Two cortical systems for memory-guided behaviour

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Abstract | Although the perirhinal cortex (PRC), parahippocampal cortex (PHC) and retrosplenial cortex (RSC) have an essential role in memory, the precise functions of these areas are poorly understood. Here, we review the anatomical and functional characteristics of these areas based on studies in humans, monkeys and rats. Our Review suggests that the PRC and PHC–RSC are core components of two separate large-scale cortical networks that are dissociable by neuroanatomy, susceptibility to disease and function. These networks not only support different types of memory but also appear to support different aspects of cognition.

Hippocampal formation
A term used to collectively describe the entorhinal cortex, dentate gyrus, subfields CA1, CA2 and CA3, and the subiculum.

Since Milner's pioneering studies of the densely amnesic patient H.M., investigations into the neural bases of memory have targeted the medial temporal lobes (MTL). For instance, according to one influential framework, the hippocampal formation, the perirhinal cortex (PRC) and the parahippocampal cortex (PHC) comprise an 'MTL memory system' (REF. 1) that collectively supports memory for facts and events. Subsequent research has made it clear that damage limited to the hippocampus causes relatively specific memory deficits, whereas the kind of dense amnesia seen in H.M. is typically associated with additional damage to cortical and subcortical areas outside the hippocampus. In addition to the PRC and PHC[1–4], it is now clear that damage to the retrosplenial cortex (RSC)[5,6] — an area not included in the MTL memory system — is sufficient to cause substantial memory impairments. Accordingly, in order to understand the organization of brain areas that support memory, it is essential to consider the functions of neocortical areas, particularly the PRC, PHC and RSC.

Accumulating evidence has converged on the idea that the PRC, PHC and RSC can be functionally differentiated from one another, and that these areas contribute to cognitive functions beyond those that are studied in traditional memory paradigms. Here, we will review this evidence and propose a framework for understanding how the PRC, PHC and RSC might functionally interact with other neocortical and subcortical areas (including the hippocampus) in order to support memory-guided behaviour. We will first review current evidence regarding the connectivity of the PRC, PHC and RSC and then consider the functional properties of these regions on the basis of neuroimaging and neuropsychological studies in humans, and neurophysiological and lesion studies in rats and monkeys. The evidence indicates that these cortical regions are heavily involved in memory, but they also differentially interact with brain regions with functions that are not traditionally considered in memory research. As we will describe below, the functional organization of these regions may be best understood in the context of two distinct cortical networks that support different kinds of memory-guided behaviour.

Anatomical and functional connectivity

Connectivity with subcortical regions. The hippocampal formation is usually depicted as a site of anatomical convergence for connections from the PRC and PHC, but detailed anatomical studies have demonstrated that there is substantial segregation between the hippocampal pathways involving the PRC and those involving the PHC and RSC[7,8]. In rats, the postrhinal cortex (which is thought to be the rodent homologue of the PHC) and RSC are predominantly interconnected with the medial entorhinal cortex, whereas the PRC is predominantly interconnected with the lateral entorhinal cortex; direct connections of the PRC and PHC with CA1 and the subiculum are likewise segregated along the longitudinal (that is, septal-to-temporal) and transverse (that is, proximal-to-distal) axes of the hippocampus[7–9]. Furthermore, the pre- and parasubiculum, along with nuclei in the anterior thalamus and mammillary bodies[8–10], are directly interconnected with the PHC and RSC but only weakly with the PRC. The amygdala, by contrast, is heavily interconnected with the PRC, whereas connections with the PHC and RSC are relatively weak[9–11]. It is not clear whether the segregation of subcortical pathways

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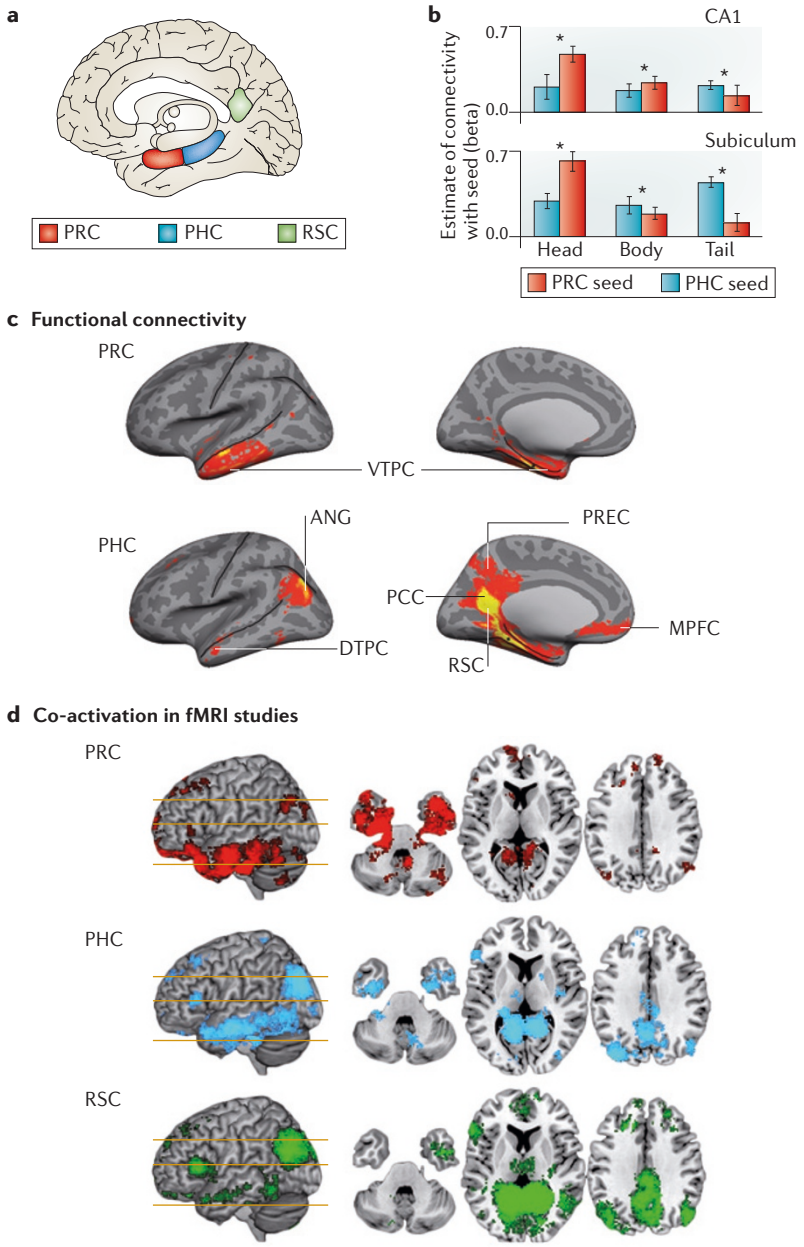


