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Shared Functions of Perirhinal and Parahippocampal Cortices: Implications for Cognitive Aging

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Abstract

A predominant view of perirhinal cortex (PRC) and postrhinal/parahippocampal cortex (POR/PHC) function contends that these structures are tuned to represent objects and spatial information, respectively. Known anatomical connectivity, along with recent electrophysiological, neuroimaging, and lesion data, however, indicate that both brain areas participate in spatial and nonspatial processing. Rather than content-based organization, the PRC and PHC/POR may participate in two computationally distinct cortical-hippocampal networks: one network tuned to process coarse information quickly, forming gist-like representations of scenes/environments; the other network tuned to process information about specific sensory details necessary for discrimination across sensory modalities. Available data suggest that the latter network may be more vulnerable in advanced age.

Keywords

entorhinal cortex; hippocampus; MRI; memory; postrhinal cortex; process model

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THE PERIRHINAL AND PARAHIPPOCAMPAL CORTICES COME OF AGE

Advanced age is characterized by neurobiological alterations within the medial temporal lobe (MTL) that are linked to cognitive dysfunction in older adults and other animals [1]. While dysfunction within the hippocampus (HPC) and impairments in HPC-dependent behaviors are well documented with age, a debate has emerged regarding age-associated vulnerabilities within other cortical MTL regions. The **perirhinal cortex** (PRC; see glossary) and **parahippocampal cortex** (PHC) are in the **parahippocampal region** (Figure 1 A and B) of the MTL and reciprocally connect with HPC. The PHC in primates is homologous to the rodent **postrhinal cortex** (POR). Recently, there has been an emerging interest in the respective contributions of PRC and PHC/POR to cognition, and vulnerability of these regions to advanced age and early stages of Alzheimer's disease.

A commonly held view is that PRC and POR/PHC are preprocessors for 'nonspatial' and 'spatial' information streams to HPC that are tuned to represent information regarding objects and scenes, respectively [2–4]. The outputs from these regions are fed forward via the lateral (LEC) and medial entorhinal cortices (MEC) (Box 1) to HPC where they are bound to form a cohesive representation of an environment or episode [4]. Rather than taking a purely content-driven view of regional specialization within the MTL, here we review recent data that cannot be reconciled with a segregation of function between the PRC and PHC/POR, and present an updated **process-based model** of these regions' contributions to cognition. By this hypothesis, both PRC and PHC/POR contribute to two networks. One network projects through the entorhinal cortex (EC) to HPC to support the formation of coarse "gist-like" representations of scenes or environments. The second network projects directly to HPC to add fine-grained details of relevant stimuli to the broader representation.

Critically, age-related neurobiological alterations within PRC-HPC circuits have been linked to impairments in specific cognitive functions that can be attributed to processing-based deficits of fine-grained representations of sensory details. While this model requires additional empirical data to defend or refute its veracity, the goal of the updated framework presented here is to generate new testable hypotheses regarding the contributions of specific MTL regions to memory and cognitive aging.

RETHINKING CONTENT-BASED ISOLATION OF PRC AND PHC/POR FUNCTIONS

Anatomy

While PRC and PHC/POR both receive sensory information from neocortex [5], and are densely reciprocally connected [6, 7], these structures are commonly described as part of two distinct large-scale cortical systems – an anterior temporal network that is functionally connected to the PRC and critical for object and nonspatial information processing, and a posterior medial network that is critical for spatial information and scene processing [4, 8, 9]. By this view, PRC and PHC/POR send projections to the LEC and MEC, respectively [7], maintaining an isolation of nonspatial and spatial information. LEC and MEC layer II neurons then project to the dentate gyrus (DG)/CA3 subregions of HPC through the

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perforant pathway to integrate these information streams along the longitudinal axis of HPC [10, 11]. In support of this anterior temporal/posterior medial framework, functional connectivity studies in humans [12] and anatomical tracer studies in monkeys [13] and rats [5] have shown that the PRC receives relatively more input from ventral visual areas in inferior temporal cortex, while the PHC/POR receives more input from cortical regions involved in visuospatial processing such as retrosplenial and posterior parietal cortices. While the idea of the nonspatial and spatial segregation of information streams between the LEC and MEC has been updated recently [14, 15], such a refinement has not been extended to the PRC and PHC/POR.

