


REVIEW ARTICLE

Reconciling the object and spatial processing views of the perirhinal cortex through task-relevant unitization

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Abstract

The perirhinal cortex is situated on the border between sensory association cortex and the hippocampal formation. It serves an important function as a transition area between the sensory neocortex and the medial temporal lobe. While the perirhinal cortex has traditionally been associated with object coding and the “what” pathway of the temporal lobe, current evidence suggests a broader function of the perirhinal cortex in solving feature ambiguity and processing complex stimuli. Besides fulfilling functions in object coding, recent neurophysiological findings in freely moving rodents indicate that the perirhinal cortex also contributes to spatial and contextual processing beyond individual sensory modalities. Here, we address how these two opposing views on perirhinal cortex—the object-centered and spatial-contextual processing hypotheses—may be reconciled. The perirhinal cortex is consistently recruited when different features can be merged perceptually or conceptually into a single entity. Features that are unitized in these entities include object information from multiple sensory domains, reward associations, semantic features and spatial/contextual associations. We propose that the same perirhinal network circuits can be flexibly deployed for multiple cognitive functions, such that the perirhinal cortex performs similar unitization operations on different types of information, depending on behavioral demands and ranging from the object-related domain to spatial, contextual and semantic information.

KEYWORDS

contextual processing, hippocampus, multisensory integration, perirhinal cortex, spatial coding

1 | INTRODUCTION

The perirhinal cortex (PER) is situated at the border between the higher sensory cortices and the entorhinal-hippocampal complex. On the one hand, the PER can be characterized as a polymodal

association area, receiving inputs from many uni- and polysensory areas (Burwell, 2001; Burwell & Amaral, 1998a; Burwell & Amaral, 1998b; Burwell, Witter, & Amaral, 1995; Furtak, Wei, Agster, & Burwell, 2007; Suzuki & Amaral, 1994). On the other hand, it is an input and output hub of the medial temporal lobe (MTL), having direct and indirect connections with the hippocampus (HPC) (Burwell et al., 1995; Burwell & Amaral, 1998a; Burwell & Amaral, 1998b; Insausti,

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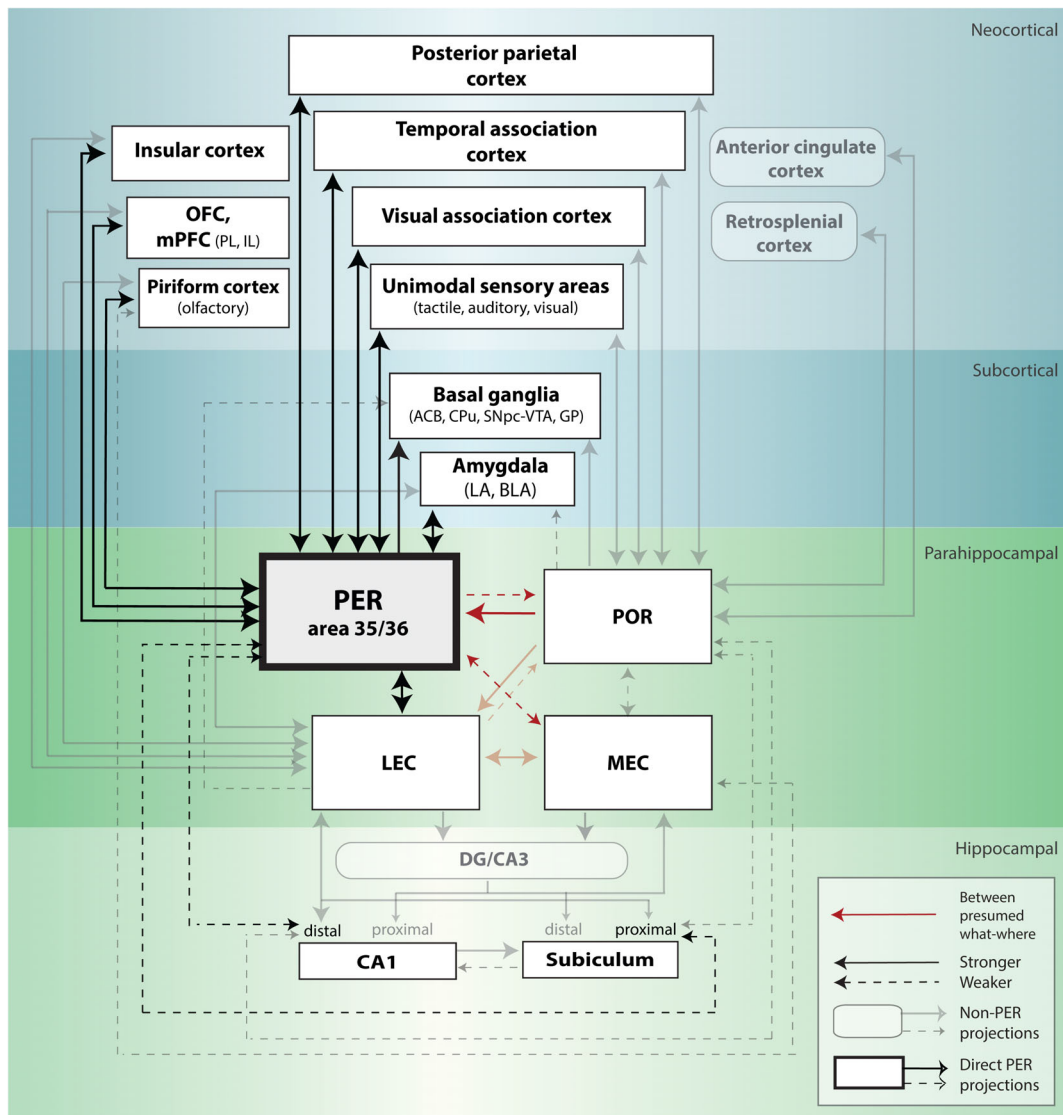


FIGURE 1 Schematic overview of main anatomical connections to and from the perirhinal cortex in the rat brain. Reappraisal of parahippocampal connectivity has led to an updated anatomical wiring scheme incompatible with a strict “what” versus “where” dichotomy. Notably, LEC is targeted by both POR and PER. PER receives direct and dense input from both POR and LEC, and also has direct reciprocal connections with MEC, CA1, and subiculum. The PER can be differentiated from other parahippocampal regions by appreciating its wide variety of direct connections with areas central in sensory, spatial, motivational and emotional processing (i.e., amygdala, OFC, mPFC, and unimodal sensory areas). Connections between areas are indicated schematically as arrows with uniform or dashed lines for relatively strong and weak projections, respectively. Dark arrows (and associated regions) indicate direct projections to and from the PER. Other connections and areas are indicated as semi-transparent. Note that many weaker connections to or from non-PER areas are not included, for example, neocortical projections to the LEC and MEC (schematic connectivity based on Burwell, 2000; Agster & Burwell, 2009; Doan, Lagartos-Donate, Nilssen, Ohara, & Witter, 2019, Nilssen, Doan, Nigro, Ohara, & Witter, 2019; OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; amygdala (LA, lateral nucleus of the amygdala; BLA, basolateral nucleus of the amygdala); POR, postrhinal cortex; PER, perirhinal cortex; LEC, lateral entorhinal cortex; MEC, medial entorhinal cortex; DG, dentate gyrus; CA1, cornu ammonis 1; CA3, cornu ammonis 3; PL, prelimbic; IL, infralimbic; VTA, ventral tegmental area; GP, globus pallidus; CPu, caudate putamen; SNpc, substantia nigra pars compacta; ACB, accumbens nucleus)

Herrero, & Witter, 1997; Witter, Naber, et al., 2000). PER has been defined as consisting of cytoarchitecturally defined Brodmann areas 35 and 36. In the rat, Area 35 receives most projections from the entorhinal cortex (EC), piriform cortex, insular cortex and the amygdala. Area 36 receives major projections from temporal association areas, insular cortex, EC and amygdala (Figure 1; Burwell et al., 1995; Furtak et al., 2007; Agster, Tomás Pereira, Saddoris, & Burwell, 2016;

Tomás Pereira, Agster, & Burwell, 2016; Burwell, 2000). The PER has return projections to all of these input areas. The PER is traditionally considered part of a cortico-hippocampal pathway that is associated with object coding (the “what” pathway), routing this information to the HPC via the lateral EC (LEC). A second pathway, related to spatial coding, (the “where” pathway) has been proposed to comprise the postrhinal cortex (POR), projecting to the medial EC (MEC), which in

turn connects to the HPC (Burwell, 2000; Furtak et al., 2007; Goodale & Milner, 1992; Knierim, Neunuebel, & Deshmukh, 2014; Otto & Eichenbaum, 1992; Witter, Wouterlood, Naber, & Haeflén, 2000). More recently, however, this strict anatomical dissociation has been disputed (Agster & Burwell, 2009; Doan et al., 2019; Nilssen et al., 2019). Additionally, direct reciprocal connections have been described between PER, the distal CA1, and proximal subiculum (Naber, Silva, & Witter, 2001).

The classical distinction between a “what” and a “where” pathway has been supported by evidence for spatial information coded by grid cells in MEC and the absence of spatial correlates in LEC, that is in the absence of objects (Hafting, Fyhn, Molden, Moser, & Moser, 2005; McNaughton, Battaglia, Jensen, Moser, & Moser, 2006; Knierim et al., 2014; but see below for PER). Important evidence for a perirhinal function in object processing comes from PER lesion studies in rats, resulting in impairments in delayed object recognition (Albasser et al., 2015; Bartko, Winters, Cowell, Saksida, & Bussey, 2007; Ennaceur & Aggleton, 1997; Ennaceur, Neave, & Aggleton, 1996; Norman & Eacott, 2005; Otto & Eichenbaum, 1992). Moreover, single unit recordings in the PER of monkeys and rodents demonstrated that PER neurons are sensitive to the prior presentation of objects, typically showing decreased activation with repeated presentations (Brown & Banks, 2015; von Linstow Roloff, Muller, & Brown, 2016; Young, Otto, Fox, & Eichenbaum, 1997; Zhu & Brown, 1995).

In addition to its role in object recognition, the PER has been suggested to be important for solving feature ambiguity (Buckley & Gaffan, 1998; Buffalo et al., 1999; Bussey & Saksida, 2005; Bussey & Saksida, 2007; Bussey, Saksida, & Murray, 2002; Meunier, Bachevalier, Mishkin, & Murray, 1993; Saksida, Bussey, Buckmaster, & Murray, 2006; Saksida, Bussey, Buckmaster, & Murray, 2007) and for the processing of complex stimuli, both within and across different sensory modalities (Bartko et al., 2007; Feinberg, Allen, Ly, & Fortin, 2012; Jacklin, Cloke, Potvin, Garrett, & Winters, 2016; Kent & Brown, 2012; Ramos, 2016). More recently, work in rodents and monkeys also suggested that the PER processes information on task-related context, either spatial or temporal (Bos et al., 2017; Eradath, Mogami, Wang, & Tanaka, 2015; Keene et al., 2016), in line with studies reporting a much denser interconnectivity between the traditionally segregated information-specific pathways (Figure 1; Kerr, Agster, Furtak, & Burwell, 2007; van Strien, Cappaert, & Witter, 2009; Agster & Burwell, 2013; Doan et al., 2019; Nilssen et al., 2019). The main goal of this review is to examine whether the seemingly contradictory findings on object versus spatial-contextual processing can be reconciled under a broader functional scope for the PER in information processing that emphasizes unitization of task-relevant information.

2 | PERIRHINAL CORTEX: SENSORY PROCESSING AND OBJECT RECOGNITION

2.1 | Lesion studies

Animal and human lesion studies have made important contributions to our understanding of the neural basis of behavior. The strength of

lesion studies lies in the provision of causal evidence on functional contributions of specific brain regions to cognitive functions. In humans, two principal approaches have been taken. First, focal lesions have been investigated that overlap anatomically with the PER. Here, drawing specific conclusions on PER functionality is difficult as these lesions are mostly unilateral (and therefore cause limited impairment) or cover more areas than only the PER. Second, widespread neural injury is studied that can be acute in nature (e.g., due to an encephalitis) or caused by progressive neurodegeneration as in the context of Alzheimer's, semantic or frontotemporal dementia. The relationship between PER damage and cognitive impairment then has to be established through quantification of PER integrity (i.e., volume or cortical thickness). Accurate identification of anatomical PER borders is, however, challenging (Berron et al., 2017; Ding & van Hoesen, 2010). Animal models suffer similar difficulties. However, induced lesions allow more control of the focus of the lesioned areas, and reversible lesions allow within-subject comparisons.

For decades, the tradition of region–function mapping dominated research on PER. One central question was whether the region should be considered perceptual or mnemonic. Moreover, within the field of memory research an intense debate arose about the mnemonic processes (familiarity or recollection) that are served by the HPC versus other MTL regions, including the PER (see, e.g., Brown & Aggleton, 2001; Squire, Stark, & Clark, 2004; Buckley & Gaffan, 2006; Eichenbaum, Yonelinas, & Ranganath, 2007; Wais, 2008; Naya, 2016). This subsection summarizes reported deficits in memory and sensory processing caused by lesions to the PER in the rodent, primate, and human brain.

