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Why is there a special issue on perirhinal cortex in a journal called *Hippocampus*?: The perirhinal cortex in historical perspective

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Abstract

Despite its small size, the perirhinal cortex (PRh) plays a central role in understanding the cerebral cortex, vision and memory; it figures in discussions of cognitive capacities as diverse as object perception, semantic knowledge, feelings of familiarity and conscious recollection. Two conceptual constructs have encompassed PRh. The current orthodoxy incorporates PRh within the medial temporal lobe (MTL) as a memory area; an alternative considers PRh to be a sensory area with a role in both perception and memory. A historical perspective provides insight into both of these ideas. PRh came to be included in the MTL because of two accidents of history. In evolutionary history, the hippocampus migrated from its ancestral situation, as medial cortex, into the temporal lobe; in the history of neuropsychology, a “memory system” that originally consisted of the amygdala and hippocampus came to include PRh. These two histories explain why a part of the sensory neocortex, PRh, entered into the conceptual construct called the MTL. They also explain why some experimental results seem to exclude a perceptual function for this sensory area, while others embrace perception. The exclusion of perceptual functions results from a history of categorizing tasks as perceptual or mnemonic, often on inadequate grounds. By instead exploring the role of PRh in encoding, representing and retrieving stimulus information, it can be understood as a part of the sensory neocortex, one that has much the same relationship with the hippocampus as do other parts of the neocortex that evolved at about the same time.

Keywords

medial temporal lobe; memory systems; prefrontal cortex; ventral stream

INTRODUCTION

Yesterday is History,

'Tis so far away –

Yesterday is Poetry –

'Tis Philosophy –

Yesterday is mystery –
 Where it is Today
 While we shrewdly speculate
 Flutter both away

– Emily Dickinson, poem #1292

It might seem odd that a journal entitled *Hippocampus* would publish a special issue on the perirhinal cortex (PRh). But the journal's masthead explains its goal of presenting "research on the hippocampal formation and related structures..." So there is a simple explanation: PRh is related to the hippocampal formation in some way.

Yet little in systems neuroscience is so straightforward. The poet points to a deeper explanation: "Yesterday is History", and two kinds of history account for a special issue of *Hippocampus* on a cortical area that is, quite obviously, not part of the hippocampal formation. One involves evolutionary history and the other involves the history of neuropsychology.

- During mammalian evolution, the medial allocortex migrated toward the temporal (lateral) telencephalon, making it seem to be part of the same "thing" as PRh. The medial allocortex is called the hippocampus in mammals, and the "thing" is called the medial temporal lobe (MTL).
- During the history of neuropsychology, a series of experimental results and clinical observations—some right, some wrong—led to the current orthodoxy, which holds that the MTL functions as a neural center for explicit memory: the MTL memory system. An influential variant maintains that the MTL mediates memory but not perception, which implies that PRh neurons represent objects in memory but have no role in perceiving the same objects.

This article advances a different view, one that treats PRh as a sensory area and rejects the conceptual construct of an MTL memory system. It explains that the concept of an MTL, the inclusion of PRh in it, and the memory – perception dichotomy all result from accidents of history. To this end, we address four topics: (1) the evolution of visual cortex and the MTL; (2) the idea that PRh serves as a "gateway" between association cortex and the hippocampus; (3) the history behind the conceptual construct of an MTL; and (4) the reason that some findings seem to suggest that PRh lacks a perceptual function.

To preview our conclusions, which develop ideas advanced by Bussey and Saksida (2007) and by Murray et al. (2007), the evidence shows that PRh processes, represents and stores high-order sensory information and in this way contributes crucially to both object perception and object memory. PRh has these functions because the ventral visual areas represent information in the form of conjunctions among sensory features, and only PRh encodes feature conjunctions at the level typical of complex objects.

COMPARATIVE ANATOMY

The comparative evidence indicates that PRh evolved in early mammals. We can infer this history for two main reasons. First, a homologue of PRh can be found in a broad diversity of mammals, including carnivores (Markow-Rajkowska and Kosmal, 1987; Witter and Groenewegen, 1984), ungulates (Meurisse et al., 2009) and marsupials (McDonald and Culbertson, 1986), as well as in rodents, primates and other mammals. It has the same topological location in all mammals: dorsal to the rhinal sulcus, caudal to orbitofrontal

cortex at about the level of the entorhinal cortex (ERh). Second, no homologue of PRh has been identified in any nonmammal.

