
Perirhinal and Postrhinal Functional Inputs to the Hippocampus

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Abstract

There is widespread agreement that perirhinal (PER) and postrhinal (POR) cortices are essential for episodic memory. The conventional view is that PER provides object information, and POR provides spatial and contextual information to the hippocampus through different information streams to support episodic memory. There is, however, considerable integration across these two information streams. Moreover, PER and POR also participate in non-mnemonic cognitive processes. PER is necessary for object recognition memory and is involved in high-level perceptual processing that conjoins elemental features to represent unique objects and items. POR represents the spatial layout of the current context, including objects and patterns located in that context, and then monitors the context for changes. Such object and pattern information in POR most likely arrives via a direct PER to POR pathway. Thus, the PER provides object information to both the POR and to the hippocampus, but for different purposes. Object information in POR would be used to represent and update the spatial layout of physical features of the local environment and for forming contextual associations. Such contextual information from the POR together with object and item information from the PER are made available to the hippocampus for associative learning and episodic memory.

3.1 Introduction

There is widespread agreement that the hippocampal formation and nearby parahippocampal structures are essential for episodic memory. There is less agreement about whether these regions also participate in other cognitive processes. Yet,

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in order to remember events, we need to perceive the event and attend to certain aspects of the episode. What regions are most likely to provide the interface between perception and memory and attention and memory? The parahippocampal region includes two structures organized near the rhinal sulcus, the perirhinal cortex (PER) and the postrhinal cortex (POR), that exhibit structural and connectional homology across rodent and monkey brains based on established criteria (Campbell and Hodos 1970). Anatomical, experimental lesion and electrophysiological evidence suggest these two regions provide gateways for perception and attention into the hippocampal memory system.

3.2 Overview of the Anatomy of the Perirhinal and Postrhinal Cortices

The PER in both rodents and monkeys comprises two subregions, areas 35 and 36. In the rat the two regions are narrow, rostrocaudally oriented strips of cortex with area 36 lying dorsal to area 35 (Fig. 3.1a). Neuroanatomical studies of PER, including cytoarchitecture, histochemistry, and connections, suggest the rostral border with insular cortex arises at the caudal limit of the claustrum (Burwell 2001). The placement of this border is consistent with traditional definitions of the insular cortex as overlying the claustrum (Rose 1928). The most rostral part of PER area 35 is bordered ventrally by piriform cortex. At caudal levels, piriform cortex is replaced by the lateral entorhinal area (LEA) to form the ventral border. The dorsal border of PER area 36 is with ventral temporal cortex. This dorsally adjacent region goes by different nomenclatures depending on the atlas consulted. At rostral levels, area 35 lies ventral to the fundus of the rhinal sulcus and area 36 lies above. More caudally, area 35 encompasses the fundus and area 36 lies above it. The most caudal portion of the PER consists mainly of area 36, which also lies above the rhinal sulcus (Burwell 2001).

The POR, in its current form, was defined in 1995 (Burwell et al. 1995). It occupies all that was formally the caudal portion of perirhinal and/or entorhinal cortex, depending on the atlas. Unfortunately, most rodent atlases persist in using the old nomenclature. The border between the PER and the POR usually coincides with the caudal limit of the angular bundle. In coronal sections, the white matter forming the angular bundle at this level has an elongated teardrop-shaped appearance. In atlases that have not adopted the newer nomenclature, the POR is roughly equivalent to the combination of regions designated as PER 35 and 36 (or PER and entorhinal) caudal to this landmark (Lein et al. 2007; Paxinos and Watson 2006; Swanson 2004). The POR lies entirely dorsal to the caudal extension of the rhinal sulcus. At this level the rhinal sulcus is occupied by the entorhinal cortex (Dolorfo and Amaral 1998b). The ventral borders of the POR with medial entorhinal area (MEA) are consistent with the description by Insausti et al. (1997) and Dolorfo and Amaral (1998b).

Functional anatomical studies show that the unimodal and polymodal associational inputs to the PER and POR are very different (Burwell and Amaral 1998a).

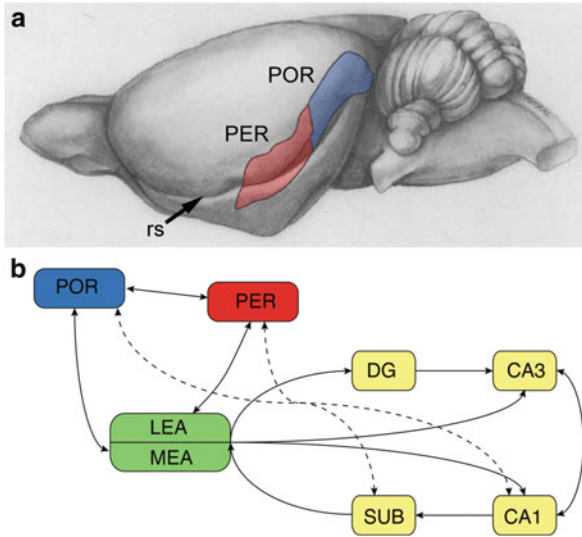


Fig. 3.1 Rodent perirhinal (PER) and postrhinal (POR) cortices. (a) Three-quarter view showing the locations of the PER (red) and POR (blue). (b) Simplified schematic connections among the PER, POR, lateral (LEA) and medial (MEA) entorhinal cortex, and hippocampal structures. The schematic includes the hippocampal formation (structures in yellow) and the parahippocampal region (structures in red, blue, and green). Note that the perirhinal and postrhinal cortices (PER and POR) have reciprocal connections with CA1 and the subiculum. Other abbreviations: *DG* dentate gyrus, *CA1* field CA1, *CA3* field CA3, *SUB* subiculum. Figures adapted from Burwell and Agster (2008) and Burwell et al. (1995)

In rodents, although input from all modalities targets all parts of the PER, there is a topography of unimodal association inputs. Somatosensory, auditory, and visual inputs preferentially target rostral, mid-rostrocaudal, and caudal area 36, respectively, and olfactory input preferentially targets area 35 (Burwell 2001). Whereas the PER receives input from multiple sensory modalities, the POR is dominated by input from secondary visual cortex and visuospatial areas, including retrosplenial and posterior parietal cortices. The PER and POR also preferentially target different parts of the hippocampal formation.

The current view of the hippocampal formation emphasizes that spatial and nonspatial information are transmitted through different parahippocampal pathways (Fig. 3.1b) (Eichenbaum et al. 2007; Knierim et al. in press; Naber et al. 1997). Spatial information originating in multiple cortical regions converges on the POR (parahippocampal cortex (PHC) in the primate brain) and is transmitted to the hippocampal formation through the MEA (Burwell and Amaral 1998b; Suzuki and Amaral 1994). Likewise, nonspatial or item information converges on the PER and is then transmitted to the hippocampal formation through a pathway that includes the LEA. Both the PER and the POR project directly to the hippocampal field CA1 and the subiculum, although they terminate at different proximodistal levels (Naber et al. 1997, 2001).