Often overlooked are the abundant anatomical data showing that anterior temporal/nonspatial and posterior medial/spatial cortical streams of information are integrated before reaching HPC [6, 7, 16–18]. In fact, recent imaging data from human subjects has identified a region of caudal PRC that is connected to both the anterior temporal and posterior medial networks [19]. Figure 1C summarizes the cortical input to MTL in rats [5, 16, 17] and monkeys [13, 20, 21], highlighting the relative strength of afferents from different cortical regions. As evident in Figure 1C, across species there are dense connections between PRC and PHC/POR, as well as among the subdivisions of EC [7, 20, 22]. Moreover, the connections between PRC-LEC and PHC/POR-MEC are not isolated from each other. In fact, there are modest connections between PRC-MEC and PHC/POR-LEC [16], demonstrating crosstalk between the PRC-LEC and PHC/POR-MEC pathways. In line with these data, a recent graph analysis of 117 different anatomical studies of MTL connectivity from rats identified the POR as a connector hub, meaning that this region is highly connected with other nodes of the MTL network including PRC, LEC and MEC. Moreover, both LEC and MEC were clustered together with HPC, PER and POR [17]. Finally, while the strength of certain cortical input to PRC versus PHC/POR varies, many areas project to both regions. Thus, there is not a complete isolation of sensory input within the MTL. These anatomical observations suggest that a reconsideration of the extent of segregation between nonspatial and spatial information streams into the HPC is warranted.

A few variants between species are worth mentioning. First, cortical input to the MTL is not as extensively characterized in the primate as it is in the rodent. Due to the difficulty of limiting retrograde tracer injections to the fundus of the rhinal sulcus, the inputs to area 35 of PRC are not well defined for monkey [13], and the connectivity between the piriform cortex and MTL in the primate has not been elucidated. Second, the primate EC receives less direct sensory input than does the rodent [5, 22]. For example, the projection from TE to LEC that has been noted in rat [5] is absent in monkey [21]. Finally, the connectivity between the prefrontal cortices and PRC/PHC/POR is denser in rodents than in monkeys [5, 22].

Neurophysiology

Single-unit recording data from rats also do not support the view that there is isolation of object and spatial information to the PRC and PHC/POR [23, 24]. While PRC cells recorded from rats are selectively active at spatial locations that contain objects [25, 26], PRC neurons are also spatially tuned to large segments of an environment, providing large-scale position

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information [23]. Similarly, the activity patterns of PHC/POR neurons do not appear to convey strictly spatial inputs to the HPC. For example, PHC/POR neuron activity in rats can be tuned to specific object-location conjunctions [24], providing additional evidence that the integration of information about spatial layouts with discrete stimuli occurs before the level of the EC and HPC.

Behavior

In rats, early lesion studies characterizing deficits in contextual information processing following either PRC or POR lesions did not detect functional dissociations between regions [27, 28]. While dissociations between PRC and PHC/POR for processing objects versus spatial/contextual information have been reported in rats [29], more recent lesion data have shown that PRC activity is critical for processing object-place associations [30, 31], and that the PRC is involved in allocentric spatial learning [32]. Moreover, inactivation of either PRC or POR in rats produces impairments in the ability to use scenes to cue correct behavioral responses [33], indicating that both areas are involved in processing spatial input. Furthermore, functional connectivity between the PRC and PHC/POR is critical for accurate recognition of objects in context [34].

Cognitive research in human subjects also supports the view that PRC and PHC/POR functions cannot be dissociated based on content representations. In the real world, objects are always experienced in the broader visual context of a scene or environment – there is no such thing as an “object alone”, and both the feature elements of the object and the surrounding context contribute to subsequent identification [35] and recognition [36]. In fact, data indicate that there may be an automatic and obligatory binding at encoding between an object and its context [36, 37] resulting in an integrated representation [see also, 38]. In support of this view, object recognition in humans is exquisitely sensitive to changes in scene context, even when the encoding task directs attention to the object or participants are informed that the scene may be altered at test. Moreover, a white background increases object recognition when the same white background is reinstated at retrieval [36], further suggesting that objects are always experienced in a broader visual context. Perceptual work on scene processing further supports this notion, suggesting that the representation of a scene is not based solely on individual objects and object-to-object relations, but also includes a holistic statistical summary of the scene that provides an effective source of information for contextual inference [39]. Interestingly, PRC activity measured by fMRI has shown that activation in this region is related to novel versus familiar stimulus discrimination for both scenes and objects [40].