Similar evidence shows that the striate cortex (V1) and one or more extrastriate areas (including V2) also evolved by the time of the early mammals (Lyon, 2007). The inferior temporal cortex (IT), by contrast, evolved much later than PRh, in early primates (Kaas, 2012). Areas similar to IT exist in nonprimates, as a result of parallel evolution, but this does not alter the status of IT as a shared derived trait of primates. Mammals arose as small animals, and a period of diversification occurred before they became much larger. As many kinds of mammals increased in size, their brains expanded and new areas appeared. In several of these lineages, a new group of areas appeared between the V1/V2 complex and PRh. In primates, these areas compose IT, which in macaque monkeys includes areas TE and TEO. (In this article, the term IT excludes PRh.)

Unfortunately, some misconceptions have prevented the widespread recognition of this history. The poet pointed to speculation, seemingly shrewd, that endures as history and the present “flutter both away”. Much the same can be said of some writing on cortical evolution. Sanides (1970) has had the most influence. He imagined that primary sensory areas of cortex, such as V1, evolved most recently among cortical areas. His “evidence” was that they had more complicated lamination than other areas, and on this basis he developed an elaborate scheme of evolutionary “trends”. Unfortunately, only a few of his suppositions have withstood comparative analysis, which indicates that the primary sensory areas evolved no later than in early mammals, at about the same time as PRh (Kaas, 2011). Despite their popularity in certain circles, the speculative ideas of Sanides and his followers do not reflect the actual history of the brain.

A different set of issues involve the hippocampus and the MTL. Partly because of an emphasis on the brains of humans and other large primates, it seems obvious that the hippocampus is part of the temporal lobe. According to the current orthodoxy, the MTL includes PRh, ERh, the parahippocampal cortex (PHC), the subicular complex, the hippocampus, and the fornix. Although it *seems* obvious that these structures compose a “thing”, the MTL, comparative anatomy fails to provide any support for this construct.

Understanding the evolution of the hippocampus is complicated by radical changes in its architecture and topology, but a homologue probably evolved in early vertebrates (Northcutt, 1996; Striedter, 2005). Yet stronger evidence identifies a homologue of the hippocampus in a variety of amniotes (Fig. 1C), which includes the animals traditionally classified as reptiles, mammals and birds. In snakes and lizards, for example, the medial cortex (Fig. 1B) closely resembles the mammalian hippocampus, and both its connections (Ulinski, 1990) and the behavioral effects of lesions (Day et al., 2001) support the proposed homology. In both mammals and reptiles, the hippocampus and its homologues have the three-layered structure that characterizes allocortex.

As the cortex expanded in mammals, the medial cortex became displaced caudally and laterally in the telencephalon, and its septal pole came to reside more caudally than its amygdaloid (temporal) pole (Fig. 1A). Despite its migration, the fundamental connectional affinities of the hippocampus have been conserved. It remains a medial cortical area, not a temporal (i.e., lateral) one, regardless of the distortions imposed by cortical expansion. The dislocation of the hippocampus probably has little functional significance, if any. Evolutionary changes often occur as a secondary consequence of selection for some other trait, a concept known as a spandrel. It seems likely that brain expansion pushed the hippocampus into the temporal lobe as such an accident of history.

To summarize the two main points of this section:

1. IT is a shared derived trait of primates, one that evolved much later than PRh, V1 or V2.
2. The mammalian hippocampus only *seems* to be a temporal area; it is instead medial allocortex, as it has been since the early amniotes.

CONNECTIONAL ANATOMY

The orthodox view of an MTL memory system implies that PRh has a privileged relationship with the hippocampal formation, serving as the key “gateway” to the hippocampus for nonspatial information.

Fig. 2A shows an often-reproduced anatomical summary (Zola-Morgan et al., 1991), one that has changed little in the past twenty years (Wixted and Squire, 2011). It implies that association areas of cortex must relay their inputs to ERh – hippocampal pathways through either PRh, PHC or both. These connections exist, of course, but Fig. 2A does not capture the published anatomical literature very successfully. Specifically, it ignores the many direct connections between ERh and cortical areas other than either PRh or PHC, in both monkeys and rats. It seems to us that the prevailing neuropsychological theory has affected the way in which neuroanatomical data have been summarized and described, and not always in a way best suited to understanding brain organization.