2.1.1 | Lesions in rats

In rodents, object recognition is commonly assessed using a spontaneous object recognition paradigm (Ennaceur & Delacour, 1988; Albasser et al., 2010.) Initially, rats are allowed to explore two objects. In a subsequent recognition phase, one of the two objects is exchanged for a novel one. The innate preference of rodents to explore novel objects over familiar ones is used to assess whether rats recognize objects as familiar or not. Impairments in recognizing objects as familiar are characterized by a failure to preferentially explore the new object over the old one (Albasser et al., 2010; Ennaceur & Delacour, 1988). It is important to emphasize that differences in exploration times reflect object familiarity, and that this might occur without recollection of object identity from episodic memory.

In PER-lesioned rats, familiarity-based object recognition is often spared when delays between object sampling and object recognition are short (<10–40 min). With increased delays, however, these animals display impaired familiarity-based recognition (Ennaceur & Aggleton, 1997; Ennaceur et al., 1996; Norman & Eacott, 2005; Otto & Eichenbaum, 1992). Other studies have shown that impairments can also be present at zero (or very short) delays (Albasser et al., 2015; Bartko et al., 2007). The duration of delays which can be bridged without impairments caused by PER lesions is dependent on the complexity of the stimuli (Norman & Eacott, 2004). PER-lesioned rats were

able to bridge very long delays (24 hr) when presented with distinct objects. If the objects were very similar this duration decreased to less than 5 min. Similarly, Bartko et al. (2007) reported zero-delay deficits for PER-lesioned rats in an oddity discrimination task, where physical objects were explicitly manipulated to be perceptually similar. These results suggest that the role of PER in object recognition measured by means of spontaneous exploration is heavily dependent on object complexity and perceptual ambiguity and that impairments can occur in the absence of a heavy memory load.

The described impairments following PER lesioning may be due to deficits in signaling novelty, sensory processing, or retrieval processes. To clarify this, McTighe, Cowell, Winters, Bussey, and Saksida (2010) used a simplified version of the spontaneous recognition task by presenting either two novel or two familiar objects during the recognition phase. As expected, PER-lesioned rats showed impairments in familiarity-based recognition. Strikingly, this impairment was caused by reduced exploration of novel objects by PER-lesioned rats, rather than increased exploration of familiar objects as one would expect from an impairment in recalling previous object encounters. Instead, the animals either incorrectly recognized new objects as familiar, or failed to signal their novelty. This impairment of familiarity-based recognition was rescued when the rats were placed in a dark environment during the retention period. McTighe et al. (2010) hypothesize that visual input during the retention period leads to interference in memory for the PER-lesioned animals. PER lesions thus would induce an increased susceptibility to visual input. This hypothesis has been challenged by other studies that found no or only weak indications of interference (Albasser et al., 2015; Olarte-Sánchez, Amin, Warburton, & Aggleton, 2015). Differences between the results of these studies may have arisen due to differences in the experimental setups. Studies that found no effect of proactive interference baited the objects to ensure that rats remained exploring objects consecutively, whereas the exploration of rats in McTighe et al. (2010) was driven by mere curiosity. Differences in the extent of PER lesions might also play a role in these inconsistencies (Olarte-Sánchez et al., 2015).

It can be challenging to disentangle whether mnemonic or perceptual deficits lead to impairments in spontaneous object exploration due to the limited experimental control over sensory input and the inability to repeatedly assess recognition of a familiar stimulus. Other studies have therefore quantified the effect of PER lesions on performance in stimulus discriminations by operant conditioning. Eacott, Machin, and Gaffan (2001) trained rats on approaching one out of two visual stimuli. For simple visual stimuli (rectangle versus square), PER-lesioned rats were unimpaired, even when the stimuli were warped to increase stimulus resemblance and thereby task difficulty. In contrast, impairments only arose when complex visual stimuli with shared features were used (Eacott et al., 2001). This result indicates that PER cortex is only necessary when different visual features need to be integrated, but not for solving feature ambiguity of just one visual feature. Comparable results were found in tactile, auditory and olfactory tasks (Feinberg et al., 2012; Kent & Brown, 2012; Kholodar-Smith, Allen, & Brown, 2008; Lindquist, Jarrard, & Brown, 2004;

Ramos, 2014, 2016). For instance, PER excitotoxic ablation had no effect on the performance of a whisker-based tactile discrimination task when discrimination could be achieved by individual tactile features (particle diameter or grain density of sandpaper). This holds even with increased task difficulty due to more similar stimuli. PER-lesioned rats only showed deficits when the combination of individual tactile features was crucial to solve the task. By contrast, HPC lesions did not result in any impairment in the same task (Ramos, 2014, 2016). Moreover, PER lesions impair fear conditioning to discontinuous or complex (natural) sounds, but not to pure tones (Lindquist et al., 2004; Kholodar-Smith et al., 2008; Kent & Brown, 2012, and Section 3). Together, these studies demonstrate a function of PER for the processing of complex (i.e., consisting of multiple sensory features) but not simple stimuli, independently of the sensory modality. Nonetheless, opposing evidence also exists. Clark, Reinagel, Broadbent, Flister, and Squire (2011) did not find impairments after PER lesions for any condition in a visual discrimination task that gradually morphed stimuli to become increasingly similar perceptually. Murray and Wise (2012) argued that rats could have solved this task by attending to specific parts of the visual stimuli, leaving unresolved to what extent multiple features had been used to categorize the stimuli.

In addition to PER functions in unisensory processing, the convergent innervation of the PER by all sensory cortical systems suggests a potential contribution to multisensory processing (Burwell, 2000; Furtak et al., 2007; Naber, Witter, & da Silva, 2000; Naber, Witter, & Silva, 1999; Witter, Wouterlood, et al., 2000). Causal evidence for the involvement of PER in multisensory processing comes from a cross-modal version of the spontaneous object recognition paradigm. In this variant, rats either first sample an object in the dark (using their whiskers) and later resample it in the light with a translucent plate placed before the objects (preventing the use of whiskers) or vice versa. Rats that received PER lesions prior to training had deficits in cross-modal object familiarity-based recognition, while lesions of the HPC had no effect (Albasser et al., 2010; Reid, Jacklin, & Winters, 2012). In addition to the deficits in cross-modal familiarity-based recognition, PER-lesioned rats showed deficits in visual familiarity-based recognition (when both initial sampling and later resampling relied on vision). However, these rats were not impaired in the olfactory- and/or tactile-only versions of the same task (Winters & Reid, 2010). Strikingly, multisensory pre-exposure caused later familiarity-based recognition to become completely PER-dependent, even under conditions that were initially PER-independent. Reversible PER inactivation with lidocaine impaired familiarity-based recognition in all task variants (cross-modal, visual, and tactile) compared to control rats with saline injections, even after a single multisensory pre-exposure. This effect occurred regardless of the timepoint of inactivation during any sampling phase (pre-exposure or later resampling, Jacklin et al., 2016). Presumably, PER-mediated neural mechanisms formed a multisensory object representation after the exploration via multiple sensory modalities. These results indicate a functional role of PER in multisensory processing in addition to its role in complex unisensory processing.

2.1.2 | Lesions in primates

While the abovementioned studies were conducted in rats, the phylogenetically preserved role of PER in resolving feature ambiguity has been extensively documented for monkeys (Buckley & Gaffan, 1998; Buffalo et al., 1999; Bussey et al., 2002; Bussey & Saksida, 2005; Bussey & Saksida, 2007; Meunier et al., 1993; Saksida et al., 2006; Saksida et al., 2007). Bussey et al. (2002) tested control and PER-lesioned monkeys in a visual paired associate task. In this task, monkeys were required to discriminate between pairs of pictures and learned to touch reward-associated pairs while ignoring other pairs. The monkeys were tested in three different conditions. First, in the low-ambiguity condition of the task, all individual pictures constituting the rewarded pairs were different from the pictures in the unrewarded pairs. Merely remembering the outcome related to individual images is thus sufficient to solve this condition. Second, in high-ambiguity trials, all individual pictures were both part of one unrewarded and one rewarded pair. Here, a correct choice can only be made based on the combined information of both paired images. Third, in trials with intermediate levels of ambiguity only one picture from each pair was ambiguous. Lesions of the PER severely impaired monkeys in the high-ambiguity condition and mildly impaired them in the intermediate-ambiguity condition. They were not impaired in the low-ambiguity condition. Altogether, rodent and monkey lesion studies indicate that the PER is necessary for reward-related recognition of object identity, complex stimulus processing and for solving feature ambiguity.

Likewise, the role of the PER has been investigated in human lesion studies. Impairment in memory tasks for humans has been particularly noted when familiarity judgments had to be made about object stimuli or item information (Bowles et al., 2007; Brown & Aggleton, 2001; Buffalo, Reber, & Squire, 1998; Stark & Squire, 2000). Several lesion studies found evidence for specific impairment of object recognition in contrast to recollection, when PER damage was apparent but the HPC was spared (Bowles et al., 2007, 2010; Martin, Bowles, Mirsattari, & Köhler, 2011). Also in terms of perceptual discrimination, object processing specifically seems to be impaired, notably when the complexity and feature ambiguity of the stimuli is high and when integration of multisensory information takes place (Barense, 2005; Barense, Gaffan, & Graham, 2007; Lee, Bussey, et al., 2005; Lee, Buckley, et al., 2005; Lee et al., 2006; Mundy, Downing, Dwyer, Honey, & Graham, 2013; Newsome, Duarte, & Barense, 2012; Taylor, Moss, Stamatakis, & Tyler, 2006). A recent study with rare cases of focal PER lesions confirmed impairment in visual discrimination when feature ambiguity was high. However, memory judgment was unimpaired (Inhoff et al., 2019). Overall, it is still subject to debate whether there is a specific mnemonic in addition to the perceptual function of PER and direct involvement of the human PER in familiarity-based recognition, but not in recollection (Brown & Aggleton, 2001; Brown & Banks, 2015; Graham, Barense, & Lee, 2010; Squire, Wixted, & Clark, 2007).

The overall picture arising from the lesion literature supports a role of PER in object-related recognition (mainly familiarity) and

perception, particularly multisensory and complex feature integration of objects. Regarding the perceptual and mnemonic functions of the PER, we note that these may be fundamentally entangled because perception is partly driven from memory, at least in many task settings (Graham et al., 2010; Pennatz, 2015; Peterson & Enns, 2015).

2.2 | Neural correlates

Permanent lesions may cause other brain regions to take over functions of a damaged region. Moreover, behavioral effects alone do not illuminate the neural mechanisms underlying a structure's functions. Therefore, additional evidence for the involvement of the PER in object recognition and sensory processing comes from animal electrophysiology and human neuroimaging studies.

2.2.1 | Neural correlates in rats

Single PER units recorded from rats display elevated firing rates in the vicinity of multiple physical objects—defined as discrete and movable objects in a maze or open field environment (Burke, Maurer, et al., 2012; Deshmukh, Johnson, & Knierim, 2012). Neurons in the rat PER can also be sensitive to the prior presentation of objects. These neurons typically decrease their firing rate for repeated exposures to the same stimulus (“repetition suppression,” Zhu & Brown, 1995; Young et al., 1997; Brown & Banks, 2015; von Linstow Roloff et al., 2016, Ahn, Lee, & Lee, 2019). Support comes from immediate early gene studies that show increased *c-fos* expression in PER upon exposure to new objects (Zhu, Brown, McCabe, & Aggleton, 1995). This increase was specific to object novelty, as a new environment increased immediate early gene expression only in HPC and not PER. Interestingly, rearranging familiar objects led to *c-fos* activations in PER but not in HPC (Aggleton & Brown, 2006; Zhu et al., 1995; Zhu, McCabe, Aggleton, & Brown, 1997). However, repetition suppression is not commonly observed in object exploration in an open field (Burke, Hartzell, Lister, Hoang, & Barnes, 2012; von Linstow Roloff et al., 2016). It has been argued that novelty signals could be fleeting and average out during the relatively long bouts of exploration seen in object recognition tasks, compared to the short and more controlled presentations on stimulus display screens. Another factor influencing repetition suppression effects in PER could lie in reward contingencies (von Linstow Roloff et al., 2016).

To gain insights in the mnemonic and perceptual roles of the PER, Ahn and Lee (2017) recorded PER neurons while rats categorized visual stimuli on a touchscreen as being an egg or a toy figure. Rats were rewarded after correctly categorizing a presented stimulus by touching a disk on the category-associated left or right side when the stimulus disappeared. Morphing the presented stimuli to achieve various degrees of similarity enabled the authors to quantify whether activity of PER neurons correlated with continuous changes in sensory features of the stimulus, or rather with the animal's perceptual categorization (egg or toy template). In line with a dual role of PER in

memory and perception, nearly equal proportions of single units represented the perceptual stimulus feature (degree of warping) and stimulus category (egg or toy).

2.2.2 | Neural correlates in primates

Experiments in macaques have addressed how associations between different visual stimuli are encoded in the PER (Fujimichi et al., 2010; Naya, Yoshida, & Miyashita, 2003; Naya, Yoshida, Takeda, Fujimichi, & Miyashita, 2003; Sakai & Miyashita, 1991). In these studies, monkeys were trained to memorize pairs of images. A trial started with the presentation of a cue picture, followed by a delay of a few seconds in which no stimulus was presented. After the delay, two different pictures were presented on the same screen. The monkeys were trained to touch the learned paired associate picture and ignore the distractor picture. Some neurons responded selectively to only one picture of the pair, and showed ramping activity during the delay when the preferred picture was about to be shown as the paired associate. This increase in activity suggested anticipation and recall of the paired image (Sakai & Miyashita, 1991). Other PER neurons responded equally to individual pictures that were paired to each other. These neurons did not distinguish between the two stimuli, but instead only coded the paired stimulus combination (Fujimichi et al., 2010). Individual neurons in the PER thus represented paired stimuli as single integrated items. Coding of stimulus associations in PER can emerge a few days after a stimulus pairing has been learned, suggesting a role for PER in long-term memory formation (Erickson & Desimone, 1999).