Based on the data discussed above, it may be parsimonious to offer an alternative hypothesis to the nonspatial/spatial two-stream memory model of PRC and PHC/POR function. Here we propose a novel process-based model that the PRC and PHC/POR are both integrated into two larger HPC-cortical networks that are tuned for coarse versus fine-detailed representations. These coarse and detailed networks form HPC-cortical recurrent loops that update representations iteratively so that fine-grained details are incorporated into broader representations, which is critical for resolving ambiguity.

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Figure 2 summarizes the circuitry of the proposed coarse and detail networks. In this schematic, the coarse network (green) involves projections from the PRC and PHC/POR that synapse in superficial layers of the LEC and MEC, which are the origins of the perforant pathway input to DG/CA3. The detail network (blue) is composed of the direct input from PRC and PHC/POR to the HPC subregion CA1. The detail and coarse networks may act as two interactive circuits that are engaged to process objects within a scene as an integrated unit [41]. The coarse network computes a holistic, but relatively gist-like representation based on the inputs from PRC and PHC/POR to DG/CA3 through EC. This coarse representation can be utilized to infer the semantic context of a space, to identify whether a space is familiar or novel, and to aid in early and fast detection of objects. When overlap or ambiguity exists between sensory stimuli, additional details may be necessary to disambiguate overlapping inputs, which engages the detail network. Resolving ambiguity is also more likely to engage decision making and evaluative processes that are mediated by prefrontal and ventromedial cortices [42]. In line with this idea, neuron spiking in prefrontal cortical regions is known to influence how activity propagates across the PRC, PHC/POR and EC [43].

EVIDENCE FOR PARALLEL COARSE AND DETAIL-ORIENTED CORTICAL-HPC NETWORKS

As discussed above, the PRC and PHC/POR are reciprocally connected to each other [6, 7], as well as to EC [7, 21, 44] and HPC [16, 45]. It has been previously suggested that these parallel pathways serve different functions [45, 46]. Activity in the proposed coarse network, which provides gist-like information for quickly informing adaptive behavior, propagates between cortical-HPC circuits iteratively and updates during ambulation or saccades in primates [47]. This framework is consistent with a view that as an animal explores its environment, MEC activity couples internally generated proprioceptive input to external features to update representations across cortical-hippocampal loops as sensory input changes [15]. Moreover, this classic trisynaptic circuit though DG/CA3 may support **pattern separation** or **pattern completion** of different episodes over time based on the coarse global features. Notably, within the PRC, area 35 sends a stronger projection to EC than does 36 [7], suggesting that area 35 may be relatively more connected to the course network than area 36. Interestingly, area 35 is among the first sites of tau pathology in aging and preclinical Alzheimer’s disease (Box 2).

The PRC and PHC/POR direct projection to CA1 may update information as it is iteratively processed by cortical-HPC circuits to add specific sensory details to established coarse representations. Within the PRC, the direct projection to CA1 originates primarily from the superficial layers of area 36 [45]. Thus, area 35 may be more connected to the coarse network while area 36 is more connected to the detail network. Compared to area 35, area 36 receives relatively more direct input from visual cortical regions (including inferior temporal cortex), and is more connected to the PHC/POR [7]. The direct projections from PRC and PHC/POR to CA1 may therefore be more influenced by specific sensory features represented in neocortical regions, such as primary and associational visual cortex. In contrast, as sensory input is further processed through area 35 and EC of the coarse network,

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fine-grained sensory details may become bound together via plasticity mechanisms. This binding broadens tuning curves to promote more global representations over specific stimulus features.