The segregation of spatial and nonspatial information may be overemphasized in both anatomical and functional descriptions of the PER and POR. For example, in addition to its MEA projection, the POR also targets caudal LEA (Burwell and Amaral 1998b). Moreover, the LEA and MEA in both rats and monkeys are interconnected (Chrobak and Amaral 2007; Dolorfo and Amaral 1998a). Finally, in both species, the PER located in the nonspatial pathway is robustly and reciprocally connected with the POR/PHC in the spatial pathway (Burwell and Amaral 1998b; Suzuki and Amaral 1994).

3.3 Functions of the Perirhinal Cortex

The hippocampus was implicated in memory in the 1950s by Milner and colleagues (Scolville and Milner 1957; Milner and Penfield 1955). Object recognition memory tasks were commonly used as a standard test for declarative memory, and early investigations suggested a central role of the hippocampus for object recognition memory. It was not until the 1980s that neocortical regions emerged as contributing to object recognition memory (Murray and Mishkin 1986; Zola-Morgan et al. 1989). Ensuing human clinical cases and animal lesion studies rapidly established that severe impairments in object recognition memory tasks occurred with PER damage and not hippocampal damage. Subsequent neuropsychological research into the neural bases of declarative memory has since included the PER as a focus for memory research.

3.3.1 Perirhinal Cortex and Object Recognition Memory

Recognition memory is the judgment of prior occurrence of an item or event (Mandler 1980). Object recognition memory tasks such as the delayed nonmatch-to-sample (DNMS) task can be solved on the basis of familiarity, i.e., context-free judgment of prior occurrence. DNMS tasks usually comprise two phases. In the sample phase, the subject is presented with the sample object. Following a delay, in the test phase the subject is presented with a copy of the now familiar sample object and a novel object. According to the nonmatch-to-sample rule, the subject must displace the novel object to obtain a reward. Correct displacement of the novel object implies that the subject recognizes the familiar object.

Experimental lesions to PER in rats and monkeys were shown to impair object recognition memory in DNMS tasks (Meunier et al. 1993; Mumby and Pinel 1994). The rat version of the DNMS task, however, required months of training (Mumby and Pinel 1994; Rothblat and Hayes 1987). Consequently, a variant of DNMS tasks, the spontaneous object recognition (SOR) task (Fig. 3.2), invented by Ennaceur and Delacour (1988), has become the preferred experimental paradigm to investigate neurobiological mechanisms of recognition memory in rodents. The SOR task follows the general framework of DNMS tasks except that no pretraining is required. Instead, the task relies on rats' innate preference for novelty in a familiar

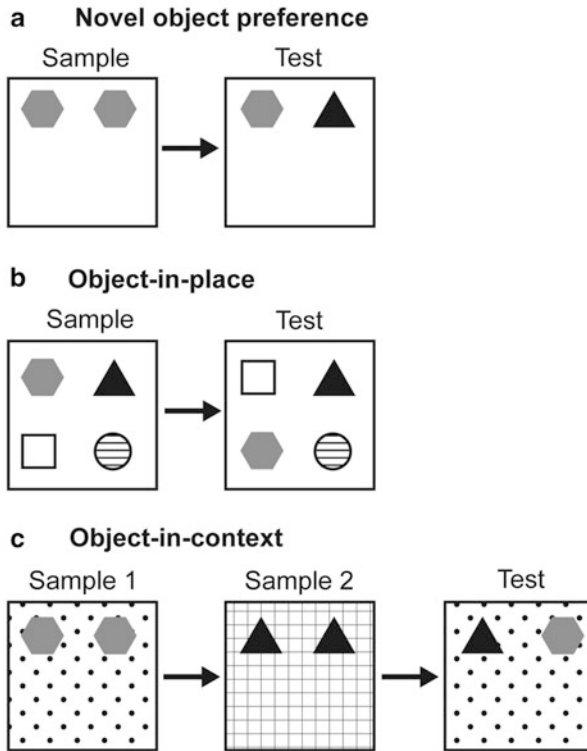


Fig. 3.2 Spontaneous object recognition (SOR) tasks. SOR tasks have been used to test recognition memory for single items and for spatial and contextual associations between objects. Experiments are carried out in an open-field arena that minimizes the availability of external visual cues. Objects are “junk” objects (e.g., candle sticks) or constructed of Duplo™. (a) In the novel object preference task, rats demonstrate recognition memory for familiar items (*grey hexagon*) by preferentially exploring the novel object in the test phase (*black triangle*). (b) In the object-in-place task, rats demonstrate recognition memory for familiar spatial associations between objects by preferentially exploring the objects that switched places (*white square* and *grey hexagon*). (c) In the object-in-context task, rats encounter two pairs of objects in different contexts (sample 1 and 2). Contexts are manipulated by carrying out the sample phases in different rooms or by altering the interior of the test arenas. Recognition memory of the familiar object-in-context construct is expressed by preferential exploration of the object that is incongruent with the context in the test phase (*black triangle*)

environment (Ennaceur and Delacour 1988). Performance is quantified by measuring the ratio of exploration of the novel and familiar objects (Fig. 3.2a). As no pretraining is necessary, experiments using SOR tasks as paradigms of object recognition memory can be completed in a matter of weeks. SOR tasks used to investigate mnemonic functions of PER explicitly use objects that share as few common features as possible in order to decouple mnemonic from perceptual demands. Thus, behavioral deficits in these conditions are considered to be a result of recognition memory impairments. The novel object preference version of the

SOR task has been used to test recognition memory for single objects (e.g., Dix and Aggleton 1999), but the SOR task paradigm is powerful in that it can also be used to assess recognition memory that involves associations of objects in place and objects in context (Dix and Aggleton 1999; Norman and Eacott 2005) (Fig. 3.2b, c).

Experimental lesions of PER severely impair object recognition memory in SOR tasks (Winters et al. 2004; Ennaceur et al. 1996), but this does not reflect a general memory deficit as PER lesions have no effect on pure spatial memory tasks (Winters et al. 2004). In contrast, hippocampal damage impaired spatial memory, but not object recognition memory (Forwood et al. 2005; Winters et al. 2004; but see Broadbent et al. 2010). Also, addition of PER damage to fornix transection did not exacerbate spatial memory impairments (Ennaceur and Aggleton 1997; Ennaceur et al. 1996). Transection of the fornix has been shown to produce deficits similar to hippocampectomy. Together, these findings demonstrate a double dissociation of PER and hippocampus for object recognition memory and spatial memory such that PER is necessary for object recognition memory, but not spatial memory, and the hippocampus is necessary for spatial memory, but not object recognition memory.