Figure 1 | **Anatomy of the perirhinal, parahippocampal and retrosplenial cortices. a** | Relative locations of the perirhinal cortex (PRC) (areas 35 and 36, shown in red), parahippocampal cortex (PHC) (areas TF and TH, shown in blue) and retrosplenial cortex (RSC) (areas 29 and 30, shown in green) in the human brain. **b** | Estimates of functional connectivity between the PRC (red bars) and PHC (blue bars) with hippocampal subregions CA1 (top) and subiculum (bottom)[13]. **c** | Functional connectivity profiles of the PRC (top) and PHC (bottom), displaying regions that were significantly correlated with seed regions in the PRC and PHC during resting-state scans[12]. **d** | Brain regions that typically co-activate with the PRC (coordinates –24, –20, –28), PHC (coordinates –24, –40, –12) and RSC (coordinates 16, –52, 8), as identified through a meta-analysis conducted by the authors via the database at NeuroSynth[180]. Note that both the functional connectivity and co-activation maps for the PRC show involvement of the ventral temporopolar cortex (VTPC) and lateral orbitofrontal cortex (along with the amygdala, which is not shown), whereas the PHC and RSC maps include each other as well as the angular gyrus (ANG), posterior cingulate (PCC), precuneus (PREC), medial prefrontal cortex (MPFC) and dorsal temporopolar cortex (DTPC). * indicates a statistically significant difference. fMRI, functional MRI. Part **b** is reproduced, with permission, from REF. 13 © 2012 Society for Neuroscience. Part **c** is reproduced, with permission, from REF. 12 © 2008 American Physiological Society.

involving the PRC and those involving the PHC and RSC is as strong in primates as it is in rats, but resting-state functional MRI (fMRI) studies in humans have revealed substantial differences in functional connectivity along the longitudinal axis of the hippocampus[12,13] such that the PRC is more strongly connected with anterior CA1 and subiculum, and the PHC is more strongly connected with posterior CA1 and subiculum[13].

Cortical connectivity. The connections between the PHC, RSC and PRC are illustrative of the relationships between these regions. The RSC has extensive reciprocal connections with the PHC, but connections between the RSC and PRC are relatively sparse[14,15]. The PRC is strongly interconnected with the PHC, although the connections are asymmetric — the PRC receives more projections from the PHC than it sends back[16], and the laminar pattern of these connections is such that projections from PHC to PRC are of the feedforward type and projections from PRC to PHC are of the feedback type[17].

Many studies have characterized connections between sensory cortices and the PRC, PHC and RSC. Within the visual modality, tract-tracing data from monkeys[14,15,18] and functional connectivity analyses in humans[12,13] (FIG. 1) are in agreement that the PRC is primarily connected with higher-order visual areas in the temporal cortex, whereas the PHC and RSC have more connectivity from earlier occipital and temporal areas. Specifically, the PRC is heavily connected with temporal lobe areas at the apex of the ventral visual processing stream (anterior portions of areas TE and TEO in monkeys, possibly corresponding to the anterior fusiform gyrus in humans)[16,18]. The PHC is also connected with these areas but has more extensive connectivity with occipital and posterior temporal visual areas, including V4 and V3 (REFS 16,18), and the RSC is primarily interconnected with V4 and occipital areas[14,15]. Connections in other sensory modalities are not as well characterized, but available anatomical evidence suggests that the PRC is more connected with olfactory and gustatory areas[16] than the PHC and RSC. Connectivity with auditory and somatosensory areas may be comparable across the three areas[13].

More striking differences among the PRC, PHC and RSC are apparent when one considers connections with cortical association areas[12,13,19] (FIG. 1). Via the cingulum bundle[20,21], the PHC and RSC are interconnected with the medial parietal cortex (posterior cingulate (Brodmann's area 23 (BA23) and BA31) and precuneus (BA7)), ventrolateral parietal cortex (angular gyrus (BA39)) and medial prefrontal cortex (BA32 and BA10). This is a highly interconnected network of cortical association areas that has been termed the 'default network'[22]. Functional connectivity analyses of fMRI data converge with the tract-tracing studies described above[12,13], and additionally suggest that the PHC and RSC are more closely coupled with one another than they are with many components of the default network[23]. The PRC, by contrast, does not have prominent connections with the default network but instead is heavily interconnected, via the uncinate fasciculus, with a network that includes

Box 1 | **Dissociations between the perirhinal and parahippocampal cortices with respect to memory**

Many studies have shown that the perirhinal cortex (PRC) and parahippocampal cortex (PHC) have qualitatively distinct roles in memory. In rodents, lesions of the postrhinal cortex (the rodent homologue of the PHC) but not lesions of the PRC impair memory for object–context associations at short delays, whereas the opposite is true for memory for object–object associations[105]. Additionally, expression of the immediate early gene *Fos* in the rat PRC was shown to be sensitive to object familiarity and not to the spatial arrangement of objects, whereas the opposite pattern was found for *Fos* expression in the postrhinal cortex[106]. Similar effects have been reported in lesion studies in monkeys, in which parahippocampal lesions impaired recognition memory for spatial locations, whereas perirhinal lesions impaired object recognition memory[111]. In human neuroimaging studies, encoding and retrieval activation in the PRC has been correlated with item familiarity and with successful recollection of details about specific entities (for example, the colour of an object), whereas activation in the PHC is increased during successful encoding and retrieval of contextual associations with these items (for example, the task that was used to study the word)[45,46,176]. Differences in the recruitment of the PRC and PHC have been attributed to the type of stimulus that is being processed, such as objects versus scenes[70,143], or the underlying representational characteristics, such as item versus context information[3,82,83].

the lateral orbitofrontal cortex (BA13 and BA47) and the anterior ventrolateral temporal cortex (also known as the ventral temporopolar cortex (BA38))[19,24].

To summarize, the RSC and PHC are extensively connected with one another and interface with similar regions in the posterior hippocampal formation, pre- and parasubiculum, nuclei in the mammillary bodies and anterior thalamus, and the default network. The PRC exhibits a different pattern of connectivity, interfacing primarily with the anterior hippocampal formation, amygdala, ventral temporopolar cortex and lateral orbitofrontal cortex. As we describe in the next two sections, several lines of evidence indicate that, consistent with the anatomy, the functional characteristics of the PRC can also be contrasted with those of the PHC and RSC.

Functional characteristics of the PRC

Recognition and associative memory. The PRC is clearly involved in memory, and a great deal of evidence suggests that its function can be dissociated from that of the hippocampus and PHC (BOX 1). For instance, PRC lesions in monkeys[25] severely impair visual object recognition memory, and this deficit is much more severe than that produced by lesions to the hippocampus and/or PHC[25,26]. Furthermore, performance of visual object recognition tasks is associated with increased immediate early gene (*Fos*) expression in the rat PRC[27] and increased glucose metabolism in the monkey PRC[28].

Humans with damage to the anterior MTL, including the PRC, temporopolar cortex and the anterior hippocampal formation, show substantial deficits in recognition memory for many types of stimuli, including words and faces[3,29,30]. One human patient has been reported with more restricted MTL damage in an area encompassing most of the left PRC, amygdala, temporopolar and entorhinal cortex but sparing the hippocampus and PHC[31]. The patient showed severe impairments in familiarity-based item recognition memory but displayed a normal ability to recollect the context associated with specific items[31]. These findings suggest that the PRC may be crucial for familiarity-based item recognition but other regions, such as the PHC and hippocampus, may be sufficient to support memory for context[2,3,29,30].