Monkeys

A recent review considers the relevant connections in detail (Aggleton, 2011), so we emphasize just a few points here. Fig. 2B illustrates the areas most heavily connected to ERh in monkeys (Insausti et al., 1987; Mohedano-Moriano et al., 2007). Taken together, they compose a ring of neocortex that has often been linked to the limbic system. The word ‘limbic’ means ‘border’, and many neuroanatomists have noticed that the cortex bordering the bulk of the neocortex in primates has a specialized character. The published anatomy therefore suggests a summary more like Fig. 2C than like Fig. 2A. Of course, both diagrams omit many connections, but Fig. 2C conveys the idea that a ring of limbic areas has reciprocal connections with ERh. In addition to retrosplenial, posterior cingulate and PRh cortex, this ring includes prefrontal areas such as infralimbic, prelimbic, anterior cingulate, and agranular insular and orbital cortex (Fig. 2B).

Although we do not question the dense and reciprocal nature of the connections between PRh and ERh in monkeys, and we accept they outnumber those of other neocortical areas (Insausti et al., 1987), the basic picture that emerges from Fig. 2B is that PRh is one among a number of cortical areas that pass information to and from the hippocampus through ERh. Thus, PRh and PHC do not appear to be privileged “gateways” to the hippocampus.

Direct ERh connections do not involve all prefrontal areas (Muñoz and Insausti, 2005), but other routes connect the frontal cortex with ERh–hippocampal pathways, and they include some additional parts of the prefrontal cortex. Among them, the hippocampus has an impressive route to the dorsolateral prefrontal cortex via the retrosplenial cortex (Morris et al., 1999). And, as shown in Fig. 3, several prefrontal areas have direct connections with the hippocampus and subiculum (Barbas and Blatt, 1995). Evidently, and in distinct contrast to the current orthodoxy (Fig. 2A), the interactions between hippocampus and the prefrontal “association” cortex do not depend on PRh and PHC.

Rats

The relevant connections in rats resemble those just described for macaque monkeys. In rats, the ERh has impressive interconnections with PRh and the postrhinal cortex (a putative homologue of PHC). In addition, dense efferent projections from ERh go to the piriform, agranular insular and medial frontal cortex, including the infralimbic and prelimbic cortex, with weaker projections going to the orbital and anterior cingulate cortex. These projections are, for the most part, reciprocated. And, as in monkeys, the retrosplenial cortex is heavily connected with ERh, as well (Agster and Burwell, 2009; Burwell and Amaral, 1998; Jones and Witter, 2007).

In both monkeys and rats, therefore, the current orthodoxy (Fig. 2A) seems to place undue emphasis on PRh, PHC, or postrhinal cortex as “gateway” routes to the hippocampal formation.

THE MTL CONSTRUCT

Given the comparative and connectional neuroanatomy just reviewed, readers might wonder how PRh came to be a pivotal component of the conceptual construct called the MTL. The primate PRh first came into prominence through studies of memory. In the 1960s, neuropsychologists began to investigate the neural basis for the severe amnesia observed in patient H.M.

As reviewed elsewhere (Buckley and Gaffan, 2000; Murray, 1996; Murray and Wise, 2010), many of these studies employed the delayed matching-to-sample and delayed nonmatching-to-sample tasks, which for convenience we call the *short-interval matching task* or, simply, the *matching task*. In these tasks, monkeys see a sample object and need to choose or avoid it after a variable delay period, depending on a rule: matching or nonmatching. In part because they were called ‘object recognition’ or ‘visual recognition’ tasks, matching tasks came to be considered as the canonical tests of explicit memory. Despite these names, monkeys can perform these tasks in ways that do not require an explicit memory of the sample: notably by familiarity or recency strategies, depending on details of the experimental design. Furthermore, in retrospect, matching tasks seem an odd choice for exploring H.M.’s memory impairment. These tasks usually measure task performance over relatively brief delay periods of seconds or minutes, whereas H.M. had no memory problem over such short intervals, unless distracted.

In studying the neural substrates of memory, Mishkin (1978) did an experiment that led him to conclude that monkeys with combined lesions of the amygdala and hippocampus had a memory deficit like H.M.’s. He tested monkeys on a short-interval matching task and found a severe impairment after such lesions (Fig. 4A). These monkeys could perform the task at very brief delays, which ruled out discrimination impairments and a failure to remember or apply the task rules. Over longer intervals and for longer lists of objects, however, the monkeys with “amygdala plus hippocampus” lesions performed poorly (Fig. 4A). (We place quotation marks around “amygdala and hippocampus” because later research showed that the impairment actually arose from unintended damage to other structures.)