Neurophysiological data provide evidence that coarse and detailed-oriented object and spatial information is represented within PRC and PHC/POR. As mentioned previously, PRC cells respond selectively to specific objects [25, 26], and to large segments of an environment [23]. The spatial selectivity of PRC neurons could serve the coarse network by unitizing large environmental segments for quickly processing a holistic statistical summary of a spatial context or scene. Conversely, PRC activity that reflects specific objects may serve the detail pathway by identifying discrete feature information necessary to guide behavior. In line with this idea, two distinct types of tuning properties emerge in the activity of rat PRC cells as a rewarded stimulus is morphed into a non-rewarded stimulus [48]. One firing pattern incrementally maps the stimulus change by proportional alterations in rate – a property that may facilitate detail processing. The other activity pattern generalizes across the morph conditions showing similar activity levels to the initial stimulus even as it changes [48], which may reflect coarse information processing. Although comparable experiments have not been conducted during PHC/POR recordings, based on the current model, we would predict that a similar heterogeneity in neuronal response properties would be observed as scenes are morphed. Finally, adding objects to an environment changes activity properties of CA1 pyramidal cells in rats by narrowing the spatial tuning curves of place fields [49]. Taken together, these findings suggest that detail pathway input can bias CA1 cells to process discrete feature information about stimuli over general information about the environment.

The activity patterns of PHC/POR neurons also do not functionally segregate into conveying strictly spatial or nonspatial inputs to HPC. In humans, imaging data have shown that the parahippocampal place area, which anatomically maps onto the primate PHC, is not modulated just by spatial stimuli. Specifically, the anterior parahippocampal place area responds to both objects and scenes, while the posterior portion responds more to objects [50]. Moreover, PHC/POR neuron activity is tuned to specific object-location conjunctions in rats [24], and to face-scene associations in humans [51]. These data provide additional evidence that spatial information is integrated with specific sensory features of discrete stimuli before being projected to the HPC.

LEC neurophysiological recordings and lesion data from rats also argue against a content-based organization of MTL, and support the coarse and detail network framework outlined above. While LEC cells do show elevated firing in the vicinity of objects, this activity is less related to the specific features of an object compared to cell activity in PRC [26]. Additionally, LEC cell activity can also be selective for specific event-environment associations, and shows rapid updating when the environment or a salient event changes [52]. Moreover, LEC lesions in rats result in deficits in forming and maintaining object-context associations, while leaving overall object recognition intact [53]. Finally, when the LEC is inactivated, spatial tuning curves of CA1 place fields in rats become narrower and tend to orient more to visual features within the environment than when the LEC is active [54]. This suggests that when the LEC is offline, the HPC may be biased towards processing

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specific feature information relayed by the intact direct PRC and PHC/POR pathway to CA1 rather than relying on global representations from LEC.

SELECTIVE VULNERABILITY OF THE DETAIL NETWORKS IN ADVANCED AGE

The susceptibility of PRC to age-associated dysfunction has been a topic of debate [55–58]. While neurobiological studies in rodents have shown that physiological [56, 58, 59] and biochemical properties [60] of PRC are altered in advanced age, the PRC-dependent familiarity signal that supports recognition memory is intact in older adults [55]. In contrast to processing familiarity, the ability to discriminate between similar objects, which is often attributed to PRC functioning [61, 62], has been demonstrated to decline in older human adults [56] and other animals [56, 63, 64]. Importantly, differential vulnerabilities of the coarse and detail networks with advancing age could account for the observation of an intact familiarity signal in the presence of discrimination deficits, which is observed in older subjects across species.

Several studies have shown that PRC activity is reduced in old age in both humans [56] and rats [58, 65]. Critically, this attenuated activity could impact coarse and detail networks in distinct ways (Figure 2). Within the detail network, reduced principal cell activity [58, 59] means that there is less feed forward excitation from area 36 to CA1. In the coarse network, reduced PRC excitation is associated with diminished afferent drive onto interneurons in PRC [59]. These interneurons normally synapse onto layer II LEC cells to gate the flow of information into DG/CA3 [66]. An age-related reduction in feedforward inhibition from the PRC to LEC could lead to enhanced LEC activity [67], biasing the coarse network to emphasize gist-like over detailed representations. Several lines of evidence support this view. Older adults rely more heavily on gist for memory retrieval [68], and recall fewer perceptual details [69]. Furthermore, older adults are impaired at perceptual oddity judgements [56] and discriminating between familiar and novel lures [70, 71] when the test stimuli share overlapping features. Interestingly, deficits in discriminating between similar test stimuli are observed for both objects and scenes [40, 72], suggesting that the role of PRC and its vulnerability in advanced aged is not domain specific. Age-associated discrimination deficits are also observed in monkeys and rats, in which older animals are impaired at distinguishing between objects that have a high levels of feature ambiguity [63, 64]. At the physiological level, it has also been shown that CA3 is hyperactive in older adults [73, 74], monkeys [75], and aged rats with memory impairments [67, 76], which would further contribute to a bias towards coarse over detailed representations.