Studies in monkeys and humans are consistent with the idea that the PRC might have a specific role in signalling the familiarity of objects. For instance, single-unit recording studies have identified a subclass of 'familiarity neurons' in the monkey PRC that show reduced responses to repeated presentations of a visual stimulus, even with a 24-hour delay between repetitions[32]. Studies in humans have also shown that activity in the PRC is reduced during recognition of repeated items relative to novel items for a diverse class of stimuli, including objects, words and scenes[30,33]. Notably, the degree of activity reduction is correlated with the subjective sense of familiarity for the item[34–36]. Additionally, PRC activation during memory encoding predicts the extent to which the item will subsequently be experienced as familiar[37,38].

Considerable evidence indicates that the PRC also plays a part in learning associations about and between objects. Single-unit recording studies have shown that neurons in the PRC, anterior inferior temporal cortex and temporopolar cortex show persistent stimulus-specific activity while visual objects are actively maintained across short delays[39], and this activity may facilitate the learning of associations between objects[40]. Following repeated exposure to pairs of objects, neurons in the monkey PRC acquire selectivity for the pair associations[41,42], and the ability to learn these associations is severely impaired following PRC lesions[43]. Consistent with these results, fMRI studies in humans suggest that the PRC contributes to learning of associations between words or objects. For instance, perirhinal activity is increased during successful learning of associations between words that can be linked to a single object or concept[44] or to an object feature, such as colour[45,46].

The PRC also supports learning about the affective or motivational significance of objects. For instance, neural activity in the monkey PRC has been shown to reflect learning about objects that are cues for upcoming rewards[47], and this learning is abolished following lesions to the PRC[48] or interference with dopamine D2 receptors in the PRC[49]. In rats, PRC lesions impair fear conditioning to complex auditory[50–52] or olfactory object cues[53], and PRC neurons show increased firing during the presentation of auditory objects that have been associated with an aversive, unconditioned stimulus[54].

Immediate early gene
A gene that encodes a transcription factor that is induced within minutes of raised neuronal activity without requiring a protein signal. Immediate early gene activation is therefore used as an indirect marker of neuronal activation.

Semantic cognition. Some researchers have argued that the PRC has a role in semantic memory on the basis of research on patients with semantic dementia[55–57], which is the temporal lobe variant of frontotemporal lobar degeneration. Semantic dementia is associated with extensive damage to the anterior temporal lobes and is characterized by a loss of knowledge about objects, particularly ones that are uncommon (for example, patients will mistake a zebra for a horse). Although patients with anterior medial temporal damage due to herpes encephalitis or temporal lobe epilepsy show less severe degradation of semantic memory than do patients with semantic dementia, all of these patient groups show impairments in the ability to make fine semantic discriminations and in the use of semantic knowledge to differentiate between visually similar objects[58–62].

Further evidence has come from imaging and intracranial electroencephalography (EEG) studies. Numerous intracranial EEG studies have identified a field potential in the PRC termed the AMTL N400, the amplitude of which is selectively enhanced during semantic processing of meaningful words or objects and is modulated by semantic priming[63]. Positron emission tomography (PET) and magnetoencephalography (MEG) studies, along with some fMRI studies, have provided convergent evidence suggesting that the PRC shows increased activation during fine semantic discriminations[61,64–66], and that activity in the left PRC is sensitive to semantic priming[67–69]. One recent study showed that left PRC activation during verbal semantic discrimination predicts subsequent priming of the underlying concept and that such conceptual priming was severely impaired in patients with damage to the same left perirhinal region[67].

Object perception. Several lines of evidence suggest that the PRC may also contribute to perceptual processing of objects[70,71]. For example, single-unit recording studies in monkeys suggest that PRC neurons show a high degree of object selectivity, much like inferior temporal lobe neurons in area TE. However, the visual responses of neurons differ across the two areas, such that the activity of perirhinal neurons is more rapidly influenced by learning[32,72]. Lesion studies in monkeys also suggest that the PRC contributes to object perception, although in a more limited manner than area TE. For instance, PRC lesions in monkeys impair performance of 'oddity judgements', in which animals must discriminate between different views of a single complex object (such as a face) and a distinct but perceptually similar object[73]. In addition, PRC lesions in monkeys impaired discriminations between objects that share many features but did not affect performance on difficult discriminations that could be solved on the basis of a single visual feature dimension, such as colour[74]. Thus, the PRC may be most important for perception under conditions that require integration of object features across multiple dimensions[70,71]. Some studies have shown that humans with anterior temporal damage that includes the PRC exhibit impairments on perceptual discriminations between objects that have high feature overlap[75–77], although not all studies obtained such results[78]. Imaging studies, however, provide convergent evidence by demonstrating that PRC activity is increased during complex visual discrimination tasks[79] and that this activity is predictive of accurate discriminations[80].

In addition to visual perception, the PRC may be especially involved in associating features of objects across modalities. Patients with PRC damage due to herpes encephalitis have been shown to exhibit deficits in determining the congruency between the auditory and visual features of an object[61], and left PRC activation in healthy individuals is increased during association of visual object features and auditory[61] or tactile[81] features. These findings indicate a central role for the PRC in forming multidimensional object representations.

Functional characteristics of the PHC and RSC

In addition to their similarities in terms of anatomical connectivity, the PHC and RSC reliably co-activate in task-based fMRI studies (FIG. 1d), suggesting they have functional similarities as well. Accordingly, we will review the functional properties of these regions together.

Episodic memory. Numerous fMRI studies have shown that activation in the PHC and RSC[3,82–84], as well as in anatomically connected regions in the default network[84,85], is associated with successful memory of the context of an event. Much of this evidence has come from 'source memory' studies in which lists of words, objects or other stimuli are studied and then memory is tested for each item and its associated context information (for example, the question that was asked when a word was studied). Several source memory studies have shown that PHC activity selectively increases during encoding and retrieval of items for which the context information is successfully remembered, such as memory for the encoding task[36–38] or memory for temporal context associated with a word or object[86,87]. PHC activity is also enhanced during encoding and retrieval of words and objects for which participants subjectively report spontaneous recollection of contextual details from the study episode[82]. These data are consistent with the idea that the PHC supports representations of the situational context associated with items that are the target of processing[29,30,82].

The RSC also shows enhanced activation during successful memory retrieval[84], particularly during successful recollection of contextual information[88–90]. One difference between PHC and RSC involvement in memory tasks is that PHC activity is typically associated with successful encoding and successful retrieval of context information, whereas activity in the RSC (along with anatomically connected areas in the default network) is only reliably associated with successful recollection during retrieval, and it is often negatively associated with successful encoding[91]. However, when items are encoded in a self-relevant manner[92] or include materials that are likely to evoke emotional or self-referential processing[93,94], both RSC and PHC activation during encoding are correlated with subsequent memory performance.

Semantic priming
A quickening in reaction time for responding to words that are preceded by a semantically related 'priming stimulus'.

This point of divergence indicates that, relative to the PHC, the RSC may be more attuned to internal sources of information[22,95].

Autobiographical memory and episodic simulation. The PHC and RSC are involved in both the recollection of autobiographical memories and the imagination of hypothetical events (known as episodic simulation). Patients with RSC damage show retrograde amnesia for autobiographical events[6,96]. In healthy individuals, retrieval of autobiographical memories elicits more activity in the PHC and RSC relative to memories of stimuli learned in the laboratory[97]. Moreover, RSC responses scale with the degree of subjective 'reliving' during autobiographical memory retrieval[98].