Object recognition paradigms are not limited to short duration delays. Rats demonstrate robust recognition memory with delays up to 24 h between encoding and testing. Under certain conditions, rats show object recognition memory up to 3 weeks after encoding indicating that PER is necessary for very long-lasting object memory (Mumby et al. 2007). Pharmacological techniques have shed light on the time course and phases of object recognition memory. Inactivation of PER using lidocaine, a sodium channel blocker, impaired encoding, early consolidation, and retrieval of object recognition memory (Winters and Bussey 2005b). In addition, local infusions of pharmacological antagonists have shown that shorter-term and longer-term object recognition memories are qualitatively independent processes supported by different neurotransmitter systems and synaptic plasticity mechanisms (Brown et al. 2012).

PER-dependent recognition memory is not limited to three-dimensional objects. PER receives multimodal input, and it is not surprising that PER would support recognition memory and discrimination learning for stimuli presented in various sensory modalities. Indeed, PER is necessary for odor recognition memory (Otto and Eichenbaum 1992; Feinberg et al. 2012), and PER neurons in rats performing an odor recognition task fired to nearly all the events in a trial (Young et al. 1997). PER is also necessary for integrating information across visual and tactile modalities (Winters and Reid 2010). Processing of auditory stimuli is also sensitive to PER damage under some conditions. PER damage impairs conditioning to auditory stimuli when the stimuli are complex, but not when the stimulus is a simple continuous tone (Kholodar-Smith et al. 2008a, b; Bang and Brown 2009). Rats also show robust object recognition memory of at least 1 h for two-dimensional visual images (Forwood et al. 2007) and for objects viewed behind a clear Perspex screen (Winters and Reid 2010). Importantly, PER damage impairs recognition memory under conditions in which stimuli are purely visual

allowing findings from rodent models to be better compared to those in human studies.

3.3.2 Perirhinal Cortex and Recency

Although experimental lesion studies are useful for assessing contributions of particular brain regions to specific functions, electrophysiology is more useful for understanding how information might be processed. Neuronal activity recorded in monkey anterior temporal lobe, including PER, suggested a mechanism capable of supporting recognition memory (Brown et al. 1987; Fahy et al. 1993). The proposed mechanism was neuronal response decrements to item repetition. Electrophysiological recordings in anterior temporal lobe were carried out in monkeys performing a serial visual recognition task in which individual novel and familiar images were repeatedly presented. Over half the recorded neurons were visually responsive, firing to the presentation of an image; some fired to multiple images and others to a few images. The firing rates of 38 % of the visually sensitive neurons in PER were maximal to the initial presentation of an item but significantly reduced to subsequent presentations (Xiang and Brown 1998). Therefore, information concerning familiarity and recency of an item can be inferred at the single neuron level when comparing the firing rate between the first presentation of an item and its subsequent presentation (Fahy et al. 1993; Xiang and Brown 1998). Neurons that responded maximally to unfamiliar objects but decreased firing rates in response to highly familiar objects carried information concerning relative familiarity; these neurons were termed “familiarity neurons.” Some neurons fired maximally to the initial presentation of an item regardless of whether it was unfamiliar or highly familiar and were significantly reduced to the repeated presentation; these neurons were termed “recency neurons.” Hence, recency neurons carry information on whether a given item was encountered recently regardless whether it was novel or familiar. A third type of neuron recorded in monkey PER responded maximally to an unfamiliar stimulus and briefly to a highly familiar stimulus; these neurons were termed “novelty neurons” (Xiang and Brown 1998). Together “familiarity” and “novelty neurons” are informative of the relative familiarity of an item, and “recency neurons” provide temporal information about items. Neurons that possess similar patterns of firing to item repetition to those recorded in the monkey have been recorded in rat PER (Zhu et al. 1995a). Burke et al. (2012), however, concluded that the relative familiarity of objects did not alter neuronal firing in rat PER. The absence of any neuronal decrements to familiar objects in Burke et al. (2012) may be explained, however, by differences in task design. In Burke et al. (2012), rats were trained to complete laps on a circular track containing objects to obtain a food reward. In their paradigm, the presentation of the objects was not closely controlled making it difficult to correlate changes in neuronal activity with the encountered objects. In serial recognition tasks in which repetition-sensitive neurons have been recorded in rats (Zhu et al. 1995a), behavior

and presentation of objects were closely controlled allowing precise correlation of neuronal activity with image presentation.

Rat imaging studies quantifying c-fos activity as a marker of neuronal activation to presentation of novel and familiar images have complemented electrophysiological evidence for neuronal response decrements signaling relative familiarity (Wan et al. 1999; Zhu et al. 1995b; Albasser et al. 2010). c-fos activity can be quantified by labeling its protein product, Fos, by standard immunohistochemical techniques. Using a “paired viewing procedure” in rats, novel and familiar images were presented to each eye. As visual information from each eye crosses to the opposite hemisphere, the effects of image familiarity on PER neuronal activity can be compared within an animal. Presentation of novel images increased neuronal activation compared with familiar images (Wan et al. 1999; Zhu et al. 1995b; Seoane et al. 2012; Warburton et al. 2003) consistent with electrophysiological recordings in rats and monkeys (Brown et al. 1987; Fahy et al. 1993; Xiang and Brown 1998; Zhu et al. 1995a). Moreover, successful object recognition memory in a modified SOR task was associated with increased PER neuronal activation (Albasser et al. 2010) demonstrating a correlational relationship between high neuronal activity in PER and preferential novelty exploration. In vivo pharmacological manipulations further strengthen the relationship between differential neuronal activity in PER to signal novelty and familiarity. Systemic injection of scopolamine, a cholinergic antagonist, disrupted increased neuronal activation to novel visual stimuli as measured by Fos staining and impaired object recognition memory in vivo (Warburton et al. 2003). Local infusion of antisense Fos oligodeoxynucleotide into PER disrupted differential Fos expression to novel and familiar visual stimuli and disrupted consolidation processes for longer-term object recognition memory in vivo (Seoane et al. 2012). Together, these studies (Albasser et al. 2010; Seoane et al. 2012; Warburton et al. 2003) complement electrophysiological and lesion data suggesting that a mechanism in PER centered on differential neuronal activity to item repetition is a potential mechanism underlying object recognition memory.