Regarding the human PER, functional neuroimaging studies provide evidence that generally supports and extends the findings from animal and human lesion studies. Supporting evidence for a special bias of the human PER cortex to process item (object and often also face) information is reported throughout the literature (for reviews, see, e.g., Graham et al., 2010; Ranganath & Ritchey, 2012). Related to this type of information, PER activity was functionally modulated when multiple types of information needed to be associated with an item, when new items were encountered, when items had to be (mostly visually) discriminated or when item-related information had to be retrieved (Awipi & Davachi, 2008; Barense et al., 2007; Barense, Henson, & Graham, 2011; Barense, Henson, Lee, & Graham, 2009; Bowles et al., 2010; Devlin & Price, 2007; Diana, Yonelinas, & Ranganath, 2010; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Lee et al., 2006; Lee, Scahill, & Graham, 2008; Martin et al., 2011; Martin, Cowell, Gribble, Wright, & Köhler, 2016; Montaldi, Spencer, Roberts, & Mayes, 2006; Mundy et al., 2013; O'Neil, Barkley, & Köhler, 2013; Staresina & Davachi, 2008; Staresina, Duncan, & Davachi, 2011). O'Neil et al. (2012) demonstrated differential functional connectivity profiles of the PER, depending on whether a task required more perceptual or mnemonic judgments on stimulus material. In the memory task the PER was functionally connected to, a.o. ventrolateral prefrontal, anterior cingulate and posterior cingulate cortices, whereas in the perceptual task functional connectivity was stronger to, a.o. fusiform regions and dorsolateral prefrontal cortex

(O'Neil et al., 2012). Indeed, recent accounts of human PER function attempt to move away from a process-specific dissociation of function and rather attribute a specific representational role for the PER in object-related information that may serve memory or perception, depending on task requirements (Bastin et al., 2019; Bussey & Saksida, 2005, 2007; Graham et al., 2010; Murray, Bussey, & Saksida, 2007).

Overall, the PER appears to be particularly engaged by complex stimulus material that entails multiple dimensions. Not only the association of attributes (e.g., an adjective associated with an object) and multisensory information (e.g., auditory, visual or tactile features of an object), but also information on the relationship to other objects and object familiarity over the subject's lifetime can increase functional PER activity in humans (Bowles, Duke, Rosenbaum, McRae, & Köhler, 2016; Duke, Martin, Bowles, McRae, & Köhler, 2017; Holdstock, Hocking, Notley, Devlin, & Price, 2009; Staresina & Davachi, 2008; Taylor et al., 2006; Taylor, Stamatakis, & Tyler, 2009; Zeithamova, Manthuruthil, & Preston, 2016). Again, this reflects the richness and multidimensionality of the object information assembled in the PER, which can be utilized for both perceptual and mnemonic functions.

3 | PERIRHINAL CORTEX: PROCESSING SPATIAL CONTEXT AND TASK CONTINGENCIES

3.1 | Lesion studies

Over the last decade, lesion studies in rats have provided convincing evidence for the involvement of PER in contextual memory. For instance, the PER was shown to be important for the memorization of contextual fear because bilateral PER lesions reduce freezing behavior in prelesion conditioned spatial contexts, but not in other types of fear conditioning (Bucci, Phillips, & Burwell, 2005; Bucci, Saddoris, & Burwell, 2002; Kent & Brown, 2012). Moreover, Jo and Lee (2010) demonstrated that excitotoxic PER lesions severely impair rats in the acquisition of an object discrimination task that required the correct identification of an object's location (in a multiarm maze). The acquisition of object-discrimination in itself (i.e., independent of location) was completely spared (see also Bussey, Wise, & Murray, 2001). Here, the acquisition of object discriminations might have been guided by differences in simple features, thereby alleviating the loss of PER.

While at least some consensus exists for a contribution of PER to contextual memory in rats, rodent studies often report only mild or no effects of PER lesions in allocentric spatial reference tasks (Liu & Bilkey, 2001; Ramos, 2013; Wiig & Bilkey, 1994). Ramos and Vaquero (2005) reported no effect of PER lesions on the acquisition and short-term retention (24 hr) in an allocentric navigation task. However, PER lesioned rats were impaired in retention and relearning of the task after long delays (74 days). This points toward a potential role of PER in long-term allocentric spatial memory. Abe, Ishida, Nonaka, and Iwasaki (2009) also reported that PER lesions impaired previously learned place discriminations in addition to object discrimination.

Postlesion acquisition of new place discriminations was intact, indicating that this functionality is not strictly dependent on the PER, but might only rely on it under certain conditions. Additionally, rats might adapt their navigation strategies after PER lesions. Indeed, PER lesions may bias spatial processing toward egocentric navigation strategies. Ramos (2017) investigated how PER lesions affect spatial strategies in rats navigating to a baited goal arm in a plus maze. In two versions of this task, the goal arm could be initially found by using both allocentric and egocentric navigation strategies. In the first version of the task, the animals could use an alternative egocentric strategy by making body turns at maze junctions instead of allocentric orientation. In the second experiment, rats could use intramaze stimuli such as sandpaper covered floors for egocentric navigation, as well as a large constellation of distal landmarks as allocentric reference points. After task acquisition, navigation strategies were tested by rotating the maze or intramaze cues so that allocentric navigation was required to find the reward. Healthy control rats mainly used allocentric strategies to navigate to the goal in both versions of the task. By contrast, PER lesioned animals predominantly used non-allocentric strategies. This aligns with a role for PER in allocentric spatial processing and, by the same token, in the integration of different, spatially distributed stimuli into a representation of spatial configuration. Even though PER may facilitate allocentric strategies, it is not unconditionally required for allocentric spatial memory in rats, because other studies report no effect of PER lesioning in allocentric tasks (Liu & Bilkey, 2001; Ramos, 2013; Wiig & Bilkey, 1994). Lesion studies thus indicate that PER is recruited for some specific forms of spatial navigation, but we are not aware of a study that demonstrates a general necessity of PER for spatial navigation.

To our knowledge, spatial processing under focal PER lesions in humans and non-human primates has not been systematically studied to date. However, perseverance of scene discrimination is reported when the HPC, but not the PER, is affected by dementia-related pathology in humans (see Graham et al., 2010 for an overview).

3.2 | Neural correlates

3.2.1 | Neural correlates of spatial context in rats

Important empirical evidence for a more complex interaction between the two streams (“what” vs. “where”) is the presence of spatial firing fields in LEC for locations in which rats previously encountered an object (Deshmukh & Knierim, 2011). These firing fields have been shown to be stable for multiple days after an object is removed and thus code for the memorized object location rather than the object itself (Tsao, Moser, & Moser, 2013). This is reminiscent of a mixture of spatial and object coding within the LEC. Single units recorded from PER of rats in an open field or circular arena also show elevated firing rates around one or multiple objects. When an object is added or moved to another location, PER units change their activity patterns to incorporate the changed object, and do not display firing fields on the previous location of an object (Burke, Maurer, et al., 2012; Deshmukh

et al., 2012). Thus, in settings without elaborate task contingencies and in relatively simple environments, PER cells display firing fields locked to objects in the environment but not to (allocentric) spatial locations.

In contrast to studies that did not report spatial coding in PER, Bos et al. (2017) found that 72% of PER units showed activations and deactivations locked to spatial segments of a figure-8 maze. PER units were recorded during a visual discrimination task in which rats were trained to collect a reward on the left or right side-arm of the maze. Visual stimuli were displayed on two screens in front of the middle arm. During each trial the conditioned stimulus was presented on one screen (e.g., the left screen), while the distractor stimulus was presented on the other (i.e., the right). Rats were rewarded for choosing the side-arm that was on the same side as the rewarded stimulus and ignoring the other side arm marked by a distractor stimulus. Proximal tactile cues on the side walls of the maze consisted of rough or smooth sandpaper which were pseudo-randomly exchanged and thus independent of the visual stimuli or side arm. PER neurons displayed sustained activations and deactivations with sharp transitions when the rat navigated from one maze segment to the next. However, they were not affected by choices being correct or incorrect, the spatial location or identity of the visual stimuli, or by the sandpaper structure of the maze walls. These segment-specific responses also occurred when rats ran in a direction opposing the conventional running direction, supporting the notion that these fields were not a pure reflection of acute sensory input. The boundaries of PER firing fields were better locked to task-relevant spatial segments (branch points) than simultaneously recorded CA1 place field activity. These responses indicate a role for PER in spatially bounded segmentation of the environment, potentially based on task contingencies.

Similarly, Keene et al. (2016) reported that a significant proportion of PER cells differentiates between spatial contexts rather than mere objects in a context-guided olfactory association task. Here, rats were trained to dig for reward in one of two cups with scented sand. The cups of sand were positioned in one of two square arenas (contexts) which were linked by an alleyway and with different visual and tactile cues on the walls and floor. The context determined which of the two scented cups was baited with reward. While 16.5% of PER cells differentiated between objects, 29.9% of PER cells differentiated between the two spatial contexts independently of the baited scented objects. Twenty-eight percent of PER neurons were affected by the combination of object and context. Keene et al. (2016) thus demonstrated that neurons in the PER responded to multiple task components, whether they were object related or contextual.

So far, spatial context modulations by PER have only been reported during tasks with clearly defined task contingencies where stimuli, actions and reward were spatially separated (Bos et al., 2017; Keene et al., 2016). When a task context is absent or simple (e.g., foraging in an open field or spontaneous behavior), activity of PER neurons appears to be mainly related to objects in the environment (Burke, Maurer, et al., 2012; Deshmukh et al., 2012). When tasks become more complex PER neurons get involved in segmenting the environment in task-relevant chunks (Bos et al., 2017). Another possibility to explain sensitivity to spatial context is that the degree of

physical segmentation of the context itself affects the degree of spatial correlates in PER. By making use of physical doors, the environments in experiments from Bos et al. (2017) and Keene et al. (2016) were naturally segmented into different spatial chunks. In contrast, in the studies by Burke, Maurer, et al. (2012) and Deshmukh et al. (2012), complex objects were present in environments which were otherwise homogeneous. Here, the most salient proximal features to encode were the objects. Neural segmentation of the environment may not have occurred due to the circular or open field nature of the maze and/or the lack of spatial task constraints. Thus, from these studies it appears plausible that the degree of physical segmentation of the environment and task demands both play a role in the observed spatial-contextual responses of PER neurons.

3.2.2 | Neural correlates of task contingencies

The relevance of specific task contingencies for PER engagement is supported by multiple reports of PER activity modulations by a wide variety of task rules and reward schedules (Ahn & Lee, 2015; Bos et al., 2017; Kreher et al., 2019; Liu & Richmond, 2000; von Linstow Roloff et al., 2016; Young et al., 1997). Eradath et al. (2015) demonstrated that PER cells in the macaque can represent cue-outcome associations and the temporal context in which the association occurs. Macaques were trained to associate 12 out of 24 visual cues with a reward while the other 12 cues predicted a sound (but no reward). A single trial consisted of a sequence of two visual cues and outcome. The first part of the trial occurred according to the learned cue-outcome contingency, whereas in the second part the two types of outcome were randomly provided. PER mainly represented the outcome type (water or sound) contingent on the cue. This representation was dependent on the presentation of visual stimuli, as reward expectancy was not represented by these PER units when rewards were given at predictable time points independently of a visual stimulus. Moreover, PER activity only represented outcome contingency in the trial part where the cue was predictive of reward and not during the randomly rewarded trial epoch, even though the cues during that epoch were previously associated with reward as well. The differentiation started from the onset of the visual cue and remained sustained after reward delivery until the next trial started. This is reminiscent of sustained postreward activations observed in the mPFC, which have been associated with cue-outcome and action-outcome learning (Histed, Pasupathy, & Miller, 2009; Mulder, Nordquist, Örgüt, & Pennartz, 2003). When the order of the trial sequence was reversed, the monkeys started to adapt their behavioral outcome expectation within 3 days (i.e., by displaying anticipatory sucking). However, representations of stimulus-outcome contingencies by PER cells only adapted after 10 days. These results suggest that PER cells represent long-term memorized cue-outcome contingencies and the temporal context in which they occurred, rather than purely an expectation of the outcome or expectation of the visual stimulus. Likewise, the behavior of PER lesioned rats in a task that required weighing of delays against reward size suggests a

similar role of PER in processing choice-outcome contingencies in rodents (Kreher et al., 2019).