The network that is engaged during episodic simulation, which includes the PHC and RSC and regions in the default network, is strikingly similar to that engaged during autobiographical memory[99]. For example, the PHC and RSC are more active in subjects while they are remembering past personal events and imagining future personal events relative to imagining events involving a famous individual[100]. Furthermore, PHC involvement during episodic simulation is enhanced during construction of episodes that occur in familiar visuospatial contexts[101,102]. These similarities have been attributed to the idea that autobiographical memory and episodic simulation both rely on the construction of an episode within a particular spatial[103] or situational[101] context from a first-person perspective[104].

Spatial memory. Multiple lines of research have linked the PHC and RSC to memory for spatial context. For example, rats can learn associations between objects and contexts (for example, whether an object was encountered in a white box versus a striped box), but rats with lesions of the postrhinal cortex (the rodent homologue of the PHC) fail to discriminate between novel and familiar object–context configurations, despite showing normal exploration of novel objects and novel configurations of pairs of familiar objects[105]. Consistent with the lesion evidence, immediate early gene expression in the postrhinal cortex is insensitive to object familiarity but is sensitive to the familiarity of spatial configurations of objects[106]. Postrhinal lesions also result in impairments in contextual fear conditioning[107,108]. Similarly, rats with RSC lesions show impaired recognition of novel locations and object–location associations, despite demonstrating normal object recognition[109]. RSC lesions also result in impairments to contextual fear conditioning[110] and performance on the radial arm and Morris water mazes[109].

PHC lesions in monkeys have also been shown to impair memory for spatial context, as assessed in the delayed non-matching to place task[111,112] and in tasks that assess spontaneous exploration of novel object–location associations[112]. These effects do not appear to be mediated by hippocampal damage because monkeys with hippocampal lesions showed normal performance in similar object–location recognition tasks[113]. These findings parallel evidence in humans showing that damage to the right PHC causes extensive impairments on object–location memory tests and on a spatial memory task modelled on the Morris water maze[114]. Neuroimaging results have also shown that activity in the PHC and RSC is associated with successful memory for object–location associations[115–118] and for information that is relevant to memory-guided navigation[119–122]. Thus, data from rodents, monkeys and humans converge on the idea that the PHC and RSC are important for spatial memory, including spatial layouts and the locations of objects in these environments.

Scene perception and spatial navigation. Regions in the PHC show disproportionate activation increases during viewing of scene images as compared with other categories of objects, and this has led some researchers to label the posterior PHC, along with portions of nearby lingual gyrus, as the parahippocampal place area[123]. The PHC also shows increased activation during viewing of objects that serve as landmarks during navigation[120], objects configured into room-like spaces[124], objects that are rated as 'defining' a space[125] and objects with strong associations to a particular situational context[126]. Consistent with the imaging results, patients with damage to the right PHC (following infarctions to the posterior cerebral artery) are often unable to recognize familiar buildings or rooms, despite being able to draw maps[127,128].

Studies of spatial navigation have also suggested that neural responses in the PHC are tied to spatial context. For example, single-unit recordings in patients undergoing surgery for epilepsy[129] have identified parahippocampal neurons that showed selective responses when viewing specific landmarks. The spatial firing characteristics of cells in the PHC have not been extensively studied in animals, but available evidence suggests that the PHC contains place cells and that these cells have larger place fields and are more sensitive to changes in environmental cues than traditional hippocampal place cells[130]. Converging with this evidence, an fMRI study in humans demonstrated that patterns of activity in the hippocampus track specific locations in a virtual environment, whereas patterns of activity in the PHC link more broadly to the room itself[131].

The RSC also shows heightened responses to images of scenes[132,133] and objects with strong associations to a particular situational context[126], and theta oscillations have been reported in both the PHC and RSC during spatial navigation[5,134]. Nevertheless, there are important differences between spatial coding in the PHC and RSC. Unlike the PHC, the RSC does not have place cells but instead has head direction cells that selectively respond when an animal's head is pointing to a particular direction in space, thereby providing crucial input about self-motion and orientation within a spatial context. Furthermore, damage to the RSC in humans is not associated with difficulties with scene perception[135] and instead is associated with topographical amnesia[96,135,136], a syndrome in which one is unable to use landmarks to orient oneself. Thus, these patients have intact scene recognition but cannot apply it to guide navigation behaviour.

Autobiographical memories
Memories of personal events from an individual's life.

Retrograde amnesia
Memory loss of events that occurred before the onset of a memory disorder. Typically, following the onset of medial temporal lobe damage, patients show a reduced ability to recollect episodes from the time period before the brain damage occurred.

Delayed non-matching to place task
A spatial recognition memory task in which animals have to distinguish a non-visited arm of a maze from a previously visited arm and enter the non-visited arm in order to receive a reward.

Theta oscillations
Large, rhythmic changes in the amplitude of local field potentials that are seen in the 5–12 Hz frequency in rodents and in the 4–8 Hz range in humans. Theta oscillations are evident during active exploration of novel environments and have been functionally associated with spatial navigation and memory for temporal sequences.

Together, this evidence from rodent physiology, human lesion patients and functional neuroimaging studies supports the idea that the PHC and RSC have complementary roles during scene perception and spatial navigation: the PHC appears to represent information about visuospatial contexts and the RSC integrates information that is crucial to orient oneself within the context.

Social cognition. Studies of social cognition indicate that the RSC is sensitive to the processing of self-relevant information. For example, the RSC, along with anatomically connected regions in the default network, is more active when personality traits are evaluated with respect to how well they describe oneself versus another[137–139]. Furthermore, the regions that show this effect overlap with regions that are active during imagining future personal events[138] and episodic memory retrieval[140]. The RSC has also been implicated in several other aspects of social cognition, including moral decision making[141] and theory of mind[99]. A recent meta-analysis of 84 fMRI studies confirmed that the RSC and PHC regions that are engaged during theory of mind overlap with those recruited during autobiographical memory, episodic simulation and spatial navigation[99]. These findings are consistent with the idea that the RSC and, to a lesser extent, the PHC support processes that contribute to social cognition in addition to memory, perception and navigation.

Two cortical systems

Several models have proposed that the PRC disproportionately supports memory for objects or, more generally, 'items', and that the PHC disproportionately supports memory for scenes and spatial layouts, or, more generally, 'contexts'[1,3,83,142,143]. The findings reviewed above are in accord with these ideas, but they additionally demonstrate that the PHC and RSC have strong similarities and that these regions can be contrasted with the PRC. In terms of connectivity with the hippocampal formation and with other subcortical and neocortical areas, the pathways that connect with the PRC are largely segregated from those that connect with the PHC and RSC. Following the anatomy, the PHC and RSC exhibit compelling functional parallels that extend beyond the domain of traditional memory paradigms, and these characteristics can be contrasted against those of the PRC. These points are not captured by the MTL memory system framework, which assumes that the PRC and PHC differ from neocortical areas outside the MTL (including the RSC) because they have a shared role in declarative memory and convergent connectivity with the hippocampus. Below, we propose a different approach, in which the PRC, PHC and RSC are situated as components of two dissociable, extended networks that support different forms of memory-guided behaviour (FIG. 2).