3.3.3 Perirhinal Cortex and Visual Perception

The current view of PER function is not restricted to a mnemonic role. PER is posited to function in visual perceptual processing in addition to object recognition memory given the pattern of impairments under certain conditions in discrimination tasks and its anatomical position at a high level in the ventral visual stream (Murray et al. 2007; Bussey and Saksida 2002; Cowell et al. 2010; Murray and Wise 2012).

Electrophysiological recordings in rats support a specialized role of PER in object information processing (Burke et al. 2012; Deshmukh et al. 2012; Zhu et al. 1995a). When rats encountered objects while navigating a circular track, a large proportion of recorded neurons in PER fired selectively when the animal was close to an object; this pattern of activity was termed the cell’s “object field” (Burke et al. 2012). Some cells had multiple “object fields” and fired close to an object

regardless of its identity suggesting that neuronal activity in “object fields” reflected processing of object information. Nonspecific activity was observed when rats navigated an empty track with no objects, supporting the lack of spatial information processing in the PER (Burwell et al. 1998). Thus, in comparison with hippocampal place fields that are modulated by the location of the animal (Muller 1996), PER “object fields” are modulated by the presence of objects. Similar object-related firing activity was seen in PER when rats foraged in an open arena containing objects (Deshmukh et al. 2012; see Deshmukh and Knierim 2014). These properties of PER cells with multiple object-related firing fields reported in independent laboratories strengthen the role of PER in processing information about objects in some capacity, e.g., perceptual processing in which objects are represented through the conjunction of its features (Murray et al. 2007).

The proposal that the PER participates in visual perceptual processing can be traced to an experimental lesion study in monkeys performing modified match-to-sample tasks in which mnemonic demands were minimized (Eacott et al. 1994). Monkeys with PER damage were impaired when trial unique images from a large pool were used, but the impairment was mitigated when the pool of images was reduced to four; the PER-lesioned monkeys were also impaired when the discriminability of the images was reduced. Eacott et al. (1994) argued that the large number of trial unique images increased the probability that images would share common features. Thus, each image had to be precisely represented to protect from interference by other images. When the pool of images was small, less precise representations of the images were sufficient for successful performance. Based on the pattern of impairments, Eacott et al. (1994) posited that the PER is necessary for the accurate representation of visual stimuli in order to prevent interference from other similar visual stimuli.

In complex discrimination problems, a feature (A) can be a component in two different compounds with different outcomes: rewarded (AB+) and unrewarded (AC−). Hence, objects that predict different outcomes may share elemental features. This property of constituent features shared across objects in discrimination problems has been termed “feature ambiguity” (Bussey and Saksida 2002). Bussey and colleagues proposed the perceptual/mnemonic feature conjunction (PMFC) connectionist model of PER function to explain the selective deficits following PER damage in object discrimination under conditions in which discriminanda have overlapping features (Bussey and Saksida 2002; Murray et al. 2007). In the PMFC connectionist model, the ventral visual stream is considered as a continuum representing increasingly complex representations. Representations of object features and their conjunctions are arranged hierarchically such that simple features of objects are processed and stored in caudal areas and increasingly complex conjunctions of features are processed and stored rostrally, ultimately in the PER. Thus, the PMFC connectionist model would predict deficits associated with PER damage on match-to-sample tasks in Eacott et al. (1994) and in two-choice visual discrimination tasks in rats in which ambiguity of the discriminations were manipulated (Eacott et al. 2001). In Eacott et al. (2001), PER lesions impaired discriminations that required the conjunction

of features; lesions were without effect on simple discriminations that could be solved on the basis of individual features. The PER also seems necessary for tasks that require unitizing simple stimuli, such as lights and tones (Campolattaro and Freeman 2006a; Nicholson and Freeman 2000). Interestingly, PER damage impaired the simultaneous but not the serial version of feature positive discrimination learning, which requires disambiguation of overlapping stimulus elements (Campolattaro and Freeman 2006b). These findings are all consistent with a role for the PER in the PMFC connectionist model in representing a conjunction of features as a unique stimulus. Other evidence in monkeys also implicated PER specifically for discriminations that require associating individual features to represent an object as a whole (Bussey et al. 2002). According to the PMFC connectionist model, discriminations soluble on the basis of elemental features are not sensitive to PER lesions, but can be supported by visual areas outside the PER. Indeed, monkeys with damage to the middle temporal gyrus were impaired on a simple color discrimination task and monkeys with bilateral damage to PER were unimpaired (Buckley et al. 1997).

Studies in rats provide additional evidence for the PER as a site for perceptual processing of complex object representations. Effects of PER damage were examined in an SOR task that assessed the effect of varying the level of feature ambiguity, i.e., overlap of features between the novel and familiar objects on object recognition memory (Norman and Eacott 2004). At the lowest feature ambiguity level, objects were “junk” objects (e.g., bottles and candlesticks) that shared fewest common features. For the medium feature ambiguity level, the novel and familiar objects were both constructed of Duplo™ (large Lego bricks) in a configuration to maximize the discriminability of the two objects. Although different numbers and types of Duplo™ blocks were used for the novel and familiar object, each object shared the inherent features of the blocks and was therefore considered more ambiguous in terms of features compared with “junk” objects. In the highest feature ambiguity condition, the novel object was reconfigured using the same number and constituent blocks as the familiar object so both objects shared the most features. PER lesions produced a delay-dependent impairment in the lowest feature ambiguity condition and severity of the impairment increased with increasing ambiguity of the novel and familiar objects; at the highest ambiguity level, PER-lesioned rats were impaired in all delays including the shortest delay of 1 min (Norman and Eacott 2004). When objects were highly discriminable, PER lesions resulted in a delay-dependent impairment indicative of a mnemonic impairment. Increasing feature ambiguity, however, increased the severity of the recognition memory impairment implicating PER in high-level visual perception as well as mnemonic function.

The PMFC connectionist model was modified to account for object recognition memory impairment in PER-lesioned animal models by introducing a function in which the representation at a given level in the continuum including PER could be sharpened with experience (Cowell et al. 2006). Computer simulations of the modified PMFC connectionist model simulated the forgetting curve of object recognition memory typical of increasing delay and list lengths in delayed match-and nonmatch-to-sample tasks in experimental animal models (Cowell et al. 2006).

Moreover, removal of the layer in the model that corresponded with the PER exacerbated the delay and list-length-dependent reduction in recognition memory score consistent with the pattern of impairment in experimental animal lesion models (Mumby and Pinel 1994; Mishkin 1978; Norman and Eacott 2004).