3.2.3 | Neural correlates of landmark and scene processing in humans

In humans, the PER (together with other MTL structures) appears to represent prospective goals in a spatial navigation task (Brown et al., 2016). This may also be interpreted as a type of item-related representation. Accordingly, functional evidence from a virtual reality study suggests a role of the human PER in wayfinding based on landmarks (Hartley, Maguire, Spiers, & Burgess, 2003). Note, a recent study that shows particularly the posterior part of PER and the human parahippocampal cortex to be associated with landmark-related object processing (Martin, Sullivan, Wright, & Köhler, 2018). A functional role of the PER specifically in navigation or spatial context has, to our knowledge, not been investigated more extensively in humans. The clear association of the PER with rich and complex object representations does not exclude a PER involvement in any scene processing. Here, scene processing does not relate to navigation directly but instead to the processing of pictures that contain scene information (cf. Berron et al., 2018; Ross, Sadil, Wilson, & Cowell, 2018). While such stimuli clearly engage spatial networks in humans, one may also argue that these scene pictures may be processed as one entity or object. In fact, integration of objects with their context is a key step in interpreting complex visual scenes. Additionally, any evidence about PER function and bias for a specific type of information is influenced heavily by task design. For instance, some fMRI studies report PER activity in relation to scenes by comparing functional activity in PER with a baseline condition (Berron et al., 2018; Ross, Sadil, Wilson, & Cowell, 2018). However, when they compared object with scene conditions, more PER activity in the object condition was shown. Based on human imaging studies we may conclude that the PER is biased toward object processing, and that its involvement in landmark-based wayfinding and scene processing cannot be excluded.

The abovementioned results, mainly from animal studies, indicate that activity patterns from PER neurons reflect more than object recognition signals or object percepts alone. Instead, the PER supports a much broader variety of representations that seem to be dependent on the cognitive task at hand. This coheres with the attribution of a role in semantic meaning to the human PER, as we outline in the following section.

4 | A SYNTHESIS OF THE OBJECT VERSUS SPATIAL PROCESSING VIEWS OF THE PERIRHINAL CORTEX

Even though two main functional pathways have been previously delineated—one consisting of the PER-LEC and the other of the POR-MEC network, associated with object and spatial coding, respectively—it has become clear that this dissociation falls short of

fully capturing the functional role of individual structures such as the PER. The foregoing overview points to the importance of the PER in processing complex and ambiguous stimuli rather than processing any object per se; processing sensory information from simple objects can occur without causal dependence on the PER. Additionally, neurons in the PER can represent a wide variety of learned constructs such as spatial context, temporal context and task contingencies (Ahn & Lee, 2015; Bos et al., 2017; Eradath et al., 2015; Keene et al., 2016; Liu & Richmond, 2000; von Linstow Roloff et al., 2016; Young et al., 1997). The modulation of PER by task contingencies can be understood by taking into consideration the dense anatomical connectivity between PER and motivational structures such as the ventral tegmental area, ventral striatum, amygdala, and orbitofrontal cortex (Figure 1; Agster et al., 2016; McIntyre, Kelly, & Staines, 1996; Witter & Groenewegen, 1986; Pikkariainen & Pitkänen, 2001). The reciprocal functional and anatomical connections between PER, medial prefrontal and orbitofrontal cortex likely convey information on task rules and predicted value of cues, action, and context (Agster & Burwell, 2009; Burwell & Amaral, 1998a; Deacon, Eichenbaum, Rosenberg, & Eckmann, 1983; Delatour & Witter, 2002; McIntyre et al., 1996; Rusu & Pennartz, 2020; Sesack, Deutch, Roth, & Bunney, 1989; van Wingerden, Vinck, Lankelma, & Pennartz, 2010a, 2010b).

Over recent years, it has become clear that there is ample crosstalk between the traditional “what” and “where” streams. PER is reciprocally connected to the LEC, but also receives projections from the “where” pathway predominantly through the POR (Burwell, 2000; Burwell & Amaral, 1998a; Burwell & Amaral, 1998b). POR additionally projects to the MEC and to the dorsolateral LEC (Burwell, 2000; Burwell & Amaral, 1998a; Burwell & Amaral, 1998b; Doan et al., 2019; Kerr et al., 2007). The POR receives modest projections from the presumed “what” pathway through the PER and LEC (Burwell, 2000; Burwell & Amaral, 1998a; Burwell & Amaral, 1998b; Kerr et al., 2007). Thus, the parahippocampal–hippocampal organization includes numerous cross-connections between the presumed “where” and “what” pathways (Figure 1; cf. Burwell, 2000; Nilssen et al., 2019; van Strien et al., 2009). Additionally, PER has direct and reciprocal connections with CA1 and subiculum (similarly to POR, although mirroring their distal/proximal CA1 target axis; Liu & Bilkey, 1996; Naber et al., 2000; Agster & Burwell, 2013). Furthermore, the crosstalk is evident from spatial firing patterns that have been found in the LEC (Connor & Knierim, 2017; Deshmukh & Knierim, 2011; Knierim et al., 2014; Neunuebel, Yoganarasimha, Rao, & Knierim, 2013; Yoganarasimha, Rao, & Knierim, 2011) and the PER responses related to spatial context (see above; Keene et al., 2016; Bos et al., 2017). Finally, ablating PER reduces HPC place field stability across delays and reduces modulation of place cells by movement (Muir & Bilkey, 2001, 2003).

An alternative hypothesis about the difference between the PER–LEC and POR–MEC pathways (instead of object vs. location) is a distinction in coding for proximal versus distal spatial cues, respectively (Knierim et al., 2014; Neunuebel et al., 2013). Activity patterns of LEC neurons preferably rotate with local cues, while activity patterns of MEC neurons follow spatial rotations of distal cues. However, to date, no double cue rotation studies have been performed in combination

with recordings from PER. Moreover, as for the “what” versus “where” dissociation, the proximal versus distal dichotomy cannot account for spatial-contextual coding by the PER (Ahn & Lee, 2015; Bos et al., 2017; Eradath et al., 2015). Others have proposed that PER is mainly engaged in processing fine-grained information of relevant stimuli (Burke et al., 2018). This proposal aligns with most abovementioned deficits in processing task-relevant and complex stimuli following PER lesions. It is, however, somewhat difficult to reconcile with the irrelevance of intact PER for very precise (detailed) perceptual discriminations based on individual sensory features (Eacott et al., 2001; Feinberg et al., 2012; Kent & Brown, 2012; Kholodar-Smith et al., 2008; Lindquist et al., 2004; Ramos, 2014, 2016).

Overall, the functional role of the PER appears to mainly be related to the complexity of task-relevant information. The rodent and monkey literature in particular emphasize the importance of the PER for the representation of complex stimuli in which diverse spatial-contextual features have to be integrated, but not of simple stimuli. One way to reconcile the results on object- versus spatial-contextual coding is by building on the proposal that the PER is recruited when different features can be merged perceptually or conceptually into a single entity (Bang & Brown, 2009; Bussey & Saksida, 2007; Ho & Burwell, 2014; Kent & Brown, 2012; Kent, Hvoslef-Eide, Saksida, & Bussey, 2016; Kholodar-Smith et al., 2008; Ranganath & Ritchey, 2012; Suzuki & Naya, 2014). Combining different features into a single entity is referred to as unitization (Graf & Schacter, 1989), and was initially proposed to be a main function of the PER in the context of fear conditioning (Kent & Brown, 2012). Adopting this broader function of the PER in unitization captures the traditional object-oriented nature of PER, but also PER response patterns emerging in specific spatial task contexts.

This functionality definition circumvents an overly strict distinction between spatial and object processing which is difficult to maintain conceptually. For instance, is a house, street or neighborhood within a city considered to be “spatial” or do these entities constitute an “object” figuring in a “what” pathway? In other words, the distinction between spatial descriptors and objects is not conceptually unambiguous and depends on the cognitive task at hand. Within a homogeneous open field or linear environment, there are no discrete spatial “chunks,” standing out a priori. In increasingly complex environments, sensory discriminants can be used to parse the complex space into simple chunks. Spatial processing may then benefit from unitization by integrating small subspaces of an environment into larger units, corresponding to large spatial fields (Bos et al., 2017). This is illustrated by the integration of assemblies of buildings and landmarks into larger chunks—for example, residential blocks, streets or neighborhoods—which can be subsequently used to avoid the curse of dimensionality when choosing an action policy for complex tasks (Pezzulo, van der Meer, Lansink, & Pennartz, 2014). Unitization can also be applied to other types of information processing, such as the processing of discrete events in time which have a shared behavioral relevance (Figure 2).

This reconceptualization of the PER can be extended to the interpretation of results from human studies. Indeed, some fMRI and lesion studies in humans as well as the computational model by Bussey and

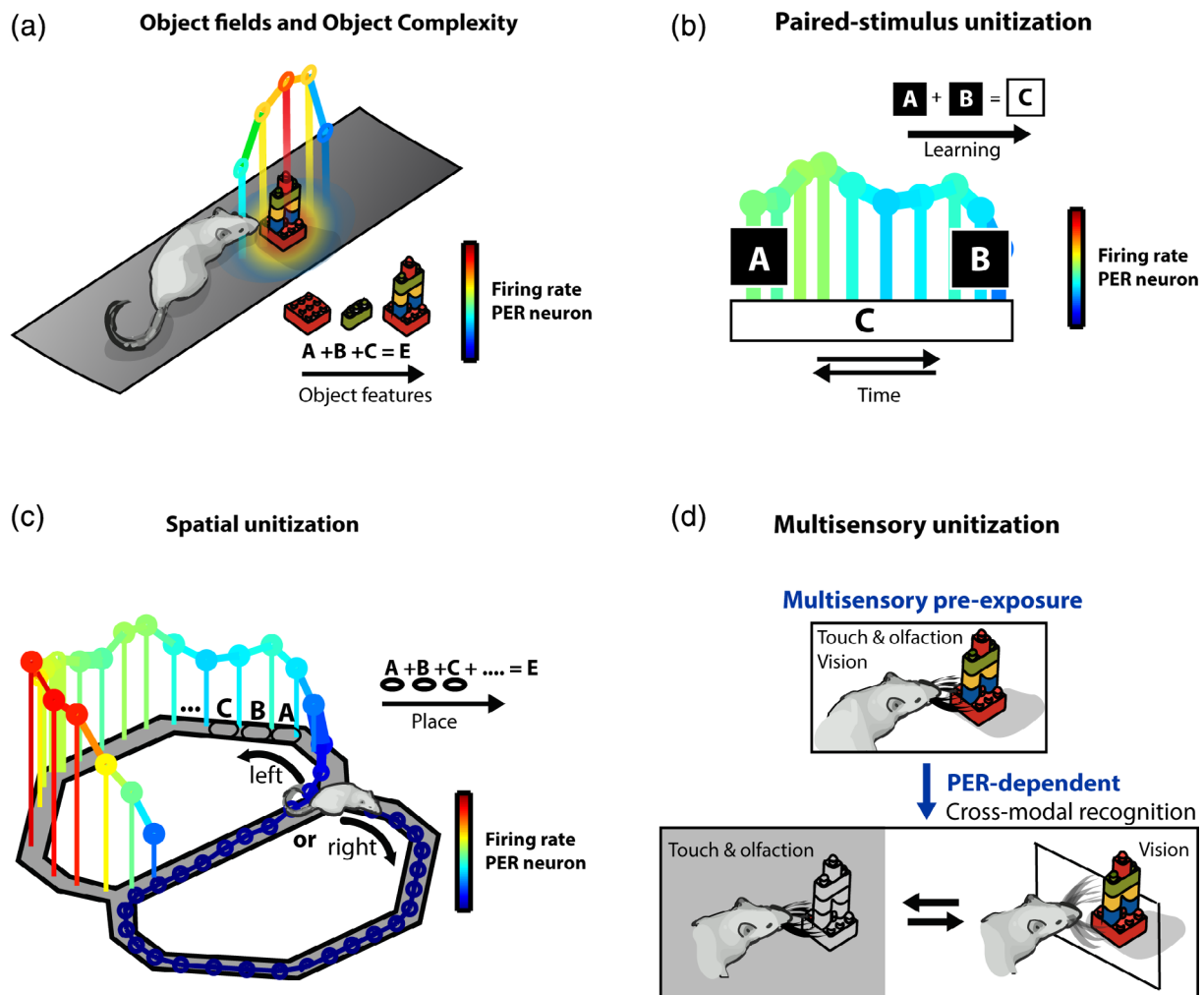


FIGURE 2 Task-dependent unitization in the perirhinal cortex. (a) Schematic illustration of reported single unit activity related to object presence in an open field or circular arena (Burke, Hartzell, et al., 2012; Burke, Maurer, et al., 2012; Deshmukh et al., 2012). PER is mainly necessary in spontaneous object recognition tasks for complex objects, but less for simple ones. This suggests a functional role of PER for the unitization of complex object features (Bartko et al., 2007; Norman & Eacott, 2004; Ramos, 2014, 2016). (b) During a visual paired-associate task, neurons in the macaque PER encode the learned pairings between stimuli in a unitized manner over time (Fujimichi et al., 2010). (c) PER neurons of rats performing a visual discrimination task on a figure-8 maze display sustained responses associated with different maze segments (Bos et al., 2017). This suggests a spatial unitization relative to finer forms of spatial coding as found in dorsal hippocampal area CA1. (d) A reversible lesion study demonstrated that multimodal preexposure increases the importance of PER in later cross-modal object recognition. This could potentially result from the formation of a unitized (multisensory) representation of the object (Jacklin et al., 2016)

Saksida et al. (2007) point to the idea that feature ambiguity can be solved efficiently by unitization. Furthermore, functional activity changes in the PER indicate unitized representations in that region (Bussey & Saksida, 2007; Cowell, Bussey, & Saksida, 2006; D'Angelo, Noly-Gandon, Kacollja, Barense, & Ryan, 2017; Delhaye, Tibon, Gronau, Levy, & Bastin, 2018; Diana et al., 2010; Fujimichi et al., 2010; Haskins, Yonelinas, Quamme, & Ranganath, 2008; O'Neil et al., 2013; Rubin, Chesney, Cohen, & Gonsalves, 2013; Taylor et al., 2009). Still, directly supporting evidence is mixed. The PER was more functionally active when unitization of words had to be carried out, for example, in a condition where compound words had to be explicitly built versus a condition in which single words had to be entered into an associative sentence (Haskins et al., 2008). PER damage affected

performance in tasks that benefit from unitization of stimulus components (Delhaye, Bahri, Salmon, & Bastin, 2019). Furthermore, adopting a unitization strategy (i.e., encoding information by creating binding relations between elements) facilitated performance of amnesic patients with hippocampal damage in an associative memory paradigm (D'Angelo, Kacollja, Rabin, Rosenbaum, & Ryan, 2015). However, in another study, the unitization of visual stimuli was not directly associated with a BOLD increase in PER activity (Staresina & Davachi, 2010). In this study, participants had to encode pictures of objects. In some conditions, these objects were displayed as being cut into two or four pieces and arranged such that they did not appear as a coherent object because each piece was attached and tilted toward the sides of the screen. In this condition, the objects needed to be visually

integrated. While PER activity parametrically increased when more item-related information was encoded, the demand of the unitization condition (e.g., whether the item was cut in multiple pieces) did not modulate PER activity. The authors speculate as to whether the PER may be involved in the unitization process itself or whether the PER exploits other functions using unitized representations.