The anterior temporal system. We propose that the PRC should be considered as a core component of an extended anterior temporal (AT) system that also includes the ventral temporopolar cortex, lateral orbitofrontal cortex and amygdala (FIG. 2). These three areas exhibit similar connectional fingerprints, including dense interconnectivity with the PRC[8,19,24,144] and, like the PRC, they have been implicated in a diverse range of cognitive functions.

One of these functions is familiarity-based recognition memory. The strongest links have been reported for the ventral temporopolar cortex, which, like the PRC, is a site for familiarity neurons[32], and the inactivation of which causes object recognition memory impairments in monkeys[145]. The role of the amygdala in recognition memory is more controversial[1], but a recent study in rats demonstrated that although amygdala lesions did not significantly impair overall recognition memory, the contribution of object familiarity to recognition was reduced, whereas recollection-based recognition remained intact[146]. Lesions to the lateral orbitofrontal cortex in monkeys also result in mild object recognition deficits[147]. Although it is not clear whether orbitofrontal lesions specifically affect familiarity, it is notable that lateral orbitofrontal neurons show higher responses to familiar objects than to novel objects (in contrast to temporal cortex neurons, which show reductions), and these familiarity modulations can be robust over retention delays up to 24 hours[148].

Components of the proposed AT system have also been implicated in emotional processing and social cognition[144,149,150]. Lesions of the entire AT system in monkeys are associated with a diverse range of emotional and social deficits (as well as the failure to recognize the significance of visual stimuli) that together are known as the Kluver–Bucy syndrome[151], and social deficits are also seen in humans with substantial AT damage due to frontotemporal dementia[149]. More recent evidence has highlighted the role of the amygdala in signalling the motivational salience of objects[152], including fear and reward associations[144,153]. Furthermore, it has been repeatedly shown that amygdala activity modulates the encoding and consolidation of emotionally salient items[154]. The lateral orbitofrontal cortex, like the amygdala, has been implicated in motivated behaviour but is more closely linked with learning and updating of associations between stimuli and specific rewards, such as during reward-motivated decision making[147,155]. Last, the ventral temporopolar cortex seems to play a part in the representation of social knowledge[149]. Ventral temporopolar damage is associated with an inability to recognize social signals[149], deficits in naming of famous faces[156] and loss of the ability to relate faces to information about that person[149].

In addition to recognition memory and social cognition, evidence strongly suggests a role for the left temporopolar cortex in semantic knowledge representation[57]. As noted earlier, patients with semantic dementia show severe deficits in conceptual knowledge, and the severity of the deficit is thought to be due to bilateral damage to the temporopolar cortex[57]. Furthermore, available evidence suggests that AMTL N400 potentials can be recorded from this region[63], suggesting a role for this region in online conceptual processing.

Integrating the information summarized above, we propose that the AT system may be essential for

Theory of mind
The ability to understand the mental states — such as beliefs, desires and intentions — of others.

Connectional fingerprints
The patterns of cortico–cortical connections exhibited by cytoarchitectonic areas.

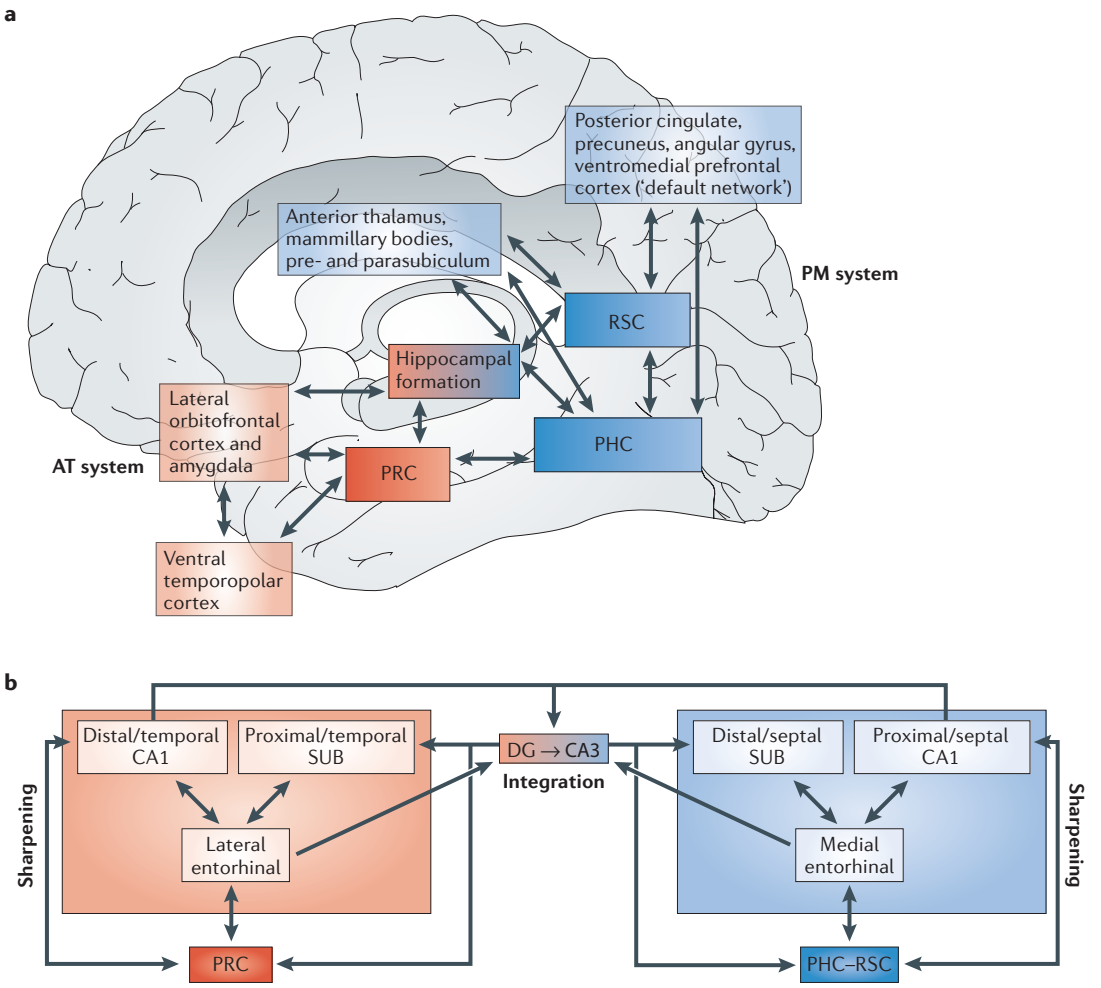


Figure 2 | **Two neocortical systems for memory-guided behaviour.** **a** | Elements of the anterior temporal (AT) system are shown in red and elements of the posterior medial (PM) system are shown in blue. Arrows denote relatively strong anatomical connections between these regions. The AT system includes the perirhinal cortex (PRC), temporopolar cortex, lateral orbitofrontal cortex and amygdala, whereas the PM system includes the parahippocampal cortex (PHC), retrosplenial cortex (RSC), anterior thalamic nuclei, mammillary bodies, pre- and parasubiculum and components of the default network, including the posterior cingulate, precuneus, angular gyrus and ventromedial prefrontal cortex. **b** | Interactions of the PRC and the PHC–RSC with subregions of the hippocampal formation. Sharpening of representations within the AT system may be mediated by interactions between the PRC and lateral entorhinal area, distal/temporal CA1 and proximal/temporal subiculum (SUB); sharpening of representations within the PM system may be mediated by interactions between the PHC and medial entorhinal area, proximal/septal CA1 and distal/septal subiculum. (For simplicity, the RSC is grouped with the PHC, but it would be expected to interact primarily with the medial entorhinal area and to receive inputs from distal/septal subiculum.) Integration of information across the two cortical systems, in turn, may depend in part on the dentate gyrus (DG) and CA3.