Perceptual processing by PER is not generalized for all difficult visual discriminations, but only for discriminations requiring the configuration of multiple features that together form a gestalt representation of a stimulus (Eacott et al. 2001; Norman and Eacott 2005). PER had no role for fine discriminations of single features (Eacott et al. 2001) or a conjunction between an object and context (Norman and Eacott 2005). POR instead was necessary for familiarity discriminations in recognition memory that involved a conjunction of objects in context (Norman and Eacott 2005). Using a zero delay SOR task designed to minimize the mnemonic component of the task, Bartko et al. (2007a) tested the role of the PER within the hierarchical continuum of the PMFC connectionist model. In the zero delay SOR task, rats explored two identical sample objects in the sample phase; immediately after the sample phase, the test phase commenced in which varying levels of feature ambiguity were tested where the novel object varied in feature ambiguity with the familiar object. Control rats with intact PER successfully discriminated by preferentially exploring the novel object at all levels of feature ambiguity; PER lesions impaired discrimination only when the familiar and novel objects shared the most features in the highest feature ambiguity condition. To preclude any mnemonic contributions even at a zero delay, a spontaneous oddity preference task was performed that consisted of a single test phase in which three objects were presented simultaneously (Bartko et al. 2007a). Two objects were identical and the third “odd” object varied in similarity from sharing few features (low feature ambiguity) to sharing the most features (high feature ambiguity) with the other objects. Oddity judgments were expressed as preferential exploration of the “odd” object. As rats had all the information from the three objects available simultaneously for comparison, any impairment was interpreted as a perceptual processing deficit [but see (Suzuki 2009, 2010)]. Similar to the pattern of impairment in the zero delay SOR task, PER lesions impaired discrimination only in the highest ambiguity conditions (Bartko et al. 2007a). Furthermore, PER lesions impaired configural object recognition further supporting a perceptual role for PER in forming complex conjunctive representations (Bartko et al. 2007b).

There are reports in rodent models, however, arguing against a role of PER in high-level perceptual processing consistent with original accounts in clinical cases where medial temporal lobe damage resulted in severe memory impairments in the absence of perceptual deficits. Clark et al. (2011) argued against a perceptual function of PER in an elegantly designed two-choice visual discrimination task. In this task, PER-lesioned rats were trained to similar levels as sham-operated control animals on a basic discrimination problem. After successful learning, the image pair was morphed resulting in discrimination trials of varying degrees of difficulty. These trials were then interleaved with the well-learned baseline discrimination trials. Performance of rats with PER lesions did not differ from sham-operated controls across any level of discriminability even in the highest level of

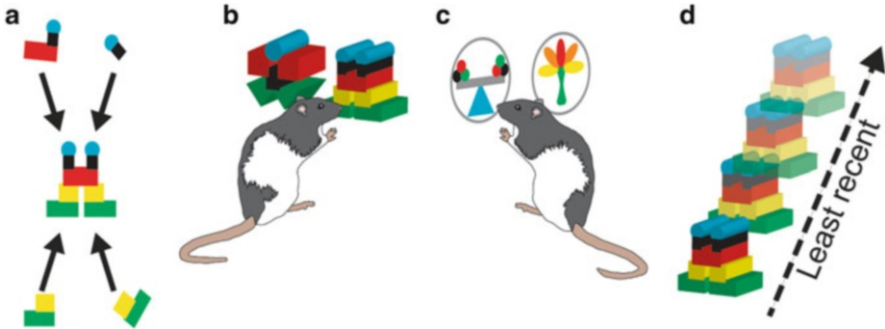


Fig. 3.3 Perirhinal cortex (PER) processes object information. (a) PER is necessary to form conjunctions of features into unique representations. (b) Such representations can be used for object recognition memory, discrimination, and disambiguation of three-dimensional objects. (c) Similar to b, the PER also processes information about two-dimensional images. (d) PER signals recency information about objects

feature ambiguity; PER lesions did, however, impair object recognition memory (Clark et al. 2011). In a separate study, PER-lesioned rats performed to similar levels compared to sham-operated controls in a configural discrimination task but were impaired in an object recognition memory task (Aggleton et al. 2010).

Although the reports (Aggleton et al. 2010; Clark et al. 2011) described above argue against a role of PER in high-level visual perceptual processing, the balance of the experimental lesion evidence supports a role for the PER in visual discrimination under conditions of high feature ambiguity when a conjunction of features is necessary to form an accurate representation of a unique stimulus (Fig. 3.3) (Bartko et al. 2007a, b; Norman and Eacott 2004). Tasks that can be solved using elemental features do not require PER, instead relying on visual ventral stream structures upstream of the PER that are sufficient to represent less complex stimuli.

3.3.4 Summary of Perirhinal Functions

Experimental lesions have established the canonical role of PER in object recognition memory. A mechanism in PER centered on response decrements is hypothesized to have the necessary speed, capacity, and properties to signal information on familiarity and recency of single items (Bogacz and Brown 2003). Additionally, this mechanism would be metabolically advantageous. In normal daily life many items will be familiar. Therefore, decremental neural activity for signaling familiarity would reduce energy demands of the system. Novel items may generate interest to the individual (e.g., a new source of food) requiring more processing and increased neuronal activity to engage the appropriate behavioral response. Evidence is available to support PER as a memory store. If PER functions as a locus of storage, then experimental lesions to this brain region should cause retrograde and anterograde amnesia. Both retrograde (Mumby et al. 2002; Wiig

et al. 1996) and anterograde (Barker and Warburton 2011; Winters et al. 2004) object recognition memory deficits have been reported in experimental lesion models in rats. Synaptic plasticity (e.g., long-term potentiation or long-term depression) is thought to be one of the underlying mechanisms of learning and memory (Lynch 2004; Martin et al. 2000). Indeed, pharmacological and genetic manipulations in PER block synaptic plasticity and impair object recognition memory (Barker et al. 2006; Warburton et al. 2005; Griffiths et al. 2008; Winters and Bussey 2005a).

A complementary view of PER function is visual perceptual processing for representations at the object level. The PMFC connectionist model (Bussey et al. 2002; Cowell et al. 2006; Murray et al. 2007) has been posited with the aim of unifying increased severity of recognition memory and discrimination impairments in conditions of high feature ambiguity in PER-lesion models. As such, the PMFC connectionist model interprets single item recognition memory impairments from PER damage not as forgetting or lack of encoding but interference of the fragmented or impoverished memory trace that would otherwise be protected by an intact PER (McTighe et al. 2010; Bussey and Saksida 2002; Cowell et al. 2006, 2010). Related views are that the PER is necessary for unitizing stimuli, e.g., lights and tones (Campolattaro and Freeman 2006b), or for encoding associative information about a cue, e.g., its relationship to reward or work schedules (Liu and Richmond 2000).