We note that there may be differences between mere perceptual, imagery-based and conceptual unitization (Rubin et al., 2013; Staresina & Davachi, 2010). In Staresina and Davachi's experiment, participants needed to form perceptual units by moving the pieces of objects mentally together (i.e., using visual imagery); however, no new concept was created (see also Delhaye et al., 2019). In contrast to such unitization by imagery-from-perception, Haskins et al. (2008) required participants to unitize the meaning of two words and thereby form a new conceptual entity (e.g., "book" and "worm" becomes "bookworm"). The latter thus refers to a higher-level cognitive task that unitizes information by attributing (new) meaning. Presumably, the human PER is specifically involved in the latter. Indeed, human fMRI studies on the PER stress its particular involvement when semantic meaning is relevant (for a related conceptual model see (Miyashita, 2019). Specifically, the medial human PER (segmented following Taylor & Probst, 2008; but note Ding & van Hoesen, 2010; Berron et al., 2017) may help to dissociate confusable objects, for example, objects that share perceptual features but also meanings (Kivisaari, Tyler, Monsch, & Taylor, 2012). These results align with a stream of human data indicating a PER function in semantic cognition. Conceptual learning, semantic processing and semantic priming have been associated with PER functional activity and PER damage leads to an inability in making fine semantic discriminations (Bowles et al., 2016; Bruffaerts et al., 2013; Clarke & Tyler, 2014, 2015; Dew & Cabeza, 2013; Kivisaari et al., 2012; Ranganath & Ritchey, 2012; Taylor et al., 2006; Tyler et al., 2004; Wang, Ranganath, & Yonelinas, 2014; Wright, Randall, Clarke, & Tyler, 2015). For example, Bruffaerts et al. (2013) presented words that were previously clustered semantically and whose semantic distances were determined. Interestingly, when analyzing multivariate representational similarities of the fMRI voxel patterns evoked by presented words, the PER reflected the semantic distances. That is, words with a more distinct meaning were associated with a multivoxel activity pattern that was likewise more distinct and vice versa. This ability to make semantic discriminations is compromised by PER damage and related to PER functional activity in healthy humans (Tyler et al., 2004). Moreover, prior exposition to a semantically similar word usually improves performance on a memory task that uses conceptual retrieval cues ("conceptual priming"). Conceptual priming is impaired by extended MTL lesions that incorporate the PER and, in healthy participants, conceptual priming is associated with an increase in PER activity (Wang et al., 2014; Wang, Lazzara, Ranganath, Knight, & Yonelinas, 2010). These human data add to PER functions in unitization by suggesting a multidimensional role in integrating conceptual information attributed to encountered objects.

It may appear as a contradiction that semantic discrimination as well as unitization are attributed to PER function. Upon closer examination, however, both functions are in fact well compatible and may

be based on the same underlying principle: unitization of information may eventually support fine semantic discrimination (Bastin et al., 2019; Cate & Köhler, 2006; Kent et al., 2016). For instance, semantically similar items also exhibit feature ambiguity (in semantic terms or perceptual terms). Unitization integrates diverse information into one entity that exceeds the amount of integration expressed by its parts (e.g., "white house" contains more information than "white" and "house" separately). This greater specificity may enable better fine discrimination. However, the rules by which certain elements are lumped together still have to be determined and may relate to current task goals. It remains to be examined whether the PER is indeed involved in these higher-level unitization processes or rather uses unitized representations for further processing.

5 | DISCUSSION

Although neural correlates of object recognition and familiarity have been documented in rodents, primates and humans, empirical evidence also points toward a contribution of PER in associating and unitizing a wide variety of other types of task-relevant information. Nonetheless, there still exists uncertainty on the extent and precise conditions of PER contributions to various types of integration. Apparent inconsistencies across the PER literature may be related to the influence of task demands on PER activity. Bos et al. (2017), for instance, also found object responses besides the previously reported spatial responses (sometimes even of the same cell). The degree to which PER codes for object or spatial information may thus greatly vary from one task to the other, in line with a more general role in unitizing meaningful entities. Reported inconsistencies between empirical results from studies investigating the PER might also partly be attributable to differences between targeted PER subregions, or in human fMRI to averaging over different subdivisions. Differences in functional and anatomical connectivity profiles between area 36 and 35 have been described in rodents and monkeys (Burwell, 2001; Burwell et al., 1995; Burwell & Amaral, 1998a; Burwell & Amaral, 1998b; Deacon et al., 1983; Furtak et al., 2007). In fact, Fujimichi et al. (2010) reported an increasing strengthened integration of two paired visual stimuli when going up the cortical hierarchy of the macaque PER, leading from area 36 to area 35. Hints for a functional gradient also exist in humans (Kafkas et al., 2017; Liang, Wagner, & Preston, 2013; Litman, Awipi, & Davachi, 2009; Zhuo et al., 2016). Additionally, differential susceptibility for neurodegeneration (tau pathology) is evident in more lateral PER versus the transition between PER and EC (taking into account the variability in anatomical nomenclature; Braak & Braak, 1991; Kaufman, del Tredici, Thomas, Braak, & Diamond, 2018; Berron et al., 2019; Maass et al., 2019). Accurate segmentation of PER in human fMRI studies, particularly the delineation of the border between area 35 and 36, is challenging (Braak & Braak, 1991; Ding & van Hoesen, 2010; Kivisaari et al., 2012). In human fMRI, this border is often defined by the collateral sulcus that exploits a considerable variety in anatomical expression between individuals (and also hemispheres; Ding & van Hoesen,

2010). More precise studies on human PER function are expected as only recently methodological advances have been made in high-resolution imaging to segment the structure with a fundamentally higher level of detail, also delineating PER subdivisions (Berron et al., 2017).

Irrespective of the anatomical subdivisions within the PER, this cortical region is thought to act as a transition or gateway area between the neocortex and hippocampal system. However, instead of being a passive gateway, the PER is often portrayed as an “inhibitory wall,” determining which neocortical information is conveyed to the hippocampal system via the LEC (Biella, Uva, & de Curtis, 2001, 2002; de Curtis & Paré, 2004; Martina, Royer, & Paré, 2001; Nilssen et al., 2019; Pelletier, Apergis, & Paré, 2004; Willems, Wadman, & Cappaert, 2016). This gating mechanism has not been widely investigated in relation to its integrative or unitizing functions. Convergent input from different distant regions may be required to reduce local inhibition in the PER to allow response transmission from the PER to the LEC and HPC (de Curtis & Paré, 2004; Unal, John, & Paré, 2012; Nilssen et al., 2019; see also below). This gating pattern may facilitate task-dependent integrative functions of PER required for both object recognition and spatial-contextual processing. To select which task-relevant information is transferred to the hippocampal system, a gating system such as PER needs information on, for instance, which elements from the sensorium belong together and are collectively predictive of outcome (e.g., reward) and which do not. In that sense, task-relevant mnemonic gating without any form of unitization seems difficult to realize. The interactions between gating and execution of unitizing operations in PER remain to be investigated, as well as how PER gating and firing may depend on hippocampal feedback, which in behaving animals may be expressed in phase locking of PER neurons to the hippocampal theta rhythm (Ahn et al., 2019; Bos et al., 2017).

The gating property of the PER may provide an intrinsic mechanism for the integrative PER functions, but does not directly explain observed differences between anterograde and retrograde memory disruptions after PER lesions. For instance, PER-lesioned rats were impaired in previously learned object discriminations (retrograde amnesia) but could relearn to discriminate between new objects after the lesions (Jo & Lee, 2010). Surprisingly, however, the same rats were unable to relearn new object-place associations. Similarly, multisensory object preexposure causes later familiarity-based recognition to be more dependent on the PER (Jacklin et al., 2016). These lesion effects indicate that stored representations are often lost after PER lesions, but that relearning can take place, possibly based on simpler (non-ambiguous, e.g., luminosity- or contrast-based) sensory features. Intriguingly, retrograde loss of object-place associations due to PER lesions could be compensated after some days of retraining, whereas new object-place associations could not be acquired. It has been proposed that memorized associations are encoded by distributed cortical assemblies across different cortical regions, which are recruited during successful memory retrieval. The ability to relearn lost associations between objects and locations after PER lesioning, but not to gain new ones, hints at assemblies outside the PER being sculpted by PER activity during learning (also see Doron et al., 2020).

The importance of PER for storing unitized representations raises questions about the underlying computational mechanisms. In this respect we can advance two hypotheses which may account for unitization of more elementary representations. First, it has been proposed before that the parahippocampal–hippocampal system may harbor plastic, recurrent networks that may implement autoassociative memories with pattern-completing capacities (e.g., in area CA3; Hopfield, 1982; Treves & Rolls, 1992; Nakazawa et al., 2002; Grande et al., 2019) as well as pattern-separating networks (especially associated with the dentate gyrus; Treves & Rolls, 1992, Leutgeb, Leutgeb, Moser, & Moser, 2007; Neunuebel & Knierim, 2012; Berron et al., 2016). Autoassociative memories are conventionally rendered as simple, amodal patterns and can be fully retrieved by offering partial cue information. We propose that their active reinstatement in, for example, HPC leads to information transmission to downstream areas including LEC and PER, where multiple simple representations may be merged into more complex ones, possibly involving acute bottom-up input from the sensory neocortices. Second, unitization can also be understood as an extended form of predictive processing, based on the tenet that lower sensory cortices reciprocally interact with higher areas to generate predictive representations as a way of modeling the causes of sensory input (Friston, 2005; Pennartz, Dora, Muckli, & Lorteije, 2019; Rao & Ballard, 1999). Whereas primary sensory cortices may be concerned with modeling causes of simple sensory patterns (e.g., a local patch with an oriented grating in the visual field), we hypothesize that higher sensory areas may interact with PER and other parahippocampal structures to integrate low-level predictions into high-level representations that combine features within and across modalities (Olcese, Oude Lohuis, & CMA, 2018; Struckmeier et al., 2019). These unitized representations may both influence, and be influenced by, hippocampal patterns characterized by a yet stronger form of invariance, expressed in allocentric and conceptual representations (Buzsáki & Moser, 2013; O'Keefe & Dostrovsky, 1971; Pennartz, 2015; Quiroga, 2012). We stress that these two computational hypotheses are not mutually exclusive and that PER may harbor additional computational functions, such as novelty filtering (Haltsonen, Jalanko, Bry, & Kohonen, 1978). Returning to the “gating” function of the PER, both computational paradigms allow to hypothesize that unitized representations, stored as such in the PER and its closely connected structures, may be evoked and reinstated when sufficient bottom-up sensory evidence is presented through lower-level cortical areas to allow completion of the unitized pattern, which then acts as a prerequisite for further transmission into the hippocampal system. Furthermore, both the associative memory-merging and predictive processing schemes are well compatible with additional Reinforcement Learning, the effects of which may reach the PER via, for example, mesencephalic dopaminergic, prefrontal, and amygdaloid structures, putatively relying on glutamatergic and/or dopaminergic transmission (Pennartz, 1997; Tomás Pereira et al., 2016). These computational hypotheses will require further development by multiarea computational modeling as well as empirical testing.

