible that this also reflects a tendency for the lesioned animals (or their hippocampus) to be biased towards responding to local olfactory cues, such as odour trails [57] or body waste on the floor of the apparatus. These, by their nature, would potentially provide for more accurate spatial localisation (at least in the short-term), and hence, smaller place fields than would distal visual cues.

Lesions of perirhinal cortex also produce changes in the synchronisation of hippocampal complex spike cells with the local ‘theta’ EEG rhythm of around 8 Hz [78,79]. For example, in lesioned animals, spikes tend to occur more closely clustered around a particular phase of the theta rhythm [78]. Furthermore, the mean phase of firing of these spikes occurs earlier in the theta cycle in lesioned animals [79]. It is unclear how these changes in firing would affect hippocampal function, although they are consistent with there being a change in phase precession, [80] the phenomenon in which the firing of a hippocampal place cell systematically advances in phase across the theta cycle as an animal travels through the place field of that cell. It has been suggested that phase precession may serve to encode precise information about the animal’s spatial location [81].

The firing rate of hippocampal complex spike cells normally has a positive correlation with the velocity of the animal. One further effect of perirhinal cortex lesions is to disrupt this relationship [79]. Further analysis of this effect indicates that it results from an increase in the number of cells that develop a negative velocity-firing rate relationship [78]. It is unlikely that this effect is simply a result of a lesion-induced change in the animals’ locomotion, as such effects are minimal [79]. This finding does indicate that hippocampal processing of an animals movement through the environment is disrupted in perirhinal cortex lesioned rats. This self-motion information could potentially be available to the hippocampus from several different sensory systems, for example via sensory flow, motor efferent copy, proprioceptive signals or through vestibular inputs, although recent findings indicate that the latter system is not the source of this signal [82,83]. It could, however, be derived from several of the inputs to the perirhinal cortex, as...
anatomical and electrophysiological evidence indicates that this region receives projections from visual [1], motor [84] and barrel [85] cortex. Although it is unclear whether the hippocampus utilises the velocity information encoded in the pyramidal cell firing rate, this signal could potentially provide important feedback about the animal’s self-movement within the environment.

The monitoring of self-movement is critical for the navigational process of path integration. This is an activity that appears to require an intact hippocampus [86]. It is possible, therefore, that perirhinal cortex lesions may disrupt path integration, in particular an animal’s ability to monitor the distance that it has travelled through the environment. The behaviour of animals with this form of deficit may be minimally affected unless they are explicitly tested under conditions where they are less able to rely on other navigational strategies such as piloting. It is possible that this occurs in tasks where distal cues are ambiguous or poorly resolvable. Specific testing of this hypothesis will be required in order to determine whether it may account for some of the deficits observed in perirhinal cortex animals run in low-light conditions.

3. Conclusions

Our starting question was whether the perirhinal cortex is necessary for normal spatial memory. From the lesion data, which principally derive from rats, the answer appears to be that sometimes it is and sometimes it isn’t. Fortunately, it is possible to draw some more definitive conclusions. The first is that the severity of the perirhinal lesion-induced deficit, when it occurs, is not as severe as that seen after hippocampal or fornix lesions. The strongest evidence comes from those studies with direct comparisons between the effects of perirhinal cortex lesions and those of hippocampal or fornix lesions on spatial memory tasks. A significantly smaller effect of perirhinal cortex damage has been found for T-maze alternation [9,14], radial-arm maze performance [10,35], reference memory in the water maze [26], and working memory in the water maze [12]. Other evidence comes from studies that have used the same protocols for both perirhinal and hippocampal system lesions, even though they are not directly compared in the same experiment. Once again, there is clear qualitative evidence that hippocampal system lesions are more disruptive on T-maze alternation [10,31,87], automated delayed-nonmatching-to-position [61], reference memory in the water maze [88], and working memory in the radial-arm maze [38,88]. A possible exception is a study in which animals with either hippocampal or perirhinal cortex lesions were directly compared on variants of radial-arm maze performance and working memory in the water maze [26]. Deficits of similar severity were observed on some working memory conditions with longer retention delays. These findings are, however, in contrast with other studies that have used longer retention delays and found no perirhinal deficit [16].