Evidence from experimental lesion studies and electrophysiological recordings is consistent with a role for PER in both a perceptual representational and a mnemonic framework. The consistent theme is the role of PER in object information processing whether for discrimination or recognition memory (Fig. 3.3). Electrophysiological recordings should be carried out in PER while rats perform visual discrimination and object recognition memory tasks in which feature ambiguity is varied. Any neuronal activity correlating with the level of feature ambiguity would support a role of PER for complex feature conjunctions and provide evidence that this brain region is capable of housing perceptual and mnemonic mechanisms.

3.4 Functions of the Postrhinal Cortex

Given that the POR is interconnected with anatomical regions implicated in the processing of spatial and visuospatial information, the first experimental lesion studies attempted to dissociate its functions from those of the PER. A reasonable hypothesis was that hippocampal-dependent spatial tasks, for example, the Morris water maze and contextual fear conditioning, would be sensitive to POR damage, but not to PER damage. Contrary to predictions, PER and POR damage resulted in deficits in contextual learning (Bucci et al. 2000, 2002; Burwell et al. 2004a), but not spatial navigation in the Morris water maze in studies using pigmented rats (Burwell et al. 2004b; Machin et al. 2002; Futter et al. 2006). This pattern of results suggested that spatial learning is qualitatively different from contextual learning and requires different brain regions and different processing abilities. Thus, when

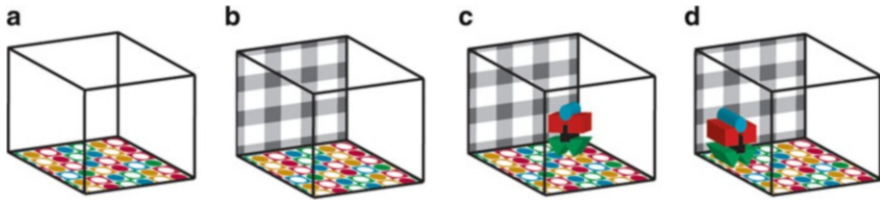


Fig. 3.4 Postrhinal cortex (POR) and processing of information in the local context. (a) POR encodes features of local contexts, such as a small room with a pattern on the floor. (b) POR signals changes such as an altered pattern on the wall. (c) POR also appears to encode the spatial layout of objects in the local context. (d) POR may also signal when there are changes in the spatial layout of objects, e.g., the transition from c to d

path integration is intact, animals might be able to complete a navigation task, but not able to process complex information about the local environment, e.g., information about patterns, objects, and the appearance of boundaries in an enclosed chamber.

3.4.1 Postrhinal Cortex and Context

Experimental lesion studies have demonstrated that the POR is necessary for processing information about objects when combined with places and contexts (Fig. 3.4). This was demonstrated in an SOR task (Fig. 3.2c) in which rats first explore two identical objects (A) that are presented in context 1 and then two different identical objects (B) in a second context (2) that differs by the interior of the testing arena. In the test phase, one copy of each of the objects (A and B) is presented in the context 1 (Norman and Eacott 2005). Normal rats will preferentially explore object B because this object is out of context compared with object A. In Norman and Eacott (2005), rats with POR damage were impaired in this task, suggesting a role in recognizing objects in different contexts. Rats with POR damage were not impaired in the standard SOR task (novel object preference task) for object recognition memory.

Based on the contextual fear learning and object-context recognition studies, one possibility is that the POR relies on information arising from the PER to process object and pattern information about the physical features of the local environment. By this view, POR is in a position to combine incoming spatial information from retrosplenial and posterior parietal cortices with incoming item, object, and pattern information from the PER to represent the spatial layout of items in the physical local context. If this is the case, one would expect to observe neuronal selectivity in POR that links objects to places. Neuronal activity was recorded in the POR in a bowtie-shaped maze during performance on an object discrimination task in which a pair of objects was presented on one side of the maze or the other (Furtak et al. 2012). With two pairs of objects and two locations in which objects were presented, it was possible to identify object-place conjunctive selectivity. As

predicted, a large proportion of POR cells exhibited object-place conjunctions. Another similar proportion of POR cells exhibited selectivity for particular locations in which objects appeared, regardless of the identity of the object in the location. Interestingly, some cells showed location or object-location selectivity during the stimulus presentation epoch when the rat was in the center of the maze viewing objects in particular locations at a distance. This phenomenon is reminiscent of monkey electrophysiology studies in which parahippocampal view cells were identified (Rolls et al. 1997) and of findings in human imaging studies in which a functionally defined parahippocampal locations show increased activity when individuals were viewing scenes or places (Epstein et al. 1999). The authors of the latter study suggest that the parahippocampal place area is involved in encoding new perceptual information about the spatial layout of scenes.

3.4.2 Postrhinal Cortex and Attention

In addition to representing the spatial layout of objects and patterns in the local context, some evidence suggests that the POR modulates attention to changes in the environmental context. For example, in rodents, damage to the POR impaired attentional orienting in a conditioned orienting task (Bucci and Burwell 2004). In a human imaging study, Yi and Chun (2005) reported that activity attenuates for repeated scenes in the parahippocampal place area. Decreases in activity were observed only when subjects attended the scenes during initial and repeated presentations. Electrophysiological studies in monkeys show that neuronal activity in the PHC is modulated by changes to stimuli in the periphery (Sato and Nakamura 2003) and by changes to the local context (Vidyasagar et al. 1991). These studies suggest a role in stimulus driven, bottom-up attention consistent with the notion that the POR and PHC automatically monitor the local environmental context for changes.

The first electrophysiological study of the rodent POR neuronal correlates employed a spatial task that had been used extensively for studies of hippocampal place cell properties in which double rotations of cues were carried out in a four-arm radial maze (Burwell and Hafeman 2003). The maze was defined by multisensory proximal (or local) cues and distal (or global) visual cues. Proximal cues consisted of visual, tactile, and olfactory cues located on the maze arms. Distal cues consisted of highly salient visual cues located on curtains surrounding the maze. On recording days, rats were run in three conditions. For the first and third baseline conditions, proximal and distal cues were organized in the standard configuration. In the second condition, the proximal and distal cues were each rotated 90° in opposite directions around the center of the maze. Hippocampal place fields recorded in this task can be controlled by either proximal or distal cues (Shapiro et al. 1997; Tanila et al. 1997). A signature of hippocampal place fields in this task is that after a place field has rotated in concordance with a rotation of either the proximal or distal cues, the field will normally return to the original location when the rotated cues are returned to the original configuration. POR neurons recorded in

this task responded quite differently. Although the majority of POR neurons appeared to form place fields using standard criteria, the fields tended not to rotate with either proximal or distal cues. Moreover, in the second baseline condition, these fields did not return to the configuration observed in the first baseline. POR neurons appeared to remap or adopt new spatial correlates, with each manipulation of proximal and distal cues. In addition, nearly all postrhinal place fields exhibited split or multiple subfields—also different from hippocampal place fields. Together with other available evidence, this study suggested that the POR might have a role in monitoring visuospatial changes in environmental stimuli as opposed to processing visual cues for purposes of navigation. In other words, POR cells appeared to participate in higher-level perceptual or attentional functions, at least in that task.