In conclusion, experiments addressing the functional role of PER across different species and behavioral paradigms strongly suggest a

function for the PER in representing different types of information as unitized entities, thereby reconciling the object- and space-processing views on PER. Rodent work indicates that the PER is primarily object-oriented in the absence of task demands, but also emphasizes that PER can support representations of spatial context, task contingencies and objects associated with both of these. Neurophysiological studies in macaques further support the notion that the PER unitizes sensory information into meaningful perceptual and conceptual entities, as illustrated by tasks for solving visual feature ambiguity, and by neural representations of learned pairings of visual stimuli or stimulus-outcome items in the PER. Finally, studies in humans underline that here the PER has become specialized in the unitization of items with related semantics. A promising approach to investigate how PER recruitment depends on task demands will be to record PER neuronal activity under different spatial and contextual task demands (e.g., recording the same neurons in different tasks and environments). Other avenues for future research involve reversible and specific inhibition of PER afferents and relating different task-dependent neural correlates to distinct PER circuits. Finally, recent methodological advances in structure segmentations for high-resolution fMRI allow researchers to investigate PER subdivisions separately and examine whether functionality fundamentally distinguishes human PER subdivisions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

- Abe, H., Ishida, Y., Nonaka, H., & Iwasaki, T. (2009). Functional difference between rat perirhinal cortex and hippocampus in object and place discrimination tasks. *Behavioural Brain Research*, *197*, 388–397. <https://doi.org/10.1016/j.bbr.2008.10.012>
- Aggleton, J. P., & Brown, M. W. (2006). Interleaving brain systems for episodic and recognition memory. *Trends in Cognitive Sciences*, *10*(10), 455–463. <https://doi.org/10.1016/j.tics.2006.08.003>
- Agster, K. L., & Burwell, R. D. (2009). Cortical efferents of the perirhinal, postrhinal, and entorhinal cortices of the rat. *Hippocampus*, *19*(12), 1159–1186.
- Agster, K. L., & Burwell, R. D. (2013). Hippocampal and subicular afferents and efferents of the perirhinal, postrhinal, and entorhinal cortices. *Behavioural Brain Research*, *254*, 50–64.
- Agster, K. L., Tomás Pereira, I., Saddoris, M. P., & Burwell, R. D. (2016). Subcortical connections of the perirhinal, postrhinal, and entorhinal cortices of the rat. II. Efferents. *Hippocampus*, *26*(9), 1213–1230. <https://doi.org/10.1002/hipo.2260>
- Ahn, J. R., & Lee, I. (2015). Neural correlates of object-associated choice behavior in the perirhinal cortex of rats. *The Journal of Neuroscience*, *35*(4), 1692–1705. <https://doi.org/10.1523/JNEUROSCI.3160-14.2015>
- Ahn, J.-R., & Lee, I. (2017). Neural correlates of both perception and memory for objects in the rodent perirhinal cortex. *Cerebral Cortex*, *27*, 3856–3868. <https://doi.org/10.1093/cercor/bhx093>
- Ahn, J. R., Lee, H. W., & Lee, I. (2019). Rhythmic pruning of perceptual noise for object representation in the hippocampus and perirhinal cortex in rats. *Cell Reports*, *26*(9), 2362–2376.e4. <https://doi.org/10.1016/j.celrep.2019.02.010>
- Albasser, M. M., Chapman, R. J., Amin, E., Iordanova, M. D., Vann, S. D., & Aggleton, J. P. (2010). New behavioral protocols to extend our knowledge of rodent object recognition memory. *Learning & Memory*, *17*, 407–419. <https://doi.org/10.1101/lm.1879610>
- van Wingerden, M., Vinck, M., Lankelma, J. V., & Pennartz, C. M. A. (2010a). Learning-associated gamma-band phase-locking of action-outcome selective neurons in orbitofrontal cortex. *The Journal of Neuroscience*, *30*, 10025–10038.
- Albasser, M., Cristian, O.-S., Amin, E., Brown, M., Kinnavane, L., & Aggleton, J. (2015). Perirhinal cortex lesions in rats: Novelty detection and sensitivity to interference. *Behavioral Neuroscience*, *129*, 227–243. <https://doi.org/10.1037/bne0000049>
- Awipi, T., & Davachi, L. (2008). Content-specific source encoding in the human medial temporal lobe. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *34*, 769–779.
- Bang, S., & Brown, T. H. (2009). Perirhinal cortex supports acquired fear of auditory objects. *Neurobiology of Learning and Memory*, *92*, 53–62. <https://doi.org/10.1016/j.nlm.2009.01.002>
- Barense, M. D. (2005). Functional specialization in the human medial temporal lobe. *The Journal of Neuroscience*, *25*, 10239–10246.
- Barense, M. D., Gaffan, D., & Graham, K. S. (2007). The human medial temporal lobe processes online representations of complex objects. *Neuropsychologia*, *45*, 2963–2974.
- Barense, M. D., Henson, R. N. A., Lee, A. C. H., & Graham, K. S. (2009). Medial temporal lobe activity during complex discrimination of faces, objects, and scenes: Effects of viewpoint. *Hippocampus*, *20*, 389–401.
- Barense, M. D., Henson, R. N. A., & Graham, K. S. (2011). Perception and conception: Temporal lobe activity during complex discriminations of familiar and novel faces and objects. *Journal of Cognitive Neuroscience*, *23*, 3052–3067.
- Bartko, S., Winters, B., Cowell, R., Saksida, L., & Bussey, T. (2007). Perceptual functions of perirhinal cortex in rats: Zero-delay object recognition and simultaneous oddity discriminations. *The Journal of Neuroscience*, *27*, 2548–2559. <https://doi.org/10.1523/JNEUROSCI.5171-06.2007>
- Bastin, C., Besson, G., Simon, J., Delhayé, E., Geurten, M., Willems, S., & Salmon, E. (2019). An integrative memory model of recollection and familiarity to understand memory deficits. *The Behavioral and Brain Sciences*, *42*, 1–66.
- Berron, D., Schütze, H., Maass, A., Cardenas-Blanco, A., Kuijff, H. J., Kumaran, D., & Düzel, E. (2016). Strong evidence for pattern separation in human dentate gyrus. *Journal of Neuroscience*, *36*(29), 7569–7579.
- Berron, D., Vieweg, P., Hochkepler, A., Pluta, J. B., Ding, S. L., Maass, A., ... Wisse, L. E. M. (2017). A protocol for manual segmentation of medial temporal lobe subregions in 7 tesla MRI. *NeuroImage: Clinical*, *15*, 466–482.

- Berron, D., Neumann, K., Maass, A., Schütze, H., Fliessbach, K., Kiven, V., ... Düzel, E. (2018). Age-related functional changes in domain-specific medial temporal lobe pathways. *Neurobiology of Aging*, *65*, 86–97.
- Berron, D., Cardenas-Blanco, A., Bittner, D., Metzger, C. D., Spottke, A., Heneka, M. T., ... Düzel, E. (2019). Higher CSF tau levels are related to hippocampal hyperactivity and object mnemonic discrimination in older adults. *The Journal of Neuroscience*, *39*, 8788–8797.
- Biella, G., Uva, L., & de Curtis, M. (2001). Network activity evoked by neocortical stimulation in area 36 of the Guinea pig perirhinal cortex. *Journal of Neurophysiology*, *86*, 164–172.
- Biella, G., Uva, L., & de Curtis, M. (2002). Propagation of neuronal activity along the neocortical-perirhinal-entorhinal pathway in the Guinea pig. *The Journal of Neuroscience*, *22*, 9972–9979.
- Bos, J. J., Vinck, M., van Mourik-Donga, L. A., Jackson, J. C., Witter, M. P., & Pennartz, C. M. A. (2017). Perirhinal firing patterns are sustained across large spatial segments of the task environment. *Nature Communications*, *8*, 15602. <https://doi.org/10.1038/ncomms15602>
- Bowles, B., Crupi, C., Mirsattari, S. M., Pigott, S. E., Parrent, A. G., Pruessner, J. C., ... Köhler, S. (2007). Impaired familiarity with preserved recollection after anterior temporal-lobe resection that spares the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 16382–16387.
- Bowles, B., Crupi, C., Pigott, S., Parrent, A., Wiebe, S., Janzen, L., & Köhler, S. (2010). Double dissociation of selective recollection and familiarity impairments following two different surgical treatments for temporal-lobe epilepsy. *Neuropsychologia*, *48*, 2640–2647.
- Bowles, B., Duke, D., Rosenbaum, R. S., McRae, K., & Köhler, S. (2016). Impaired assessment of cumulative lifetime familiarity for object concepts after left anterior temporal-lobe resection that includes perirhinal cortex but spares the hippocampus. *Neuropsychologia*, *90*, 170–179.
- Braak, H., & Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica*, *82*, 239–259.
- Brown, M. W., & Aggleton, J. P. (2001). Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nature Reviews. Neuroscience*, *2*, 51–61.
- Brown, T. I., Carr, V. A., LaRocque, K. F., Favila, S. E., Gordon, A. M., Bowles, B., ... Wagner, A. D. (2016). Prospective representation of navigational goals in the human hippocampus. *Science*, *352*, 1323–1326.
- Brown, M., & Banks, P. (2015). In search of a recognition memory engram. *Neuroscience and Biobehavioral Reviews*, *50*, 12–28. <https://doi.org/10.1016/j.neubiorev.2014.09.016>
- Bruffaerts, R., Dupont, P., Peeters, R., De Deyne, S., Storms, G., & Vandenberghe, R. (2013). Similarity of fMRI activity patterns in left perirhinal cortex reflects semantic similarity between words. *The Journal of Neuroscience*, *33*, 18597–18607.
- Bucci, D. J., Phillips, R. G., & Burwell, R. D. (2000). Contributions of post-rhinal and perirhinal cortex to contextual information processing. *Behavioral Neuroscience*, *114*, 882–894. <https://doi.org/10.1037/0735-7044.114.5.882>
- Bucci, D. J., Sadoris, M. P., & Burwell, R. D. (2002). Contextual fear discrimination is impaired by damage to the postrhinal or perirhinal cortex. *Behavioral Neuroscience*, *116*, 479–488. <https://doi.org/10.1037/0735-7044.116.3.479>
- Buckley, M., & Gaffan, D. (1998). Perirhinal cortex ablation impairs configural learning and paired-associate learning equally. *Neuropsychologia*, *36*, 535–546. [https://doi.org/10.1016/S0028-3932\(97\)00120-6](https://doi.org/10.1016/S0028-3932(97)00120-6)
- Buckley, M., & Gaffan, D. (2006). Perirhinal cortical contributions to object perception. *Trends in Cognitive Sciences*, *10*, 100–107. <https://doi.org/10.1016/j.tics.2006.01.008>
- Buffalo, E. A., Reber, P. J., & Squire, L. R. (1998). The human perirhinal cortex and recognition memory. *Hippocampus*, *8*, 330–339.
- Buffalo, E., Ramus, S., Clark, R., Teng, E., Squire, L., & Zola, S. (1999). Dissociation between the effects of damage to perirhinal cortex and area TE. *Learning & Memory*, *6*, 572–599. <https://doi.org/10.1101/lm.6.6.572>
- Burke, S. N., Maurer, A. P., Hartzell, A. L., Nematollahi, S., Uprety, A., Wallace, J. L., & Barnes, C. A. (2012). Representation of three-dimensional objects by the rat perirhinal cortex. *Hippocampus*, *22*, 2032–2044. <https://doi.org/10.1002/hipo.22060>
- Burke, S. N., Hartzell, A. L., Lister, J. P., Hoang, L. T., & Barnes, C. A. (2012). Layer V perirhinal cortical ensemble activity during object exploration: A comparison between young and aged rats. *Hippocampus*, *22*(10), 2080–2093. <https://doi.org/10.1002/hipo.22060>
- Burke, S. N., Gaynor, L. S., Barnes, C. A., Bauer, R. M., Bizon, J. L., Roberson, E. D., & Ryan, L. (2018). Shared functions of perirhinal and parahippocampal cortices: implications for cognitive aging. *Trends in Neurosciences*, *41*(6), 349–359. <https://doi.org/10.1016/j.tins.2018.03.001>
- Burwell, R., Witter, M., & Amaral, D. (1995). Perirhinal and postrhinal cortices of the rat: A review of the neuroanatomical literature and comparison with findings from the monkey brain. *Hippocampus*, *5*, 390–408. <https://doi.org/10.1002/hipo.450050503>
- Burwell, R., & Amaral, D. (1998a). Perirhinal and postrhinal cortices of the rat: Interconnectivity and connections with the entorhinal cortex. *The Journal of Comparative Neurology*, *391*, 293–321.
- Burwell, R. D., & Amaral, D. G. (1998b). Cortical afferents of the perirhinal, postrhinal, and entorhinal cortices of the rat. *The Journal of Comparative Neurology*, *398*, 179–205. [https://doi.org/10.1002/\(SICI\)1096-9861\(19980824\)398:2<179::AID-CNE3>3.0.CO;2-Y](https://doi.org/10.1002/(SICI)1096-9861(19980824)398:2<179::AID-CNE3>3.0.CO;2-Y)
- Burwell, R. (2001). Borders and cytoarchitecture of the perirhinal and postrhinal cortices in the rat. *The Journal of Comparative Neurology*, *437*, 17–41. <https://doi.org/10.1002/cne.1267>
- Burwell, R. D. (2000). The Parahippocampal region: corticocortical connectivity. *Annals of the New York Academy of Sciences*, *911*, 25–42. <https://doi.org/10.1111/j.1749-6632.2000.tb06717.x>
- Bussey, T. J., Wise, S. P., & Murray, E. A. (2001). The role of ventral and orbital prefrontal cortex in conditional visuomotor learning and strategy use in rhesus monkeys (*Macaca mulatta*). *Behavioral Neuroscience*, *115*(5), 971–982. <https://doi.org/10.1037//0735-7044.115.5.971>
- Bussey, T., & Saksida, L. (2005). Object memory and perception in the medial temporal lobe: An alternative approach. *Current Opinion in Neurobiology*, *15*, 730–737. <https://doi.org/10.1016/j.conb.2005.10.014>
- Bussey, T. J., & Saksida, L. M. (2007). Memory, perception, and the ventral visual-perirhinal-hippocampal stream: Thinking outside of the boxes. *Hippocampus*, *17*, 898–908. <https://doi.org/10.1002/hipo.20320>
- Bussey, T. J., Saksida, L. M., & Murray, E. A. (2002). Perirhinal cortex resolves feature ambiguity in complex visual discriminations. *The European Journal of Neuroscience*, *15*, 365–374. <https://doi.org/10.1046/j.0953-816x.2001.01851.x>
- Buzsáki, G., & Moser, E. I. (2013). Memory, navigation and theta rhythm in the hippocampal-entorhinal system. *Nature Neuroscience*, *16*(2), 130–138. <https://doi.org/10.1038/nn.3304>
- Cate, A. D., & Köhler, S. (2006). The missing whole in perceptual models of perirhinal cortex. *Trends in Cognitive Sciences*, *10*(9), 396–397. <https://doi.org/10.1016/j.tics.2006.07.004>
- Clark, R. E., Reinagel, P., Broadbent, N. J., Flister, E. D., & Squire, L. R. (2011). Intact performance on feature-ambiguous discriminations in rats with lesions of the perirhinal cortex. *Neuron*, *70*, 132–140.
- Clarke, A., & Tyler, L. K. (2014). Object-specific semantic coding in human perirhinal cortex. *The Journal of Neuroscience*, *34*, 4766–4775.
- Clarke, A., & Tyler, L. K. (2015). Understanding what we see: How we derive meaning from vision. *Trends in Cognitive Sciences*, *19*, 677–687.
- Connor, C. E., & Knierim, J. J. (2017). Integration of objects and space in perception and memory. *Nature Neuroscience*, *20*, 1493–1503. <https://doi.org/10.1038/nn.4657>