The age-related bias towards coarse rather than detailed processing can be understood under the framework outlined here, and leads to the prediction that older adults and other animals should show intact recognition memory when the stimuli are unambiguous and do not require a fine-grained analysis of sensory features. In fact, this prediction is consistent with observations in recognition memory studies in humans [55] and animals [77]. In contrast, this framework predicts that deficits should emerge when behaviors involve feature ambiguity, thereby requiring analysis of fine-grained detailed sensory information.

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Consistent with this idea, reduced activity within the PRC-CA1 circuit may account for the widely-reported impairments in older adults' [56, 71, 78] and other animals' abilities [63, 64] to discriminate between similar stimuli, which occurs for both objects and scenes [40, 72].

While less is known about age-related neurobiological alterations within PHC/POR, recent studies suggest that utilization of context is intact in older adults [37, 79]. These data point to a possible maintenance of coarse network function over the lifespan. If this prediction is correct, then older adults may rely to a greater degree on context to disambiguate stimuli. As an example, a recent paper by Memel and Ryan [37] showed that integrating objects into realistic scenes benefitted associative memory performance equally for young and older adults compared to a condition where objects were presented beside, but separate from, a realistic scene. Despite this, older adults remained more likely to falsely recognize similar objects when they were presented in (or beside) a familiar context. These data point to potential dissociation of detail versus coarse network function in older adults.

The model proposed here predicts that discrimination impairments manifesting from dysfunction in the detail network would not only be observed for objects. Recently, similar age-associated discrimination impairments were identified in rats using olfactory stimuli. Within a homologous series of odorants, perceptual similarity can be systematically modulated by varying the number of atoms in the carbon chain backbone [80]. While young and aged rats are similarly accurate on discriminations between structurally unrelated olfactory stimuli, aged rats are disproportionately impaired relative to young as the perceptual similarity of the odorants increases. Notably, aging does not affect odor detection thresholds, indicating the learning deficits are not attributable to general declines in olfactory function [81].

Integration of tactile and visual sensory properties is critical for stimulus identification and accurate encoding. PRC forms crossmodal associations of multimodal sensory stimuli to enable the identification of a whole stimulus when only one modality is available for recognition (for example, encoding an object using tactile information and recognizing with only visual input available). Interestingly, crossmodal recognition also depends on the posterior parietal cortex and its functional connectivity with PRC [82]. Notably, the posterior parietal cortex is only weakly connected with PRC, but strongly connected with the PHC/POR [5] (see Figure 1C), suggesting that the latter circuitry may mediate this functional association. An enticing hypothesis is that the ability to generalize across modalities to recognize a stimulus is mediated by the "coarse" pathway and requires coordinated activity in both the PRC and PHC/POR. A better understanding how this circuitry forms such polymodal associations will further clarify the role of PRC and PHC/POR in memory and age-related cognitive decline.

CONCLUDING REMARKS

Based on accumulating evidence from anatomical, functional, and behavioral studies in both humans and animals, we suggest that both PRC and PHC/POR participate in the processing of scenes and environments by contributing to coarse, large-scale representations of space as

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well as detailed processing of sensory features. As a wealth of supportive evidence lays the foundation for proposing two interactive coarse and detail networks, we hope that this model will serve to generate new and more specific predictions that will lead to a deeper understanding of MTL functioning (see Outstanding Questions). In addition, we believe this model is poised to disentangle the inconsistencies regarding PRC-associated cognitive changes that occur during normative aging.