assessing the significance of entities (that is, people and things) (FIG. 3). Within this system, the PRC and ventral temporopolar cortex might have closely related roles. Specifically, we propose that the PRC supports rapid learning about, and representation of, unique entities. We hypothesize that the PRC encodes entities in a multidimensional space, such that two entities that are similar on any single dimension (such as visual, auditory, olfactory, semantic, motivational significance and so on) would still be represented quite differently[3,70,71]. The ventral temporopolar cortex in turn might play a part in abstracting common elements across different exemplars in order to represent specific classes of entities (for example, 'zebras' and 'accountants'). The amygdala and orbitofrontal cortex might extract information about the salience and value of entities in order to guide future evaluations. Collectively, the AT system could facilitate the ability to use past experiences to infer features about objects, such as whether they are novel, edible, useful or dangerous. In social cognition, the AT system could facilitate the construction of knowledge about people, so that past experiences can be used to inform inferences about the personality and intentions of others, irrespective of their behaviour in a particular context. Lastly, in language, the AT system might support the influence of conceptual

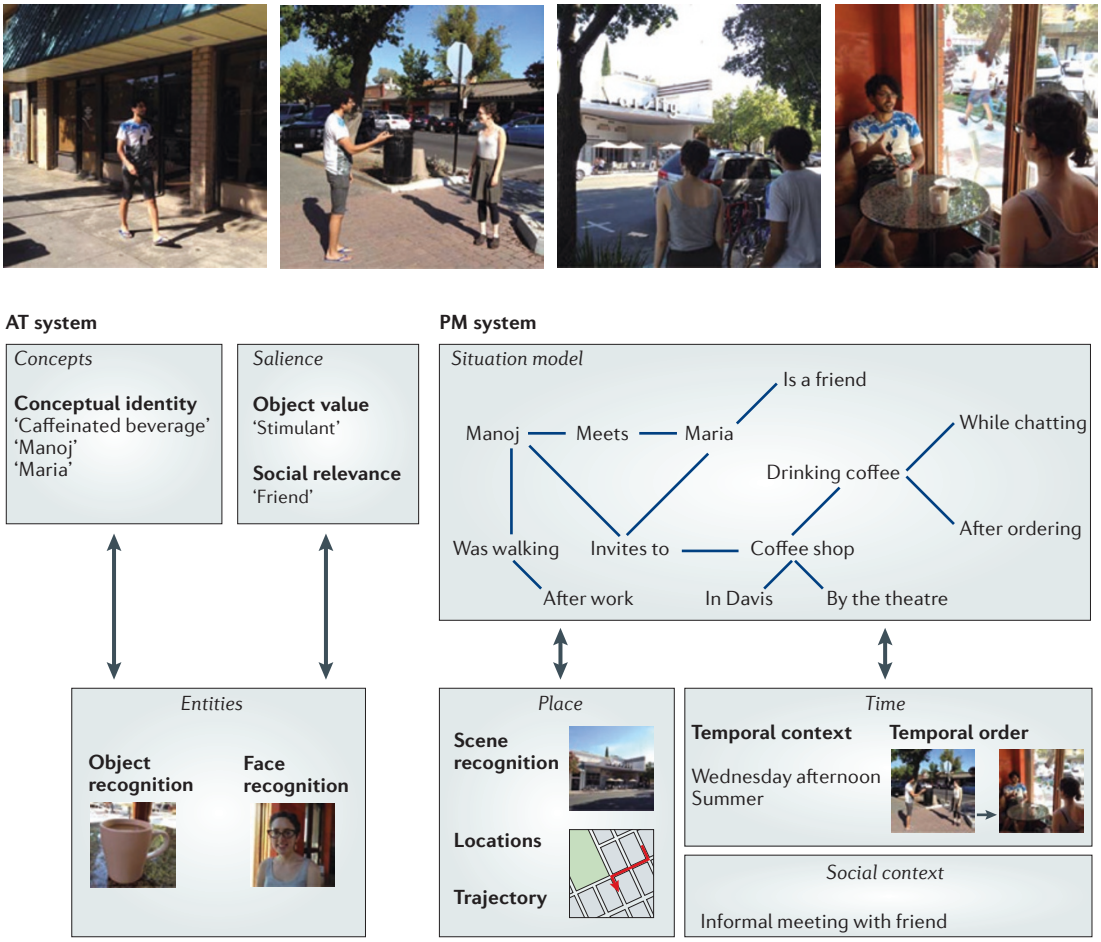


Figure 3 | **Schematic depiction of the functions of the anterior temporal and posterior medial systems.** According to the framework, the anterior temporal (AT) and posterior medial (PM) systems extract essential information during the experience of an event. For example, one might have the experience of walking down the street, meeting a friend, and then walking together to a coffee shop (top). During this experience, we propose that the AT system (bottom left) relates representations of specific entities (for example, a particular person) to existing semantic concepts (for example the name of the person, 'Maria') and its associated salience (for example, Maria's status as a friend). By contrast, the PM system (bottom right) matches incoming cues about the current context (for example, space, time and social interactions) to situation models or internal models that summarize interactions among entities and the environment during a novel experience. For example, visual cues such as landmarks (for example, the 'Varsity Theatre') might confirm one's spatial location in the model, promoting goal-relevant behaviour (for example, visiting the coffee shop next door). Photos courtesy of M.R.

knowledge on item memory and, conversely, the creation or modification of existing concepts following novel experiences.

The posterior medial system. Putting together anatomical research summarized by Kondo *et al.*[19] and Aggleton[8] with results from functional connectivity studies in humans[12,13], we suggest that the PHC and RSC should be considered as core components of an extended posterior medial (PM) network that includes the mammillary bodies and anterior thalamic nuclei, pre- and parasubiculum and the default network (including the posterior cingulate, precuneus, lateral parietal cortex and medial prefrontal cortex). All of these areas have direct connections with the PHC and RSC, and most of these areas have a similar connectional fingerprint. By contrast, connections between these areas and the PRC are either indirect or weak, which is consistent with our model of two dissociable brain networks.