At this point in history, two main ideas emerged. One held that combined damage to the “amygdala and hippocampus” caused a severe memory impairment (Mishkin, 1982). The other account held that lesions of the hippocampus, alone, caused the impairment (Zola-Morgan and Squire, 1985), which agreed with the initial emphasis on hippocampal damage as the cause of H.M.’s amnesia (Milner, 1959). Dissenting views, such as those embodied by the temporal stem hypothesis (Gaffan, 2001; Horel, 1978), were swept aside, and the conclusions of Mishkin, Squire and their colleagues became the current orthodoxy.

A series of subsequent studies seemed to support that orthodoxy, but few experiments were designed to test it by performing the appropriate control procedures. The first such tests considered the potential contributions of PRh and ERh, which lie ventral to the amygdala and the rostral third of the hippocampus. At the time, it was known that ERh had been completely removed by Mishkin's combined "amygdala and hippocampus" lesion, but not by either lesion, alone. In addition, PRh was sometimes compromised. Thus, damage to PRh-ERh could account for Mishkin's results without invoking the concept of an MTL memory system that included the hippocampus. Murray and Mishkin (1986) removed either the hippocampus plus ERh-PRh or the amygdala plus ERh-PRh. Lesions of the amygdala plus ERh-PRh produced a severe impairment on the matching task, in the absence of any direct hippocampal damage. In addition, lesions of the hippocampus plus ERh-PRh, which were incomplete for PRh but included all of the hippocampus, yielded only a mild deficit. These results suggested that ERh-PRh played a greater role in matching tasks than previously thought and that the hippocampus played a lesser role.

Fig. 4B illustrates the results of the key follow-up studies. First, complete removals of PRh and ERh caused a severe impairment on the matching task (Meunier et al., 1993). Second, combined damage to the amygdala and hippocampus, made with excitotoxins in order to spare the nearby PRh and ERh, failed to disrupt task performance (Murray and Mishkin, 1998). A severe and consistent impairment followed damage to PRh and ERh, whether the lesion was produced by aspiration (Meunier et al., 1993) or by excitotoxins to avoid fiber damage (Baxter and Murray, 2001b; Malkova et al., 2001).

The results illustrated in Fig. 4B thus overturned Mishkin's idea of an MTL memory system consisting of the amygdala and hippocampus. It also excluded hippocampal damage as a major cause of impairments on matching tasks, contradicting Squire and his colleagues. Yet the conceptual construct of an MTL memory system—anchored by the hippocampus—survived and prospered. To conserve the conceptual construct of an MTL memory system, however, proponents had little choice but to include both PRh and ERh (Squire and Zola-Morgan, 1991). The amygdala, a large component of the primate MTL by any definition, was held to be important for functions other than memory, and the historical role of "amygdala" lesions in generating the MTL construct was quietly forgotten.

Note that the current orthodoxy depends on two related assumptions: that short-interval matching tasks assess explicit memory and that an MTL memory system, which includes the hippocampus, subserves normal performance of these tasks. From the monkey work, however, there is little reason to include the hippocampus among the structures that play a major role in the normal performance of short-interval matching tasks. Indeed, hippocampal removal lessens the impairment on short-interval matching tasks that PRh-ERh lesions cause (Meunier et al., 1996). PHC, likewise, makes little contribution to the performance of short-interval matching tasks (Nemanic et al., 2004).

Although the precise contribution of the hippocampus to matching tasks remains controversial, no one has contradicted the finding that damage limited to PRh-ERh yields a severe impairment on these tasks (Fig. 4B). In contrast to these robust and consistent impairments, lesions confined to the hippocampus often have little or no effect (Baxter and Murray, 2001a). Depending on the experimental details, significant impairments on these tasks do sometimes follow damage to the hippocampal formation (Beason-Held et al., 1999; Zola et al., 2000), but some or all of these effects can be attributed to the disruption of a recency strategy rather than to a failure of explicit memory (Charles et al., 2004). In experiments that used sufficiently large stimulus sets to preclude recency strategies, lesions confined to the hippocampus have no effect on short-interval matching tasks (Murray and Mishkin, 1998).