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Glossary

Parahippocampal/postrhinal cortex (PHC/POR)
a cortical region in medial temporal lobe that is given different names in the primate and the rodent. In primate this structure is referred to as the parahippocampal cortex and can be further subdivided into area TH and TF [96]. Because of the confusion between the parahippocampal cortex and the parahippocampal region (see below), this structure in the rat was named the postrhinal cortex due to its position posterior to the rhinal sulcus [97]

Parahippocampal region
the cortical areas that surround the hippocampus including the PRC, PHC/POR, entorhinal cortices, presubiculum and parasubiculum [16]

Pattern completion
an idea from computation models that recurrent excitatory circuitry can support the formation and retrieval of a complete representation based on partial or degraded input

Pattern separation
an idea in computational neuroscience that overlapping input patterns can be disambiguated, that is, transformed into more dissimilar outputs

Perirhinal cortex (PRC)
a cortical region in the medial temporal lobe that is implicated in memory and high-level perception. It borders the rhinal sulcus and is densely connected with the hippocampus, parahippocampal/postrhinal and entorhinal cortices, as well as sensory association cortical areas. The PRC in primates and rodents is composed of area 36 (ectorhinal), which is more dorsal and borders area TE, and area 35, which is at the fundus of the rhinal sulcus

Process-based models
in cognitive psychology, process models generally refer to a category of models that focus on how information is processed to support adaptive behavior. In this review, the term process-based is used to emphasize that our focus is on how the PRC and PHC/POR use information, rather than what the information is (that is, the traditional content-based view)

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Box 1

Entorhinal subdivisions in rodents and primates

In rodents, two primary subdivisions of entorhinal cortex (EC) have been identified: the LEC and MEC. The differences in connectivity [7], neurophysiological [15] and functional dissociations [87, 88], as well as vulnerability in aging [89, 90] and disease [91] between these areas have important implications for translational human research. Therefore, identification of homologous divisions of the EC in primates is crucial. Although the shape and location of EC differs between rodents and primates, anatomical organization and afferent inputs are largely conserved. In the monkey, tracer studies indicate that PRC projects to the rostral two-thirds of EC while PHC projects to the caudal two-thirds, with substantial overlap in their projections to the middle one-third [20]. This supports a division of the primate EC in which LEC corresponds to anterior EC and MEC is homologous to posterior EC. Recent imaging studies in humans have largely supported this anatomical organization, revealing stronger connectivity between PRC and anterior lateral EC while PHC is more connected to posterior medial EC [85, 86]. This anterior-lateral/posterior medial division of EC is also consistent with functional connections to the cortex [85] and subiculum [86] that would be predicted based on LEC and MEC projections in the rodent.

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Box 2

Tau pathology in PRC

The microtubule-associated protein tau becomes abnormally phosphorylated and aggregates into neurofibrillary tangles in aging and certain disease states, most notably Alzheimer's disease (AD). Tau pathology spreads in a stereotyped pattern in AD and among the earliest brain regions to be affected is area 35 of PRC [92], known as transentorhinal cortex in the AD literature. Thus, neuronal dysfunction induced by tau in PRC may have significant implications for declining cognition in prodromal Alzheimer's disease. For example, tau imaging indicates that this pathology is associated with greater medial temporal activity and discrimination errors [93]. Age-related excitability changes in PRC, LEC, and associated hippocampal circuitry (see text) may contribute to transynaptic spread of toxic tau species and propagation of pathology to associated medial temporal lobe circuits. The process-based model presented here would predict that patients with early AD would not only show deficits in discriminating between similar objects, scenes and other sensory inputs, as seen in normal aging, but also have a reduced ability to use context. In contrast to tau, the brain areas that show the earliest deposition of amyloid-β plaques are not in the rhinal cortices. In fact, cortical areas associated with the default mode network, such as the posterior parietal cortex and posterior cingulate, appear to be particularly vulnerable to early amyloid pathology [94]. Importantly, despite the prevalence of the amyloid hypothesis, pathological burden data suggest that tau accumulation is a better predictor of cognitive decline than levels of amyloid plaque accumulation [95].

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Highlights

- Recent data do not support a content-based dissociation of perirhinal (PRC) and parahippocampal (PHC) function.
- We propose a novel process-based model, rooted in anatomy, which contends that the PRC and PHC interact to support two distinct cortical-hippocampal (HPC) pathways.
- One pathway through entorhinal cortex to the dentate gyrus and CA3 supports coarse processing of scenes and environments that quickly form gist-like representations for rapidly informing adaptive behavior.
- The other pathway is direct from PRC and PHC to CA1, and it enables detailed representations to be associated with gist-like information when a fine-grained analysis is necessary.
- Contemporary findings in cognitive aging studies in humans and other animals suggest that the PRC/PHC-hippocampal detail pathway is particularly vulnerable to the effects of aging.