The studies reviewed so far suggest that the POR encodes new information about the spatial layout of the physical environmental context. This is consistent with the view that the POR is also monitoring the spatial layout for new information or changes. Recently, we demonstrated that cells in the POR do signal the onset of changes to the local context (Kent and Burwell 2012). We recorded single units in the POR during performance on a biconditional discrimination task using an apparatus that permits automated back projection of images to the floor of the maze. In this task, the pattern on the floor determines which of two embedded two-dimensional images is rewarded. For example, if the floors are either dotted or striped and the images are a star and a circle, the star would be correct on the dotted floor and the circle would be correct on the striped floor. The beginning of a trial is signaled by the appearance of a floor pattern and the animal must approach the center of the bowtie-shaped maze accompanied by the offset of white noise. After a variable delay, the images appear, and the animal must approach the image associated with the floor pattern. We observed POR cells that signaled the onset of white noise, floors, and image, consistent with a role in attention.

In the biconditional discrimination task described above, Kent and Burwell (2012) also observed POR cells that signaled a particular image, but only when it appeared on a particular floor pattern. This could be interpreted as signaling “what-which,” a gestalt representation of an object in context, as described by Eacott and colleagues (Norman and Eacott 2005; Eacott and Gaffan 2005). In Norman and Eacott (2005), POR damage selectively impaired memory for objects in context when tested in a spontaneous object exploration task.

Available anatomical and functional evidence suggests that object information in the POR arrives directly from the PER. We suggest that the PER provides object information to both the POR and the hippocampus, but for different purposes. Object information in the POR would be used to represent and update the spatial layout of the features in the current context, including items, objects, and patterns (Fig. 3.4). Object information in the hippocampus would be used in associative learning and episodic memory.

3.4.3 Summary of POR Functions

We have suggested a model in which the POR (and PHC) encodes representations of specific contexts, monitors the current context, and updates the context representation when a change occurs (Furtak et al. 2012). By this model, the POR (1) combines spatial information with object and pattern information to form representations that link objects to places, (2) collects those item-place associations into representations of specific contexts including the spatial layout of features and items, (3) automatically monitors the current context for alterations, and (4) updates the representation of the current context with identified changes. The spatial information most likely arises from retrosplenial and posterior parietal cortices, whereas the information about individual items arises from the PER. The attentional functions would arise from interactions with posterior parietal cortex as well as the lateral posterior nucleus of the thalamus.

The POR representation of the local context would be available to other brain regions to support a number of functions, e.g., recognition of an object in a location or to guide behavior appropriate to context. It may also be that the POR signals the PER when alterations to the current context involve individual objects or patterns, resulting in further processing of the item by the PER.

3.5 Interactions Among Structures of the Hippocampal System

What information do the PER and the POR provide the hippocampus? Consistent with other proposals (Eichenbaum et al. 2007; Knierim et al. 2006; Knierim et al. in press), at the simplest level, we suggest that the PER provides information about individual items to the hippocampus. This would include not just visual cues but also discrete olfactory, tactile, and auditory cues, especially cues that have complex perceptual or associative properties. The POR provides a representation of the local context that includes the spatial layout of items and patterns. The hippocampus then forms representations of events and episodes and locates the episodes in place and time (Fig. 3.5).

Lesions to rat PER impaired object-in-place recognition memory (Barker et al. 2007). Object-in-place recognition memory can be tested using the object-in-place SOR task (Dix and Aggleton 1999) (Fig. 3.2b). In this task, rats bind object information with spatial information to form associations between the objects and their relative positions, and object-in-place memory is expressed as preferential exploration of the most salient novel spatial configuration of objects (Fig. 3.2b). Therefore, this task cannot be solved on the basis of familiarity of the objects alone nor the familiarity of the locations that are occupied as the identity of the objects and the occupied locations do not change. Rats must instead form an association between the objects and their relative positions. PER lesions impaired object-in-place recognition memory (Barker et al. 2007) leading to the possibility that the spatial relationship between objects is processed and stored within PER. The lack of

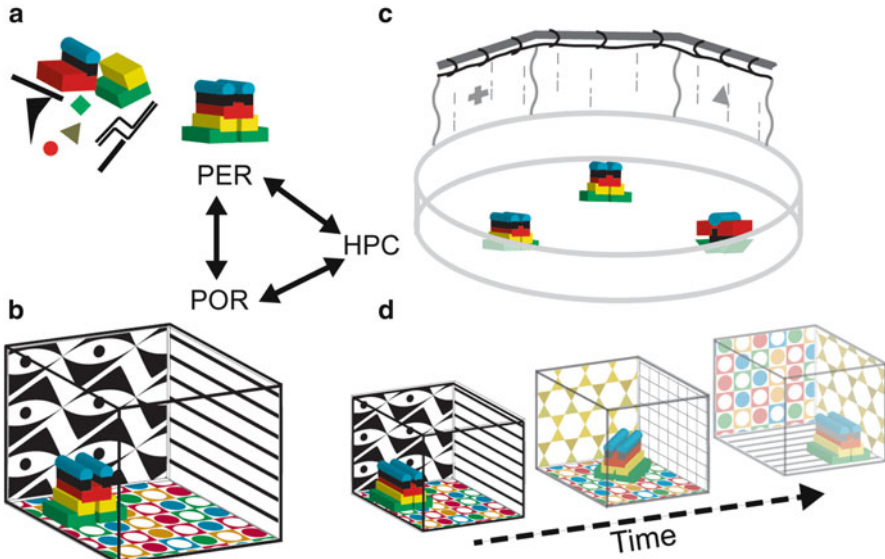


Fig. 3.5 Interactions among PER, POR, and hippocampus (HPC) for episodic memory. Hippocampus can process PER object information and POR contextual information in parallel. (a) Gestalt representations of complex objects are formed and housed in PER. (b) The spatial layout of object and pattern information is unitized in a contextual frame in POR and provided to the medial entorhinal area and the hippocampus. (c) Object information is available to hippocampus and the lateral entorhinal area from PER for accurate allocentric spatial information processing. (d) The hippocampus indexes the contexts supplied by POR and PER in a temporal framework for episodic memory