These results do not imply that the hippocampus lacks any role in matching tasks, merely that it is not necessary for their normal performance in general. In intact monkeys, the hippocampus likely contributes to the recency strategy just mentioned, as well as to other aspects of temporal and spatial context, topics taken up below.

As a consequence of this history, PRh—a narrow strip of neocortex near the rhinal sulcus—grew from relative obscurity to a prominent place in present-day neuropsychology.

MEMORY VS. PERCEPTION

Despite the dominance of the MTL construct, there is an alternative way to think about PRh. Instead of viewing PRh as part of a “memory system” or as a “memory area”, it can be viewed as a visual area. Unlike most visual areas, PRh also receives inputs from other sensory modalities (Suzuki and Amaral, 1994), but this trait does not exclude it from the visual cortex. Results that support a role for PRh in visual perception come from both monkeys and rats, and in this section we summarize results bearing on the memory versus perception debate.

Monkeys

The historically influential experiments focused on PRh and area TE, a key part of IT in macaque monkeys. Lesions of PRh caused impairments on single-pair visual discriminations but not on multiple-pair (concurrent) discriminations (Buffalo et al., 1999, 2000). In the single-pair task, the same pair of stimuli appears trial after trial; in the multiple-pair task, many pairs of stimuli intervene between trials with any given pair. Buffalo et al. assumed that the single-pair task placed low demands on perceptual processing but high demands on memory because, in their procedure, it required retention across days. Therefore they concluded that PRh functioned in the “formation and maintenance of long-term memory”, and they excluded PRh from the “perceptual processing of visual stimuli” (Buffalo et al., 2000).

The current orthodoxy assigns visual perception instead to area TE. In contrast to what they found after PRh lesions, Buffalo et al. reported that lesions of TE impaired performance on the multiple-pair discrimination task but not on the single-pair task. They supposed that the need to discriminate many pairs of stimuli placed high demands on perception, with little or no long-term memory requirement, an idea supported by the impairment caused by TE lesions on matching tasks and spontaneous visual recognition when memory periods were very short (Buffalo et al., 2000).

Note that, historically, Buffalo et al. excluded PRh from a role in perception based on a negative result from the multiple-pair task. We accept the conclusions that follow from their positive results, but reject those from their negative results. TE and other parts of IT indeed play a crucial role in visual perception, and PRh plays a crucial role in memory. But because of the stimulus material that they used, Buffalo et al. missed the critical role that PRh plays in visual perception.

Bussey, Saksida and Murray focused on the stimulus material rather than the other variables inherent in the single- and multiple-pair discrimination tasks. Based on the organization of the ventral visual areas, with more rostral regions lying higher in a sensory hierarchy, they reasoned that PRh neurons should represent complex conjunctions of stimulus features. To test this idea, they examined the ability of monkeys to discriminate objects with overlapping visual features. Because complex objects can share many sensory features, exemplified by color, shape and texture, conjunctive representation of a large set of features is required to

disambiguate them. The problem posed by overlapping feature sets is called *feature ambiguity*.

Each of their experiments required monkeys to identify and select one of two images of a pair. In the key test, the monkeys had to discriminate pairs of objects in which the correct and incorrect choices shared many features (high *feature overlap*). As a control procedure, monkeys discriminated pairs of complex objects that had little or no feature overlap. Stimuli were constructed either by adjoining images to create compound stimuli or by morphing two images. Although the use of compound stimuli established a biconditional discrimination task, the results from morphed images did not, and taken together the results support the more general interpretation of these results in terms of feature perception. Construed in this general way, both of these methods manipulated the amount of feature overlap inherent in discrimination problems. With both procedures, monkeys with PRh damage showed impairments on tests involving high feature overlap, but not on identical tests involving little or no feature overlap. Importantly, the degree of impairment correlated with the amount of feature overlap, as opposed to the number of pairs to be discriminated (Bussey et al., 2002, 2003).

These results support the idea that PRh represents feature conjunctions at a certain level of complexity. Because the memory load was the same for each condition, the findings did not result from a memory impairment. Task difficulty does not explain the results either: the same monkeys and others with PRh lesions performed normally on difficult visual discrimination problems involving small differences in color, shape or size, rotated images, or images degraded by noise (Buckley et al., 2001; Bussey et al., 2003; Hampton and Murray, 2002).