A conclusion that can safely be derived is that the perirhinal cortex is, at most, one of several routes for sensory information that is required by the hippocampus for spatial processing. This conclusion raises the question of which are the key routes. Candidate regions included the entorhinal cortex, the postrhinal cortex, and the retrosplenial cortex. In fact lesions to none of these individual sites can match the severity of the effects of hippocampal lesions [7,8,18] making it highly likely that parallel routes convey the relevant sensory information. Attempts to identify distinct roles for these routes separately is made difficult by the fact that many spatial tasks can be solved by more than one strategy and rats are adept at switching between spatial strategies [50–53].

A surprising aspect is the way in which combinations of lesions that remove sensory afferents to the hippocampus can still fail to disrupt spatial tasks that depend on the hippocampus. Examples include the combination of perirhinal plus postrhinal lesions [13,14,35,38], perirhinal plus lateral entorhinal lesions [18], and most remarkably, perirhinal plus postrhinal plus lateral and medial entorhinal lesions [18]. The final experiment examined reference memory in the water maze and presumably reveals that spatial tasks may often only require a fairly basic use of visual landmarks and that other navigation cues (e.g. vestibular) can aid task performance.

A second conclusion is that the results from within particular laboratories are largely consistent. Thus, it is the same research groups that either report no perirhinal effect or consistently report spatial deficits. The assumption must be that under some situations the perirhinal cortex contributes to task performance and that this is due to differences in material and methods that pertain across research groups. As has been pointed out, these differences may include strain type. In order to avoid post hoc explanations for these research differences, however, it is probably most helpful to consider current theories about the functions of the perirhinal cortex and how they might shed a light on these apparent inconsistencies.

It now seems agreed that one role of the perirhinal cortex is to detect the familiarity of environmental stimuli [89–91]. Evidence for this function is found both in studies with monkeys [89–91] and studies with rats [9,45,91–93]. Furthermore, this role may include visual [90,91] tactile [90], and olfactory [94] information. Studies using tests of differential exploration between novel and familiar objects show that rats with perirhinal lesions can fail to distribute their exploration in a normal manner [9,10,26,35]. This might on the face of it lead to a profound deficit in spatial memory if the rat can no longer recognise as familiar the cues used to control spatial performance. In fact, this account seems highly unlikely for several reasons. First, as has been seen, many studies report normal spatial memory performance after perirhinal lesions. This sparing of spatial learning
can occur in the same animals that are impaired on tests of object recognition [9,10,35]. Second, studies of immediate early gene expression often fail to find increased c-fos expression in the perirhinal cortex of normal rats following the performance of a spatial memory task or after exposure to a novel spatial scene [93,95], even though exposure to novel objects can increase Fos levels in the perirhinal cortex [93]. In other words, individual objects appear to be treated in quite different ways to spatial arrays of scenes or objects in a scene, and only the former increases activation in the perirhinal cortex when measured with c-fos expression [93,95–97]. Third, when animals with perirhinal lesions are switched to a novel room where performing a spatial task (e.g. water maze, or radial arm maze) a spatial deficit does not emerge [16], even though it might be predicted that intact rats would be at an advantage through their ability to detect (and presumably learn about) stimulus familiarity.

An alternative account of perirhinal cortex function is that it allows animals to resolve ambiguity in visual discriminations [46,98,99], possibly through an involvement in configural learning with complex sensory cues [34,100]. Feature ambiguity will occur when there are common elements in the stimuli to be discriminated, and so will be more pronounced in configural learning tasks, discriminations with large stimulus sets, and discriminations with morphed stimuli. Degraded stimuli also increase feature ambiguity and so are associated with perirhinal-lesion induced deficits. While much of the supporting evidence comes from studies with monkeys, recent studies with rats [31,101,102] are consistent with this view. A prediction is that perirhinal cortex lesions will only disrupt spatial discriminations if there is a high degree of stimulus ambiguity or overlap in the stimuli that the animal uses to map the environment [46]. A caveat is that the rat perirhinal cortex appears to be especially important for discrete objects [31], and so this effect may only be present on a subset of behavioural tasks i.e. those where guidance depends on more local objects. These conditions were met in a recent test of this view as Moran and Dalrymple-Alford [34] trained rats in a 12 arm radial maze in which intramaze object cues within the arms were arranged according to a negative patterning design (A+B+AB→) that predicted which arms were baited. Rats with perirhinal cortex lesions were impaired on this configural task [34], even though they performed at normal levels on a more standard radial-arm maze task.