Available evidence is strongly consistent with the involvement of the proposed PM system in episodic memory[2,3,84,99]. For instance, Korsakoff's syndrome, a disorder that is associated with the degradation of the thalamus and mammillary bodies, causes severe retrograde and anterograde amnesia as well as deficits in spatial memory[157]. Notably, patients with Korsakoff's syndrome show severe hypometabolism of the RSC and other components of the PM system, and mammillary bodies or anterior thalamic lesions in rats are associated with reduced immediate early gene expression[158] and disrupted synaptic plasticity[159] in the RSC. Studies in humans suggest that the default network is also reliably engaged during episodic memory retrieval[84,99]. In particular, activation in the left angular gyrus is increased

during conscious recollection[85,160], and lesions to the angular gyrus can result in an impaired ability to subjectively re-experience past episodes[161,162]. Although the interpretation of these findings is controversial, some have proposed that the angular gyrus might have a role in integrating or attending to contextual information retrieved via the hippocampus, PHC and RSC[85,160].

Findings also support a role for the PM system in spatial navigation[143]. For instance, the lateral mammillary bodies, anterior dorsal thalamic nucleus and presubiculum, along with the RSC, are known to contain head direction cells that encode the direction of movement through space or the perspective that one is taking when stationary[163]. Default network regions are also engaged during spatial navigation tasks[99]. According to one model, the RSC integrates information about one's location in a global spatial context (via the PHC and hippocampus) and information about perspective (via the head direction system), and this information is translated to a first-person spatial representation by default network regions such as the precuneus[143].

In addition to episodic retrieval and spatial navigation, most of the components of the PM system have been identified in previous models of episodic simulation[99,104], processing of contextually based visual associations[164] and theory of mind[99]. What do these tasks have in common? We suggest that a common theme is that each of these kinds of tasks requires the construction and use of a 'situation model'[165,166], by which we mean a mental representation of the relationships between entities, actions and outcomes. A situation model is like a schema[167] that specifies the gist of the spatial, temporal and causal relationships that apply within a particular context. For example, for the scenario depicted in FIG. 3, the corresponding situation model would specify the relative locations of the coffee shop and theatre, the temporal sequence of meeting prior to walking past the theatre, and the reason for visiting the coffee shop, that is, to get coffee with a friend. Behavioural research suggests that situation models support a diverse range of cognitive functions, such as language comprehension, inductive reasoning, decision making, learning of cause–effect relationships and social cognition[165].

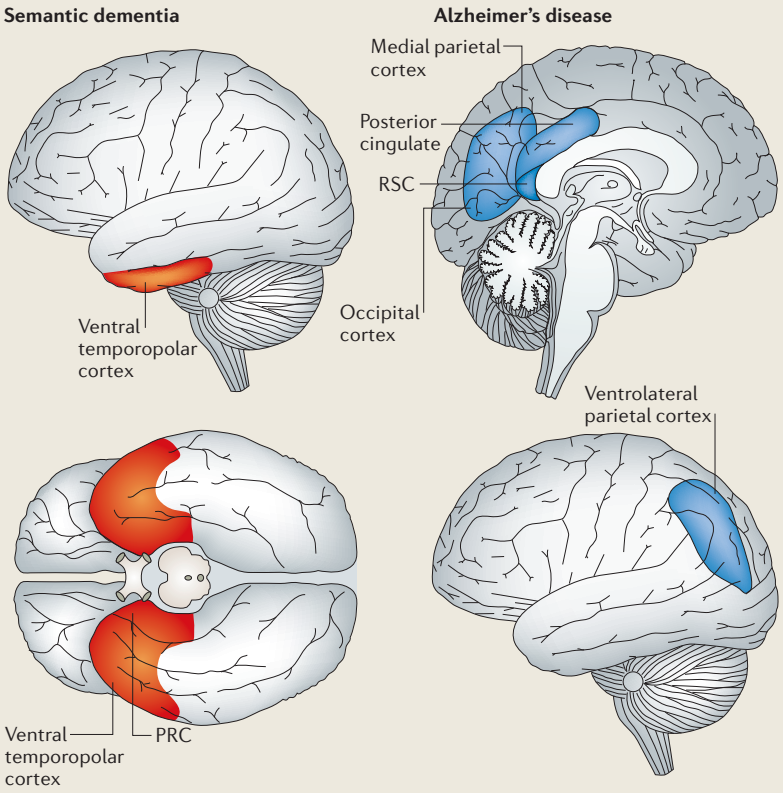
We propose that the PM system has a central role in the construction and application of situation models. The PHC and RSC play complementary parts in this system by representing contextual cues[3,82,164] that signify when a particular model will be applicable. The PHC may represent and track statistical regularities in the external environment that identify particular contexts, and the RSC may integrate these external cues with information derived from internal sources that help to associate different cues within a coherent situation. Related default network areas in the PM system (including the posterior cingulate, precuneus and angular gyrus) in turn might represent the situation model itself, thereby orienting the individual in place, time and situation. For example, in navigation, the PHC has been hypothesized to represent stable statistical regularities in sensory information that are encountered during exploration of a particular spatial context[168]. The RSC might associate changes in information about visual scenery over time with concurrent input regarding self-motion[163]. Integrating inputs from the PHC and RSC, the default network can retrieve or construct an internal model of the spatial layout. The spatial situation model can then be used to orient the individual and to generate predictions about visual input that would be expected on the basis of movement within the environment, via top-down feedback from the default network to the PHC and RSC. Prediction errors, in turn, should elicit the allocation of attentional and mnemonic resources in order to update the currently active contextual representation[169]. We can envision that the PM system has a similar role in other functions such as episodic retrieval, in which non-spatial context cues and internal state variables (such as goals and motivations) would play a more important part.

Role of the hippocampus in the anterior temporal and posterior medial systems. Given the extensive connectivity between the hippocampal formation and the PRC, PHC and RSC, an obvious question is how these areas might interact. We can only speculate on this issue, because few studies have investigated when and how neocortical areas interact with the hippocampal formation. These studies have generally suggested that such interactions occur under surprisingly restricted conditions owing to strong inhibition of inputs from the PRC, PHC and RSC to the hippocampal formation[170]. With this caveat in mind, we hypothesize that, in addition to supporting independent expressions of memory through subcortical connections, the hippocampus has a role in modulating activation dynamics within the neocortex in two ways (FIG. 2b).

First, direct interactions between the neocortex and different sectors of the hippocampal formation could be associated with refinement of, and elaboration upon, representations within the PRC and the PHC–RSC ('sharpening'). This assumption is based on evidence indicating that pathways connecting the entorhinal cortex, CA1 and subiculum with the PHC are largely segregated from those connecting CA1 and subiculum with the PRC. Thus, interactions between the PRC and distal (anterior) CA1 and proximal (anterior) subiculum could be associated with a sharpening of entity representations, whereas interactions between the PHC and proximal (posterior) CA1 and distal (posterior) subiculum could be associated with a sharpening of context representations. Second, consistent with many current theories[3,83,143], we propose that the hippocampal formation facilitates the ability to link between representations of entities in the PRC and representations of context in the PHC–RSC ('integration'). Integration would be expected to depend on the eventual convergence of the streams from the PRC and the PHC–RSC in the dentate gyrus and CA3 subfields. In other words, we propose that processing through the hippocampal trisynaptic circuit (entorhinal cortex–dentate gyrus–CA1–subiculum) associates representations of entities and contexts that are concurrently activated. The mode of hippocampal processing (sharpening versus integration) could be influenced by task factors and goals. Although

Box 2 | **Involvement of the anterior temporal and posterior medial systems in neurological diseases**

The relationships in connectivity that define the anterior temporal (AT) and posterior medial (PM) networks may be relevant to our understanding of neurological disease[174]. Regions in the AT system are the primary sites of pathology in semantic dementia and herpes simplex encephalitis[59], and these regions show substantial cortical atrophy in patients with temporal lobe epilepsy[177,178]. Although these disorders also affect the hippocampal formation, they tend to spare the PM system. For instance, atrophy of the parahippocampal cortex (PHC) and retrosplenial cortex (RSC) is less frequently observed (and when it occurs, less severe) compared with AT system atrophy in patients with temporal lobe epilepsy[177,178], herpes encephalitis[59] and semantic dementia[55,56].