A related experiment examined the ability of monkeys with PRh lesions to discriminate the “odd man out” among several images. For example, monkeys saw several views of one face, together with a different (odd) face. PRh lesions caused impairments in learning to identify the odd face. This experiment removed the memory component from the visual discrimination task. The monkeys had to remember the task rule, of course, but the correct choice on any given trial did not depend on the memory of stimuli from previous trials, as the single- and multiple-pair tasks do. Because the monkeys needed only to perceptually discriminate the items visible on the current trial, the impairment could not have resulted from a problem with stimulus memory (Buckley et al., 2001).

We think that some disagreements in the literature arise from the history of naming tasks according to unverified assumptions. It is easy to label something an ‘explicit memory task’ or an ‘object recognition task’, but does the name apply to what the monkeys do? Monkeys can perform matching tasks by using recency strategies (Charles et al., 2004), for example, and so they do not necessarily test explicit memory. Likewise, people can perform multiple-pair discrimination tasks—often construed as “perception tasks”—by using explicit memory (Hood et al., 1999).

A better way forward dispenses with the idea of “perception” and “memory” tasks and instead explores the involvement of PRh in encoding, representing and retrieving stimulus information (Bussey and Saksida, 2007). If PRh represents feature conjunctions, it should do so at a certain level of conjunction for use in both discrimination and matching tasks. And the evidence confirms that prediction in both monkeys and humans (see also Barense et al., this issue).

To bring this discussion full circle, we can now trace the history of one part of the current orthodoxy: that PRh functions in memory but not in perception. The idea that PRh

represents feature conjunctions and resolves feature ambiguity accounts for the lack of impairment on multiple-pair (concurrent) discriminations, which Buffalo et al. (2000) construed as a “perception task”. If experiments involve stimuli with an insufficient degree of feature ambiguity, PRh lesions have no effect. Instead, PRh lesions cause an impairment that correlates with the amount of feature ambiguity and not with the number of stimulus pairs to be discriminated (Bussey et al., 2002, 2003). These results directly contradict the assumption that the single-pair discrimination task is a “memory task”, whereas the multiple-pair discrimination task is a “perception task.”

Likewise, when we dispense with the conceptual construct of an MTL, other apparent contradictions in the literature become less troubling. For example, if the MTL is a single functional unit, then damage to hippocampus should lead to much the same impairments on tasks that vary feature ambiguity as do lesions of PRh. Monkeys with selective hippocampal lesions, however, perform these tasks normally (Saksida et al., 2006). Thus, structures within the MTL construct have different functions, a point documented previously (Gaffan, 2002; Murray and Wise, 2004).

The transverse patterning experiment emphasizes this point particularly well. In this task, the same object appears in more than one pair, and the correct object in one pair of objects is the incorrect one in another pair. PRh lesions cause a severe impairment on this task, but monkeys with hippocampal lesions perform better than normal monkeys (Saksida et al., 2007). This result shows that structures in the MTL not only fail to show the cooperative functions expected for an MTL memory system, but also can function in opposing ways.

Rats

In rats, the contributions of PRh to object perception and memory resemble those in monkeys. Most of the relevant tests of object recognition have involved spontaneous exploration of two objects presented simultaneously: one novel and the other familiar. In these tasks, normal rats devote exploration time disproportionately to novel objects.

Rats with PRh lesions, together with ERh or postrhinal lesions, show impairments on object recognition tasks with a delay between sample and test (Aggleton et al., 1997; Mumby and Pinel, 1994; Winters et al., 2004). When the test minimizes spatial and contextual cues, hippocampal lesions have no effect on spontaneous recognition for up to 48 hours (Forwood et al., 2005). Also, like monkeys with combined damage to PRh and ERh (Eacott et al., 1994), rats with lesions of PRh alone or together with postrhinal cortex are impaired under conditions of high feature overlap even without an appreciable delay to overcome (Bartko et al., 2007a, b; Norman and Eacott, 2004).

Rats with PRh lesions also show impairments on the same sorts of discrimination problems as do monkeys with PRh lesions. When required to discriminate objects or make oddity judgments under conditions of high feature overlap, rats with PRh lesions perform poorly (Bartko et al., 2007a, b). And, as in the monkey experiments, the impairment depends on the amount of feature overlap between the test objects (Bartko et al., 2007a; Eacott and Norman, 2004).