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Outstanding Questions

- Critical to testing the proposed model would be to remove nodes of the detail versus course networks and test the behavioral impact. Specifically, if areas 35 and 36 of PRC are more connected to the coarse and details pathways, respectively, can perceptual discrimination versus global contextual representations be dissociated between these subregions?
- Critical for supporting or refuting the current model, to what extent do neurophysiological correlates of PHC/POR neurons reflect coarse versus detail-oriented processing, and to what extent is PHC/POR critical for discriminating between scenes/environments that share features?
- To what extent can the proposed decline in processing by the detail network in advanced age be accounted for by a loss of fidelity in the afferent input to the PRC and PHC/POR from sensory cortical areas?
- Does age affect the biochemistry and cellular function of PHC/POR neurons, and to what extent, if any, can PHC/POR compensate when the PRC is compromised by aging or disease? What is the role of tau pathology in these age-related changes?
- To what extent can older adults use context to bolster recognition and overcome deficits in detail processing?
- If one can consciously decide to attend to details versus rely on gist to inform behavior, to what extent does prefrontal cortical input to the MTL influence activity through the coarse and detail networks?

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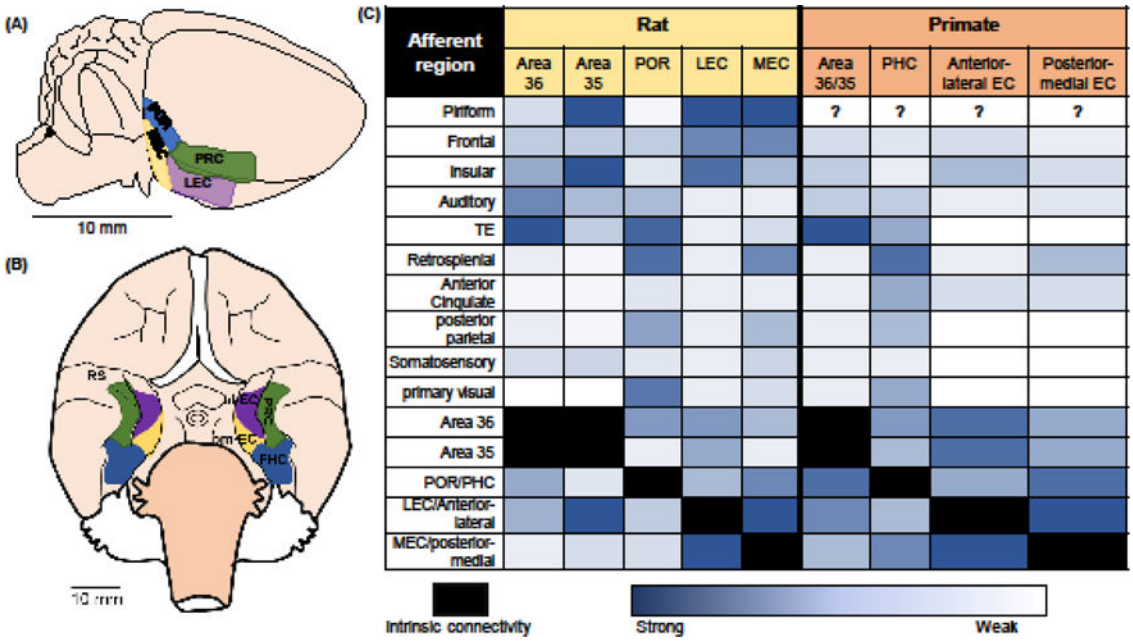