- Cowell, R. A., Bussey, T. J., & Saksida, L. M. (2006). Why does brain damage impair memory? A connectionist model of object recognition memory in perirhinal cortex. *The Journal of Neuroscience*, *26*, 12186–12197.
- D'Angelo, M. C., Kacollja, A., Rabin, J. S., Rosenbaum, R. S., & Ryan, J. D. (2015). Unitization supports lasting performance and generalization on a relational memory task: Evidence from a previously undocumented developmental amnesic case. *Neuropsychologia*, *77*, 185–200. <https://doi.org/10.1016/j.neuropsychologia.2015.07.025>
- D'Angelo, M. C., Noly-Gandon, A., Kacollja, A., Barense, M. D., & Ryan, J. D. (2017). Breaking down unitization: Is the whole greater than the sum of its parts? *Memory & Cognition*, *45*, 1306–1318.
- de Curtis, M., & Paré, D. (2004). The rhinal cortices: A wall of inhibition between the neocortex and the hippocampus. *Progress in Neurobiology*, *74*, 101–110. <https://doi.org/10.1016/j.pneurobio.2004.08.005>
- Deacon, T., Eichenbaum, H., Rosenberg, P., & Eckmann, K. (1983). Afferent connections of the perirhinal cortex in the rat. *The Journal of Comparative Neurology*, *220*, 168–190. <https://doi.org/10.1002/cne.902200205>
- Delatour, B., & Witter, M. P. (2002). Projections from the parahippocampal region to the prefrontal cortex in the rat: Evidence of multiple pathways. *European Journal of Neuroscience*, *15*(8), 1400–1407. <https://doi.org/10.1046/j.1460-9568.2002.01973.x>
- Delhaye, E., Bahri, M. A., Salmon, E., & Bastin, C. (2019). Impaired perceptual integration and memory for unitized representations are associated with perirhinal cortex atrophy in Alzheimer's disease. *Neurobiology of Aging*, *73*, 135–144.
- Delhaye, E., Tibon, R., Gronau, N., Levy, D. A., & Bastin, C. (2018). Misrecollection prevents older adults from benefitting from semantic relatedness of the memoranda in associative memory. *Aging, Neuropsychology, and Cognition*, *25*, 634–654.
- Deshmukh, S. S., Johnson, J. L., & Knierim, J. J. (2012). Perirhinal cortex represents nonspatial, but not spatial, information in rats foraging in the presence of objects: Comparison with lateral entorhinal cortex. *Hippocampus*, *22*, 2045–2058. <https://doi.org/10.1002/hipo.22046>
- Deshmukh, S. S., & Knierim, J. J. (2011). Representation of non-spatial and spatial information in the lateral entorhinal cortex. *Frontiers in Behavioral Neuroscience*, *5*, 69. <https://doi.org/10.3389/fnbeh.2011.00069>
- Devlin, J. T., & Price, C. J. (2007). Perirhinal contributions to human visual perception. *Current Biology*, *17*, 1484–1488.
- Dew, I. T. Z., & Cabeza, R. (2013). A broader view of perirhinal function: From recognition memory to fluency-based decisions. *The Journal of Neuroscience*, *33*, 14466–14474.
- Diana, R. A., Yonelinas, A. P., & Ranganath, C. (2010). Medial temporal lobe activity during source retrieval reflects information type, not memory strength. *Journal of Cognitive Neuroscience*, *22*, 1808–1818.
- Ding, S.-L., & van Hoesen, G. W. (2010). Borders, extent, and topography of human perirhinal cortex as revealed using multiple modern neuroanatomical and pathological markers. *Human Brain Mapping*, *31*, 1359–1379.
- Doan, T. P., Lagartos-Donate, M. J., Nilssen, E. S., Ohara, S., & Witter, M. P. (2019). Convergent projections from perirhinal and post-rhinal cortices suggest a multisensory nature of lateral, but not medial, entorhinal cortex. *Cell Reports*, *29*(3), 617–627.e7. <https://doi.org/10.1016/j.celrep.2019.09.005>
- Doron, G., Shin, J. N., Takahashi, N., Drüke, M., de Mont, L., Bocklisch, C., ... Larkum, M. E. (2020). Perirhinal input to neocortical layer 1 controls learning. *Science*, *370*(6523).
- Duke, D., Martin, C. B., Bowles, B., McRae, K., & Köhler, S. (2017). Perirhinal cortex tracks degree of recent as well as cumulative lifetime experience with object concepts. *Cortex*, *89*, 61–70.
- Eacott, M. J., Machin, P. E., & Gaffan, E. A. (2001). Elementar and configural visual discrimination learning following lesions to perirhinal cortex in the rat. *Behavioural Brain Research*, *124*, 55–70. [https://doi.org/10.1016/S0166-4328\(01\)00234-0](https://doi.org/10.1016/S0166-4328(01)00234-0)
- Eichenbaum, H., Yonelinas, A. R., & Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annual Review of Neuroscience*, *30*, 123–152.
- Ennaceur, A., & Aggleton, J. (1997). The effects of neurotoxic lesions of the perirhinal cortex combined to fornix transection on object recognition memory in the rat. *Behavioural Brain Research*, *88*, 181–193. [https://doi.org/10.1016/S0166-4328\(97\)02297-3](https://doi.org/10.1016/S0166-4328(97)02297-3)
- Ennaceur, A., & Delacour, J. (1988). A new one-trial test for neurobiological studies of memory in rats. 1: Behavioral data. *Behavioural Brain Research*, *31*, 47–59. [https://doi.org/10.1016/0166-4328\(88\)90157-X](https://doi.org/10.1016/0166-4328(88)90157-X)
- Ennaceur, A., Neave, N., & Aggleton, J. (1996). Neurotoxic lesions of the perirhinal cortex do not mimic the behavioural effects of fornix transection in the rat. *Behavioural Brain Research*, *80*, 9–25. [https://doi.org/10.1016/0166-4328\(96\)00006-X](https://doi.org/10.1016/0166-4328(96)00006-X)
- Eradath, M., Mogami, T., Wang, G., & Tanaka, K. (2015). Time context of cue-outcome associations represented by neurons in perirhinal cortex. *Journal of Neuroscience*, *35*, 4350–4365. <https://doi.org/10.1523/JNEUROSCI.4730-14.2015>
- Erickson, C. A., & Desimone, R. (1999). Responses of macaque perirhinal neurons during and after visual stimulus association learning. *The Journal of Neuroscience*, *19*(23), 10404–10416. <https://doi.org/10.1523/JNEUROSCI.19-23-10404.1999>
- Feinberg, L. M., Allen, T. A., Ly, D., & Fortin, N. J. (2012). Recognition memory for social and non-social odors: Differential effects of neurotoxic lesions to the hippocampus and perirhinal cortex. *Neurobiology of Learning and Memory*, *97*(1), 7–16. <https://doi.org/10.1016/j.nlm.2011.08.008>
- Friston, K. (2005). A theory of cortical responses. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *360*(1456), 815–836. <https://doi.org/10.1098/rstb.2005.1622>
- Fujimichi, R., Naya, Y., Koyano, K. W., Takeda, M., Takeuchi, D., & Miyashita, Y. (2010). Unitized representation of paired objects in area 35 of the macaque perirhinal cortex. *The European Journal of Neuroscience*, *32*, 659–667. <https://doi.org/10.1111/j.1460-9568.2010.07320.x>
- Furtak, S. C., Wei, S., Agster, K. L., & Burwell, R. D. (2007). Functional neuroanatomy of the parahippocampal region in the rat: The perirhinal and postrhinal cortices. *Hippocampus*, *17*, 709–722. <https://doi.org/10.1002/hipo.20314>
- Goodale, M., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences*, *15*, 20–25. [https://doi.org/10.1016/0166-2236\(92\)90344-8](https://doi.org/10.1016/0166-2236(92)90344-8)
- Graf, P., & Schacter, D. L. (1989). Unitization and grouping mediate dissociations in memory for new associations. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *15*, 930–940.
- Graham, K. S., Barense, M. D., & Lee, A. C. H. (2010). Going beyond LTM in the MTL: A synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. *Neuropsychologia*, *48*, 831–853.
- Grande, X., Berron, D., Horner, A. J., Bisby, J. A., Düzel, E., & Burgess, N. (2019). Holistic recollection via pattern completion involves hippocampal subfield CA3. *The Journal of Neuroscience*, *39*(41), 8100–8111. <https://doi.org/10.1523/JNEUROSCI.0722-19.2019>
- Hafting, T., Fyhn, M., Molden, S., Moser, M.-B., & Moser, E. I. (2005). Microstructure of a spatial map in the entorhinal cortex. *Nature*, *436*, 801–806. <https://doi.org/10.1038/nature03721>
- Haltsonen, S., Jalanko, M., Bry, K., & Kohonen, T. (1978). Application of novelty filter to segmentation of speech. ICASSP '78. IEEE International Conference on Acoustics, Speech, and Signal Processing.
- Hartley, T., Maguire, E. A., Spiers, H. J., & Burgess, N. (2003). The well-worn route and the path less traveled: Distinct neural bases of route following and wayfinding in humans. *Neuron*, *37*(5), 877–888. [https://doi.org/10.1016/S0896-6273\(03\)00095-3](https://doi.org/10.1016/S0896-6273(03)00095-3)
- Haskins, A. L., Yonelinas, A. P., Quamme, J. R., & Ranganath, C. (2008). Perirhinal cortex supports encoding and familiarity-based recognition of novel associations. *Neuron*, *59*, 554–560.