Recent results have advanced this analysis. McTighe et al. (2010) exposed rats to a sample object and an hour later measured their spontaneous exploration of either two copies of a novel object or two copies of the familiar (experienced) object. They found, as expected, that control rats explored novel items more than familiar ones and that rats with PRh lesions explored novel and familiar items equally. This equality came about, however, because the rats with PRh lesions *decreased* their exploration of novel items, relative to controls, and not because they *increased* their exploration of familiar ones. Thus, rather than treating familiar

items as novel, as expected if the impairment resulted from forgetting, rats with PRh lesions treated novel objects as familiar (cf. Albasser et al., 2011), called false recognition. At advanced ages, rats without such lesions behave similarly, probably due to PRh dysfunction (Burke et al., 2010).

In exploring this finding, McTighe et al. found they could restore normal task performance by reducing visual interference during the delay period. They hypothesized that rats with PRh lesions treat novel objects as familiar because they lack the conjunctive representations that uniquely specify objects. When presented with a novel object, rats with PRh lesions process its many familiar features and thus behave as they do for familiar objects. In normal rats, PRh provides protection from interference by representing complex feature sets as unique conjunctions. In rats with PRh lesions, sensory restriction can provide this protection because it reduces the interference caused by visual features encountered during the delay period.

As proponents of the orthodox view, Clark et al. (2011) have contested all of these conclusions. They reported that rats with PRh lesions performed normally on tests of visual discrimination involving feature overlap. They trained rats to discriminate a single pair of stimuli and gave them 150 trials with each of several levels of morphed stimuli. Following removal of PRh, they retrained the rats on the preoperatively learned discrimination and again presented tests involving the morphed images. Rats with PRh lesions performed as well as controls, despite the feature overlap created by morphing the stimuli. Several factors could account for this negative result. First, the stimulus material consisted of two-dimensional images of elongated objects, with the most informative aspects at each end. Consequently, the rats probably attended to one end of the stimuli to choose correctly, which makes the amount of feature overlap affecting the critical part of the object virtually impossible to discern. Second, the rats required thousands of trials—between 12,000 and 13,000—to learn the discrimination, and they were also given extensive experience with the morphed images. The need for such extensive training shows that the problems were much more difficult than those used in the monkey experiments and in the other rat experiments cited above. Accordingly, the findings of Clark et al. have little relevance to the function of PRh on more tractable discrimination problems, for reasons explained in the next section.

Cowell et al. (2010a, b) used computational modeling to explore how hierarchically organized systems solve discrimination problems. They showed that “lesions” to different layers of a connectionist model produced impairments in learning discriminations based on the properties of the simulated stimuli, thus eliminating any need to appeal to concepts such as memory or perception. Lower layers of their hierarchically organized model discriminate stimuli with low feature overlap; higher layers discriminate stimuli with high feature overlap. The former corresponds to IT, the latter to PRh. Their model also suggests levels of hierarchy beyond that of PRh, perhaps corresponding to the hippocampus. This higher level can be viewed as representing the unique conjunctions that compose typical objects, together with their spatial and temporal context (Cowell et al., 2010a).

HISTORY NOT MYSTERY

Two historical developments—one evolutionary (Fig. 1), the other experimental (Fig. 4)—converged to answer the question posed in our title: Why is there a special issue on PRh in a journal called *Hippocampus*? Evolution pushed the medial allocortex, called the hippocampus in mammals, into proximity with PRh; the history of neuropsychology required the extension to PRh of functions originally ascribed either to the hippocampus or to the amygdala and hippocampus, combined. So we can appreciate how both the current orthodoxy and this special issue came about.

However, neither comparative anatomy nor the neuropsychological data support the current orthodoxy. The inclusion of the medial allocortex (hippocampus) within a “system” that includes one area of sensory neocortex, PRh, but excludes nearly all of the others makes little sense from a comparative perspective. Results from neuropsychology provide equally little support for an MTL memory system that requires PRh to function cooperatively with the hippocampus (Fig. 4B). Only when temporal or spatial context becomes important does the hippocampus take on a critical role (Barker and Warburton, 2011; Brasted et al., 2003; Charles et al., 2004; Cowell et al., 2010a). Once we abandon the orthodoxy of a reified MTL memory system, it should come as no surprise that the PRh and the hippocampus perform different functions (Gaffan, 2002; Murray and Wise, 2004), and sometimes opposing ones (Saksida et al., 2007).