The prediction from this analysis is that perirhinal lesions will often have no apparent effect on spatial tasks because the cues used as distal landmarks are typically very different from one another. In addition, unless their arrangement is symmetrical the rat need not identify individual stimuli. Perirhinal cortex lesions may, however, impair spatial performance if the stimuli need to be individually distinguished in order to solve the task. The likelihood that this will occur will be elevated by factors that increase stimulus ambiguity. From this analysis it might be predicted that the conditions most likely to be associated with perirhinal spatial deficits are those in which distal cues are of low salience and have common elements, and in which other spatial strategies, for example, the use of directional cues, are excluded.

With these factors in mind it is noteworthy that the most consistent deficits are found in test conditions that are most likely to increase the ambiguity of the distal visual stimuli likely to guide spatial performance. The clearest examples of this come from the studies by Liu and Bilkey [22–27] in which testing is conducted under low light levels, in large rooms with cues that are relatively far away, and with a rat strain that has poor visual acuity. The implication is that under these circumstances perirhinal lesioned animals would be abnormally reliant on intramaze cues. Support for this interpretation comes from a study [23] in which T-maze rotations were conducted between the sample and test phase of the task. The rats with perirhinal lesions were less affected by a 90° rotation than the controls, suggesting a greater reliance on intramaze cues. This is also consistent with the effects of perirhinal cortex lesions on hippocampal electrophysiology. In studies reported by Lu and Bilkey [78], the firing fields of hippocampal place cells were smaller in animals with perirhinal lesions. This is what would be expected if these cells were responding to well-isolated local cues such as odour trails or body waste on the floor of the apparatus, rather than to distal visual cues. The proposal may also explain why in several previous studies, perirhinal lesions have enhanced performance in a spatial task. Since this primarily occurred in ‘dry maze’ studies it may have resulted from the lesioned animals focussing on odour traces e.g. if the environment was not cleaned to remove intramaze cues during the procedure. Under these particular circumstances, intramaze cues may be of more benefit than following distal cues, particularly if the latter are ambiguous.

In summary, the data support the hypothesis that the perirhinal cortex and hippocampus make differential contributions to spatial memory processing. Whereas under some circumstances the hippocampus may utilise information from the perirhinal cortex, it is clear that the basic functioning of the hippocampus can be relatively intact in the absence of the perirhinal cortex. It is likely, therefore, that the hippocampus accesses cortex through parallel routes such that without the perirhinal cortex, alternative sources of information are available. Under some circumstances this may produce a change in the behavioural strategy required to complete the task. This is most likely to occur in conditions where task performance depends on the use of ambiguous distal cues, for example, those containing overlapping visual features. This suggests a role for perirhinal cortex in configural learning with complex, intramodal sensory cues. The conclusion, that the perirhinal cortex is increasingly involved in spatial tasks when object identification becomes important, accords with previous analyses made by Bussey and Aggleton [46].

At present, this conclusion cannot be tested with human neuropsychological studies as this would require very discrete pathologies, to which is added the additional
complexity of laterality differences. Nevertheless, functional imaging data point to a difference between the posterior parahippocampal and perirhinal regions with regard to human spatial processing. This difference emerges because the posterior parahippocampal cortex, but not the perirhinal cortex, is activated by tasks taxing the encoding of object - location conjunctions [103,104] and by the spatial elements in visual scenes [105–107]. Indeed, part of this more posterior region is called the ‘parahippocampal place area’ [105]. In addition, damage to the posterior parahippocampal cortex is associated with topographic disorientation [108] and deficits on delayed spatial response tasks [109]. As might be predicted from the rodent data, there is evidence that the human perirhinal cortex can sometimes show increased activity during spatial tasks, an example being the correlation between good performance and accurate wayfinding in a virtual reality task [110]. This correlation was thought to reflect the ability to recognise landmark locations from novel perspectives [110], a task that may tax the ability to discriminate between scenes with common elements. It can be seen that the present analysis of animal lesion studies not only helps to reveal the functional relationship between the hippocampus and the perirhinal cortex in other mammals, but also provides a framework from which to approach the same relationship in the human brain.

Acknowledgements

We would like to thank Ping Liu for her useful comments on an earlier draft of this paper.

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