Figure 1. The parahippocampal region in rats and primates

A schematic of the rat **(A)** and the nonhuman primate brain **(B)** showing the parahippocampal region. For illustrative purposes the rat brain is scaled up approximately 3 times relative to the primate brain. In both schematics, the scales bars represent 10 mm. In the rat, the locations of the perirhinal cortex (PRC), postrhinal cortex (POR), lateral entorhinal cortex (LEC) and medial entorhinal cortex (MEC) in rats are on the lateral surface of the rodent brain and border the rhinal sulcus (RS) [83, 84]. In the primate, due to the larger neocortex, these regions are located on the ventral surface of the brain. The primate parahippocampal region is composed of the PRC, parahippocampal cortex (PHC), anterior lateral entorhinal cortex (al-EC), and posterior medial entorhinal cortex (pm-EC) in the monkey [85, 86]. As in the rat, these areas border the rhinal sulcus (RS). In both rodents and primates, the PRC can be subdivided into areas 36 and 35. As area 35 is at the fundus of the RS it is difficult to see from the brain surface. The primate PHC is homologous to the rodent POR. Moreover, the al-EC and pm-EC are homologous to the rodent LEC and MEC, respectively. **(C)** A summary of the cortical input to the medial temporal cortical areas, adapted from tracer studies [5, 7, 13, 20, 22, 44]. Darker shades of blue indicated more dense projections, and black indicates intrinsic projections within a region.

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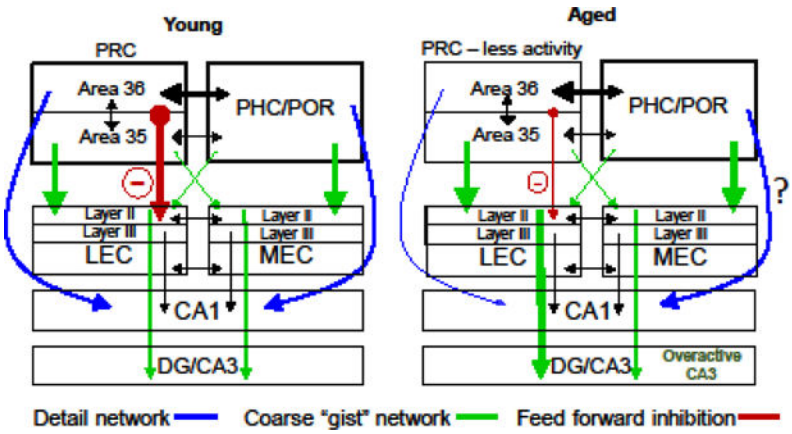

Figure 2. Proposed PRC and PHC/POR parallel networks that connect to the HPC

Illustration of the two proposed networks in young (left) subjects and how these are altered in advanced age (right). Left panel: One network is proposed to process detailed sensory information that projects directly to CA1. The connections of this network (blue arrows) are predominantly through superficial layers of PRC area 36 and the PHC/POR (blue arrows). Notably, PRC and PHC/POR are also reciprocally connected, but the projection from PHC/POR to PRC is stronger than the reverse. This projection arises from both deep and superficial layers of PHC/POR and synapses onto all layers of PRC. The projection from PRC to PHC/POR originates primarily from layers V/VI of PRC and synapses onto both deep and superficial layers of PHC/POR. Again, this projection is stronger from PRC area 36 than area 35. Area 36-PHC/POR connectivity may serve to integrate spatial/configural information with sensory details to facilitate stimulus identification, as well as to enrich the geometric details of scenes. The coarse network (green arrows) is proposed to involve connections from PRC and PHC/POR to LEC and MEC, which send projections from layer II neurons to DG/CA3 of HPC. Notably, layer III EC neurons also project directly to CA1. More data are needed to elucidate the contribution of this connection. In this model, the coarse network computes holistic, but relatively gist-like, representations of a scene/environment that are updated with exploration to quickly inform adaptive behavior. Right panel: With aging, behavior and neurophysiological data suggest that reduced principal cell and interneuron activity in PRC (– less activity) may reduce feed forward inhibition to LEC (red arrows) to bias activity in the coarse pathway over the detail pathway, which leads to sensory discrimination deficits and promotes the experience of false memories. The impact of advanced age on PHC/POR input to CA1 has not been examined (?). The weight of the arrows represents the strength of the connection. PRC = perirhinal cortex, PHC/POR = parahippocampal cortex/postrhinal cortex, LEC = lateral entorhinal cortex, MEC = medial entorhinal cortex, DG = dentate gyrus.