History also might explain Fig. 2A, which implies that association areas of cortex must gain access to ERh–hippocampal pathways via either PRh or PHC. This is not the case. For example, many prefrontal areas—which are association areas by any definition—have direct connections with ERh (Fig. 2B), as well as with the hippocampus and the subiculum (Fig. 3). Fig. 2A thus omits a lot, but it rightly depicts IT as having little direct access to ERh–hippocampal pathways. Historically, then, Fig. 2A can be understood as an unjustified generalization from a subset of association areas to all of them. An alternative view of these connections (Fig. 2C) arises from Fig. 2B, which shows PRh to be only one among a number of limbic areas that exchange information with ERh and the hippocampus.

The two histories also explain why some experiments seem to exclude a role for PRh in visual perception. In evolution, PRh and IT evolved at different times, in response to different adaptive pressures. PRh deals with feature conjunctions at the level of typical objects; IT deals with less complex conjunctions, at a level between objects and elemental features. Passingham and Wise (2012) proposed that IT’s intermediate level of conjunction represents visual signs that primates use for making foraging choices. They noted that IT evolved in concert with granular prefrontal areas, in early primates, and that IT expanded as primates evolved advances in vision, such as the fovea, trichromatic vision and enhanced stereopsis.

Viewed in historical perspective, evolution seems to have conspired to produce the experimental results that led to the memory–perception dichotomy espoused in the current orthodoxy. PRh resolves feature ambiguity at a particular level of feature overlap, which provides mammals with advantages in dealing with the complex objects that they encounter in foraging. Laboratory experiments run the risk of using stimulus material having a different level of feature conjunction than PRh represents, as in the experiments of Clark et al. (2011) and Buffalo et al. (1999, 2000). Their negative results do not indicate that PRh lacks a role in visual perception, they merely reflect its history: PRh evolved to disambiguate stimuli of a particular kind (Bussey and Saksida, 2007).

As the poet says, “Yesterday is mystery”, a far away history, and much mystery about brain history remains. We know enough, however, to help us understand PRh. PRh and IT do have different functions, of course, but not the ones championed by advocates of the current orthodoxy. As a result of evolutionary history, PRh provides an adaptive advantage to mammals by representing feature conjunctions at the level of natural objects; IT provides an advantage to primates by representing visual signs of necessary resources. By ignoring this history, investigators not only forfeit the insight that it brings, but they also risk running a long way down the wrong arm of the maze.

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FIG. 1.

A. Left to right: migration of medial cortex (hippocampal homologue) toward lateral (temporal) telencephalon as cortex expanded. The septal pole of the medial cortex is shaded lightly, its amygdaloid (temporal) pole is shaded darkly. **B.** Representative amniote cortex. Cortical areas: D, dorsal; DM, dorsomedial; M, medial; L, lateral;. Rostral: left. **C.** Cladogram of selected amniotes. Bars show derived traits. Abbreviations: CC, corpus callosum; IT, inferotemporal cortex (excluding PRh); PRh, perirhinal cortex; V1, primary (striate) visual cortex; V2, second visual area.

FIG. 2.

A. Orthodox summary of pathways from association cortex to hippocampus. **B.** Major connections with ERh. Triangles, auditory areas; cross-hatch, agranular insula; vertical hatch, temporal pole, PRh and PHC; horizontal hatch, prefrontal, cingulate and retrosplenial cortex; filled circles, orbital prefrontal cortex; unfilled circles, rostral superior temporal cortex; squares, rostral IT. **C.** Alternative summary. Hipp, hippocampus; PF, prefrontal cortex. A from Zola-Morgan et al. 1991; B from Mohedano-Moriano et al. 2007.

A Subicular complex

B Hippocampus

FIG. 3. Prefrontal–hippocampal connections in macaques. **A.** Sites in the frontal cortex receiving inputs from the subicular complex. Numbers give Walker’s areas; Ia, agranular insular cortex. **B.** Sites receiving inputs from the hippocampus. From Barbas and Blatt 1995.

FIG. 4.

A. Percent correct in a matching task as a function of delay duration and number of sample items. From Mishkin 1978. **B.** Subsequent results involving more selective lesions. From Meunier et al. 1993 and Murray and Mishkin 1998.