spatial information processing in PER (Burke et al. 2012; Burwell et al. 1998; Deshmukh et al. 2012; Hargreaves et al. 2005), however, argues against the notion that PER combines spatial information with object information. Furthermore, quantification of *c-fos* activity as a marker of neuronal activity implicated a role not of PER but of the hippocampal formation in signaling novel constellations of familiar images (Wan et al. 1999). Indeed, damage to hippocampus alone and disconnection of hippocampus from PER impaired rats in the object-in-place task prompting the hypothesis that an integrated network involving PER and hippocampus is necessary for forming representations of objects and their relative positions (Barker and Warburton 2011). The PER-hippocampal network for object-in-place associations proposed by Barker and colleagues (Barker et al. 2007; Barker and Warburton 2011), however, might be incomplete when spatial properties of POR are considered. *c-fos* imaging showed that POR was activated more to novel constellations of familiar objects (Wan et al. 1999) and electrophysiological recordings have demonstrated neural correlates of object-location conjunctions in POR (Furtak et al. 2012). Thus, the PER-hippocampal network proposed by Barker and colleagues (Barker et al. 2007; Barker and Warburton 2011) necessary for object-in-place representations should be modified to include the POR. Further

disconnection studies would establish the role of POR within a PER-hippocampal network for object-in-place recognition memory.

Although PER and hippocampus have been doubly dissociated along a nonspatial/spatial dichotomy (Ennaceur et al. 1996; Winters et al. 2004), there are reports that PER damage can impair performance in spatial memory tasks (Liu and Bilkey 1998a, b, c, 1999, 2001). A possible explanation to resolve these inconsistencies lies within the perceptual processing viewpoint of the PER (Bussey and Saksida 2002; Murray et al. 2007). The behavioral deficits in PER-lesioned animals are not thought to be a deficit in spatial information processing per se as PER lacks spatial processing properties (Burwell et al. 1998; Deshmukh et al. 2012; Hargreaves et al. 2005), but are thought to arise in situations when distal complex or ambiguous cues must be used to solve the spatial task (Aggleton et al. 2004). Thus, the requirement of PER in spatial tasks can be explained within its role in the PMFC connectionist model to provide accurate representations of cues to hippocampus for a more detailed cognitive map. Modulation of hippocampal place fields by PER lesions and effects of nonspatial object information provide evidence for this hypothesis as PER lesions destabilized place fields in the CA1 subfield of dorsal hippocampus (Muir and Bilkey 2001). The presence of objects in a testing arena increased the number and reduced the size of hippocampal place cells; moreover, these modulations in number and size of hippocampal place fields were recorded in the CA1 subfield that receives direct PER and LEA projections (Burke et al. 2011). Together, these findings implicate PER in providing detailed object information to hippocampus for a more detailed cognitive map.

PER is also necessary for forming temporal relationships between objects (Barker and Warburton 2011). Recency judgments of objects require an integrated network consisting of the PER and hippocampus as impairments resulting from disconnection of these two brain structures were the same as that resulting from damage to either region alone (Barker and Warburton 2011). “Recency cells” in PER signal whether an item has been encountered recently regardless of whether it is novel or familiar (Xiang and Brown 1998; Zhu et al. 1995a). Thus, temporal information relating to a specific item is available upstream in PER and must be further processed in hippocampus. An alternative hypothesis is that the hippocampus provides a temporal framework upon which PER simply provides object information (Fig. 3.5). “Time cells” recorded in the hippocampus are thought to form a temporally ordered structure upon which events are mapped (MacDonald et al. 2011; see Eichenbaum et al. 2014). Anatomical studies show direct connections from PER to field CA1. This direct connection allows the possibility that object information from PER can be indexed within a hippocampal temporal framework to form temporal associations among objects.

There is general agreement that both spatial and contextual information are provided to the hippocampus through a pathway that includes the POR. At the same time, the hippocampus has been implicated in contextual fear conditioning and in configural learning. How should this apparent discrepancy be understood? Based on Nadel and Wilner’s (1980) dual process theory of context representations, Rudy (2009) has suggested that the PER and POR support elemental

representations of context, whereas the hippocampus supports a hierarchical representation. By this view, representations of individual items in PER and POR are each associated with a context, whereas the hippocampus binds the individual elements and the current context into a single representation that is associated with an event. Experimental lesion and electrophysiological studies do suggest that context is processed differently by PER, POR, and the hippocampus; however, the elemental versus hierarchical views do not explain all the data.

Two primary differences between hippocampal and cortical contributions to context emerge from the experimental lesion literature. First, pretraining lesions of the PER or POR reliably impair contextual fear conditioning (Bucci et al. 2000, 2002; Burwell et al. 2004b). Pretraining hippocampal lesions, however, cause minor if any impairment (Maren and Fanselow 1997; Frankland et al. 1998; Wiltgen et al. 2006; Richmond et al. 1999; Biedenkapp and Rudy 2009). Second, PER or POR posttraining lesions impair contextual fear conditioning up to 100 days after training (Bucci et al. 2000, 2002; Burwell et al. 2004a; Corodimas and LeDoux 1995). The effects of posttraining lesions of the hippocampus are time limited and have diminished effects 50–100 days after training (Anagnostaras et al. 1999; Maren et al. 1997). Electrophysiological studies also differentiate hippocampus from adjacent cortical structures. For example, neither the PER nor the POR exhibits place fields in a paradigm used in hippocampal physiology studies (Burwell and Hafeman 2003; Burwell et al. 1998; Shapiro et al. 1997; Fyhn et al. 2004; Hargreaves et al. 2005). Both the hippocampus and the POR exhibit item-location conjunctions. In a biconditional discrimination task in which the place determined which of two odors would be rewarded, hippocampal cells developed odor-place conjunctions over time, perhaps as a consequence of associative learning (Komorowski et al. 2009). POR cells also exhibit object-location conjunctions in a visual discrimination task, but the time course of such conjunctions has not been examined (Furtak et al. 2012).

Based on the above review, we suggest a slightly altered view of the dual process of context representations proposed by Rudy (2009). We suggest that the POR represents context by binding information about individual elements arising from the PER with location information arising from the retrosplenial and posterior parietal cortices to encode the spatial layout of items and patterns in the local environment. This representation of context would be available to multiple brain regions including the hippocampus for purposes of episodic memory and associative learning.

Conclusion

Available evidence suggests that object information in the POR most likely arrives via a direct PER to POR pathway. We suggest that the PER provides object information to both the POR and to the hippocampus, but for different purposes. Object information in the POR would be used to represent and update the spatial layout of physical features of the local environment, including objects and patterns located in that context. Information in POR is then available to hippocampus for episodic memory. The parallel object information flow from

PER to hippocampus is for the purpose of associations of objects (but not limited to visual stimuli) across domains (space and time) for complex representations of detailed allocentric spatial information as well as episodic memory.

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