It is interesting to consider the differences between semantic dementia and Alzheimer's disease. Both are degenerative conditions that are associated with medial temporal lobe pathology[55,175], but episodic memory impairment is more severe in Alzheimer's disease, whereas semantic memory impairment is more severe in semantic dementia[175]. The differential patterns of cognitive deficits in the two disorders might reflect relative differences in damage to the extended AT and PM systems. Patients with semantic dementia have more cortical atrophy and lower glucose metabolism in the perirhinal cortex (PRC) and temporopolar cortex[179], whereas patients with Alzheimer's disease have more severe disruption of the RSC, posterior cingulate, precuneus and angular gyrus[55,174,175] (see the figure). Furthermore, semantic dementia is associated with disproportionate atrophy of the left anterior hippocampus, whereas Alzheimer's disease affects both the posterior and anterior hippocampus[56]. This finding may be related to the fact that the PHC and RSC show preferential connectivity with the posterior hippocampal formation, and the PRC shows preferential connectivity with the anterior hippocampal formation[12,13].

On the basis of our proposal regarding the AT and PM systems, one might expect cognitive deficits in semantic dementia and Alzheimer's disease that extend beyond semantic and episodic memory. Although few such comparisons have been made, studies of visual perception indicate that semantic dementia is associated with deficits in fine-grained object discriminations, whereas Alzheimer's disease is associated with deficits in scene discriminations[76] — which is precisely the pattern of results that would be expected if the two disorders differentially affect the AT and PM systems (TABLE 1).

speculative, this proposal is consistent with results showing that some forms of learning tasks are associated with immediate early gene expression in both the PRC and the entire hippocampal circuit, whereas other learning tasks are associated with increased gene expression specifically in the more direct PRC–entorhinal–CA1 pathway[27].

Comparison with models of medial temporal lobe organization. The AT–PM framework builds on the 'binding of items and contexts' model[3,82] and related models of MTL organization[30,83,171] that propose that the PRC and PHC differentially contribute to memory for item and context information, respectively. The AT–PM framework extends these models by including a functional role for the RSC, by more fully characterizing the functional networks with which the PRC and the PHC–RSC affiliate (including prefrontal and parietal areas that are known to contribute to memory retrieval[19,85,160,172]), and by suggesting two ways in which the hippocampal formation might modulate activity within these networks. The present account also makes new predictions about how interactions within each system link novel experiences to existing knowledge stores, mapping items to concepts in the AT system and contexts to situation models in the PM system.

The AT–PM framework also draws inspiration from models that emphasize the role of the PRC and other MTL regions in visual perception and memory processes[70,74]. However, these models cast MTL subregions as end points of the ventral and dorsal visual processing

Table 1 | **Characteristics of the anterior temporal and posterior medial systems**

System	Components	Susceptibility to disease	Functional characteristics				Potential function
			Memory	Perception	Social cognition	Language	
Anterior temporal system	Amygdala, temporopolar cortex and orbitofrontal cortex (connected via uncinate fasciculus)	Semantic dementia, herpes encephalitis, temporal lobe epilepsy and Alzheimer's disease	Semantic, familiarity	Objects	Person knowledge	Concepts	Assessing the significance of entities
Posterior medial system	Anterior thalamic nuclei, mammillary bodies, pre- and parasubiculum, and default network (connected via cingulum bundle)	Alzheimer's disease and Korsakoff's syndrome	Episodic, recollection	Scenes	Theory of mind	Situation models	Constructing situation models

streams, whereas our approach emphasizes the PRC and the PHC–RSC as crucial components of systems that contribute to behaviour in a manner that is not tied to the visual modality. In this sense, the AT–PM framework is more similar to models of spatial imagery[143], contextual associations[164], semantic cognition[4] and emotion[144] that situate the PRC and PHC within modality-independent circuits. Furthermore, some perceptual–mnemonic frameworks emphasize a central and specific role for the hippocampus in scene perception[70], whereas our framework predicts that the PHC is essential for scene perception[135], and that different subregions of the hippocampal formation should contribute to the sharpening of object and scene representations.

Implications and future directions

The framework introduced here does not propose a sharp distinction between neocortical areas within the MTL versus those outside the MTL. Of course, because damage to the PRC, RSC and PHC is associated with amnesic disorders, it is reasonable to infer that these areas are more involved in memory than are the other components of the AT and PM systems. Thus, an important direction for future research is to understand the mechanisms of plasticity in the PRC, RSC and PHC that might support rapid learning, and to differentiate these regions from other components of the AT and PM systems. There is also a need for further research on the functional differences between different components of the AT and PM systems. For instance, our Review indicates both functional parallels and reliable differences between the RSC and PHC. Further research will be needed to determine whether the difference between these areas is related to a relative sensitivity to external versus internal sources of information, or whether the areas differ on a more fundamental level[5,143]. In a similar vein, our Review points to many functional parallels between the ventral temporopolar cortex and the PRC, but the temporopolar cortex remains poorly understood[149], and even the anatomical borders between the two areas remain unclear[173]. More research is needed to address the similarities and differences, and the nature of the functional interactions, between these highly interrelated cortical areas.

The AT–PM framework also suggests new directions for research on cortico–hippocampal interactions. For instance, a great deal of research has focused on the role of the hippocampus in systems consolidation. Rather than focusing on whether the hippocampus has a time-limited or permanent role in memory, it might be more productive to investigate how interactions between the hippocampal formation, the AT system and the PM system relate to stabilization or transformation of memory traces. We speculate that the hippocampus plays a transient part in rapidly assimilating new information into existing representations carried by the AT and PM systems (sharpening)[167] and that it plays a lasting part in expressions of memory that require coordination between the systems (integration).

Last, because the AT–PM framework emphasizes the structure and function of neocortical networks, it might lead to new insights into neurodegenerative diseases, which disproportionately target specific neocortical networks[174]. For instance, Alzheimer's disease and semantic dementia are degenerative dementias that have very different behavioural profiles, even though both disorders affect the MTL[175]. As discussed in BOX 2, some of the differences between these disorders might be due to differential atrophy of the AT and PM systems. Thus, research on the functional organization of neocortical networks and the mechanisms that influence disease progression through these networks can lead to important advances in our understanding of disorders that target memory and its use to guide behaviour.

Systems consolidation
A hypothesized process by which the brain regions that support memory of a particular experience are thought to change over time. Systems consolidation theories are typically invoked to explain differential effects of brain lesions on memories of recent and remote events.

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Competing interests statement
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