- Histed, M. H., Pasupathy, A., & Miller, E. K. (2009). Learning substrates in the primate prefrontal cortex and striatum: Sustained activity related to successful actions. *Neuron*, 63(2), 244–253. <https://doi.org/10.1016/j.neuron.2009.06.019>
- Ho, J. W., & Burwell, R. D. (2014). Perirhinal and postrhinal functional inputs to the hippocampus. In D. Derdikman & J. Knierim (Eds.), *Space, time and memory in the hippocampal formation*. Vienna, Austria: Springer. https://doi.org/10.1007/978-3-7091-1292-2_3
- Holdstock, J. S., Hocking, J., Notley, P., Devlin, J. T., & Price, C. J. (2009). Integrating visual and tactile information in the perirhinal cortex. *Cerebral Cortex*, 19, 2993–3000.
- Holdstock, J. S., Mayes, A. R., Gong, Q. Y., Roberts, N., & Kapur, N. (2005). Item recognition is less impaired than recall and associative recognition in a patient with selective hippocampal damage. *Hippocampus*, 15, 203–215.
- Hopfield, J. J. (1982). Neural networks and physical systems with emergent collective computational abilities. *Proceedings of the National Academy of Sciences of the United States of America*, 79(8), 2554–2558. <https://doi.org/10.1073/pnas.79.8.2554>
- Insausti, R., Herrero, M. T., & Witter, M. P. (1997). Entorhinal cortex of the rat: Cytoarchitectonic subdivisions and the origin and distribution of cortical efferents. *Hippocampus*, 7(2), 146–183. [https://doi.org/10.1002/\(SICI\)1098-1063\(1997\)7:2<146::AID-HIPO4>3.0.CO;2-L](https://doi.org/10.1002/(SICI)1098-1063(1997)7:2<146::AID-HIPO4>3.0.CO;2-L)
- Inhoff, M. C., Heusser, A. C., Tambini, A., Martin, C. B., O'Neil, E. B., Köhler, S., ... Davachi, L. (2019). Understanding perirhinal contributions to perception and memory: Evidence through the lens of selective perirhinal damage. *Neuropsychologia*, 124, 9–18.
- Jacklin, D., Cloke, J., Potvin, A., Garrett, I., & Winters, B. (2016). The dynamic multisensory engram: Neural circuitry underlying crossmodal object recognition in rats changes with the nature of object experience. *The Journal of Neuroscience*, 36, 1273–1289. <https://doi.org/10.1523/JNEUROSCI.3043-15.2016>
- Jo, Y. S., & Lee, I. (2010). Perirhinal cortex is necessary for acquiring, but not for retrieving object-place paired association. *Learning & Memory*, 17(2), 97–103. <https://doi.org/10.1101/lm.1620410>
- Kafkas, A., Migo, E. M., Morris, R. G., Kopelman, M. D., Montaldi, D., & Mayes, A. R. (2017). Material specificity drives medial temporal lobe familiarity but not hippocampal recollection. *Hippocampus*, 27(2), 194–209. <https://doi.org/10.1002/hipo.22683>
- Kreher, M. A., Johnson, S. A., Mizell, J.-M., Chetram, D. K., Guenther, D. T., Lovett, S. D., ... Maurer, A. P. (2019). The perirhinal cortex supports spatial intertemporal choice stability. *Neurobiology of Learning and Memory*, 162, 36–46.
- Kaufman, S. K., del Tredici, K., Thomas, T. L., Braak, H., & Diamond, M. I. (2018). Tau seeding activity begins in the transentorhinal/entorhinal regions and anticipates phospho-tau pathology in Alzheimer's disease and PART. *Acta Neuropathologica*, 136, 57–67.
- Keene, C. S., Bladon, J., Sam, M., Liu, C. D., Joseph, O., & Eichenbaum, H. (2016). Complementary functional organization of neuronal activity patterns in the perirhinal, lateral entorhinal, and medial entorhinal cortices. *Journal of Neuroscience*, 36, 3660–3675. <https://doi.org/10.1523/JNEUROSCI.4368-15.2016>
- Kent, B. A., Hvoslef-Eide, M., Saksida, L. M., & Bussey, T. J. (2016). The representational-hierarchical view of pattern separation: Not just hippocampus, not just space, not just memory? *Neurobiology of Learning and Memory*, 129, 99–106.
- Kent, B. A., & Brown, T. H. (2012). Dual functions of perirhinal cortex in fear conditioning. *Hippocampus*, 22, 2068–2079. <https://doi.org/10.1002/hipo.22058>
- Kerr, K. M., Agster, K. L., Furtak, S. C., & Burwell, R. D. (2007). Functional neuroanatomy of the parahippocampal region: The lateral and medial entorhinal areas. *Hippocampus*, 17(9), 697–708. <https://doi.org/10.1002/hipo.20315>
- Kholodar-Smith, D., Allen, T., & Brown, T. (2008). Fear conditioning to discontinuous auditory cues requires perirhinal cortical function. *Behavioral Neuroscience*, 122, 1178–1185. <https://doi.org/10.1037/a0012902>
- Kivisaari, S. L., Tyler, L. K., Monsch, A. U., & Taylor, K. I. (2012). Medial perirhinal cortex disambiguates confusable objects. *Brain*, 135, 3757–3769.
- Knierim, J., Neunuebel, J., & Deshmukh, S. (2014). Functional correlates of the lateral and medial entorhinal cortex: Objects, path integration and local-global reference frames. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 369, 20130369. <https://doi.org/10.1098/rstb.2013.0369>
- Lee, A. C. H., Buckley, M. J., Gaffan, D., Emery, T., Hodges, J. R., & Graham, K. S. (2006). Differentiating the roles of the hippocampus and perirhinal cortex in processes beyond long-term declarative memory: A double dissociation in dementia. *The Journal of Neuroscience*, 26, 5198–5203.
- Lee, A. C. H., Buckley, M. J., Pegman, S. J., Spiers, H., Scahill, V. L., Gaffan, D., ... Graham, K. S. (2005). Specialization in the medial temporal lobe for processing of objects and scenes. *Hippocampus*, 15, 782–797.
- Lee, A. C. H., Bussey, T. J., Murray, E. A., Saksida, L. M., Epstein, R. A., Kapur, N., ... Graham, K. S. (2005). Perceptual deficits in amnesia: Challenging the medial temporal lobe 'mnemonic' view. *Neuropsychologia*, 43, 1–11.
- Lee, A. C. H., Scahill, V. L., & Graham, K. S. (2008). Activating the medial temporal lobe during oddity judgment for faces and scenes. *Cerebral Cortex*, 18, 683–696.
- Leutgeb, J. K., Leutgeb, S., Moser, M. B., & Moser, E. I. (2007). Pattern separation in the dentate gyrus and CA3 of the hippocampus. *Science*, 315(5814), 961–966. <https://doi.org/10.1126/science.1135801>
- Liang, J. C., Wagner, A. D., & Preston, A. R. (2013). Content representation in the human medial temporal lobe. *Cereb Cortex (New York, NY)*, 23, 80.
- Lindquist, D. H., Jarrard, L. E., & Brown, T. H. (2004). Perirhinal cortex supports delay fear conditioning to rat ultrasonic social signals. *The Journal of Neuroscience*, 24(14), 3610–3617. <https://doi.org/10.1523/JNEUROSCI.4839-03.2004>
- Litman, L., Awipi, T., & Davachi, L. (2009). Category-specificity in the human medial temporal lobe cortex. *Hippocampus*, 19, 308–319.
- Liu, P., & Bilkey, D. K. (1996). Direct connection between perirhinal cortex and hippocampus is a major constituent of the lateral perforant path. *Hippocampus*, 6(2), 125–135. [https://doi.org/10.1002/\(SICI\)1098-1063\(1996\)6:2<125::AID-HIPO4>3.0.CO;2-O](https://doi.org/10.1002/(SICI)1098-1063(1996)6:2<125::AID-HIPO4>3.0.CO;2-O)
- Liu, P., & Bilkey, D. (2001). The effect of excitotoxic lesions centered on the hippocampus or perirhinal cortex in object recognition and spatial memory tasks. *Behavioral Neuroscience*, 115, 94–111. <https://doi.org/10.1037/0735-7044.115.1.94>
- Liu, Z., & Richmond, B. (2000). Response differences in monkey TE and perirhinal cortex: Stimulus association related to reward schedules. *Journal of Neurophysiology*, 83, 1677–1692.
- Maass, A., Berron, D., Harrison, T. M., Adams, J. N., la Joie, R., Baker, S., ... Jagust, W. J. (2019). Alzheimer's pathology targets distinct memory networks in the ageing brain. *Brain*, 142, 2492–2509.
- Martin, C. B., Bowles, B., Mirsattari, S. M., & Köhler, S. (2011). Selective familiarity deficits after left anterior temporal-lobe removal with hippocampal sparing are material specific. *Neuropsychologia*, 49(7), 1870–1878.
- Martin, C. B., Cowell, R. A., Gribble, P. L., Wright, J., & Köhler, S. (2016). Distributed category-specific recognition-memory signals in human perirhinal cortex. *Hippocampus*, 26(4), 423–436.
- Martin, C. B., Sullivan, J. A., Wright, J., & Köhler, S. (2018). How landmark suitability shapes recognition memory signals for objects in the medial temporal lobes. *NeuroImage*, 166, 425–436.
- Martina, M., Royer, S., & Paré, D. (2001). Propagation of neocortical inputs in the perirhinal cortex. *The Journal of Neuroscience*, 21, 2878–2888.
- McIntyre, D. C., Kelly, M. E., & Staines, W. A. (1996). Efferent projections of the anterior perirhinal cortex in the rat. *Journal of Comparative Neurology*, 369, 302–318.

- McNaughton, B. L., Battaglia, F. P., Jensen, O., Moser, E. I., & Moser, M. B. (2006). Path integration and the neural basis of the 'cognitive map'. *Nature Reviews. Neuroscience*, 7(8), 663–678. <https://doi.org/10.1038/nrn1932>
- McTighe, S. M., Cowell, R. A., Winters, B. D., Bussey, T. J., & Saksida, L. M. (2010). Paradoxical false memory for objects after brain damage. *Science*, 330(6009), 1408–1410. <https://doi.org/10.1126/science.1194780>
- Meunier, M., Bachevalier, J., Mishkin, M., & Murray, E. (1993). Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. *The Journal of Neuroscience*, 13, 5418–5432.
- Miyashita, Y. (2019). Perirhinal circuits for memory processing. *Nature Reviews. Neuroscience*, 20, 577–592.
- Montaldi, D., Spencer, T. J., Roberts, N., & Mayes, A. R. (2006). The neural system that mediates familiarity memory. *Hippocampus*, 16, 504–520.
- Muir, G., & Bilkey, D. (2001). Instability in the place field location of hippocampal place cells after lesions centered on the perirhinal cortex. *The Journal of Neuroscience*, 21, 4016–4025.
- Muir, G., & Bilkey, D. (2003). Theta- and movement velocity-related firing of hippocampal neurons is disrupted by lesions centered on the perirhinal cortex. *Hippocampus*, 13, 93–108. <https://doi.org/10.1002/hipo.10052>
- Mulder, A. B., Nordquist, R. E., Örgüt, O., & Pennartz, C. M. A. (2003). Learning-related changes in response patterns of prefrontal neurons during instrumental conditioning. *Behavioural Brain Research*, 146, 77–88.
- Mundy, M. E., Downing, P. E., Dwyer, D. M., Honey, R. C., & Graham, K. S. (2013). A critical role for the hippocampus and perirhinal cortex in perceptual learning of scenes and faces: Complementary findings from amnesia and fMRI. *The Journal of Neuroscience*, 33, 10490–10502.
- Murray, E. A., Bussey, T. J., & Saksida, L. M. (2007). Visual perception and memory: A new view of medial temporal lobe function in primates and rodents. *Annual Review of Neuroscience*, 30, 99–122.
- Murray, E. A., & Wise, S. P. (2012). Why is there a special issue on perirhinal cortex in a journal called hippocampus? The perirhinal cortex in historical perspective. *Hippocampus*, 22(10), 1941–1951. <https://doi.org/10.1002/hipo.22055>
- Naber, P., Silva, F., & Witter, M. (2001). Reciprocal connections between the entorhinal cortex and hippocampal fields CA1 and the subiculum are in register with the projections from CA1 to the subiculum. *Hippocampus*, 11, 99–104. <https://doi.org/10.1002/hipo.1028>
- Naber, P., Witter, M., & Silva, F. (1999). Perirhinal cortex input to the hippocampus in the rat: Evidence for parallel pathways, both direct and indirect. A combined physiological and anatomical study. *The European Journal of Neuroscience*, 11, 4119–4133. <https://doi.org/10.1046/j.1460-9568.1999.00835.x>
- Naber, P. A., Witter, M. P., & da Silva, F. H. (2000). Differential distribution of barrel or visual cortex evoked responses along the rostro-caudal axis of the peri- and postrhinal cortices. *Brain Research*, 877, 298–305. [https://doi.org/10.1016/S0006-8993\(00\)02694-9](https://doi.org/10.1016/S0006-8993(00)02694-9)
- Nakazawa, K., Quirk, M. C., Chitwood, R. A., Watanabe, M., Yeckel, M. F., Sun, L. D., ... Tonegawa, S. (2002). Requirement for hippocampal CA3 NMDA receptors in associative memory recall. *Science*, 297(5579), 211–218. <https://doi.org/10.1126/science.1071795>
- Naya, Y. (2016). Declarative association in the perirhinal cortex. *Neuroscience Research*, 113, 12–18. <https://doi.org/10.1016/j.neures.2016.07.001>
- Naya, Y., Yoshida, M., & Miyashita, Y. (2003). Forward processing of long-term associative memory in monkey inferotemporal cortex. *The Journal of Neuroscience*, 23, 2861–2871.
- Naya, Y., Yoshida, M., Takeda, M., Fujimichi, R., & Miyashita, Y. (2003). Delay-period activities in two subdivisions of monkey inferotemporal cortex during pair association memory task. *The European Journal of Neuroscience*, 18, 2915–2918. <https://doi.org/10.1111/j.1460-9568.2003.03020.x>
- Neunuebel, J. P., & Knierim, J. J. (2012 Mar 14). Spatial firing correlates of physiologically distinct cell types of the rat dentate gyrus. *The Journal of Neuroscience*, 32(11), 3848–3858. <https://doi.org/10.1523/JNEUROSCI.6038-11.2012>
- Neunuebel, J., Yoganasimha, D., Rao, G., & Knierim, J. (2013). Conflicts between local and global spatial frameworks dissociate neural representations of the lateral and medial entorhinal cortex. *The Journal of Neuroscience*, 33, 9246–9258. <https://doi.org/10.1523/JNEUROSCI.0946-13.2013>
- Newsome, R. N., Duarte, A., & Barense, M. D. (2012). Reducing perceptual interference improves visual discrimination in mild cognitive impairment: Implications for a model of perirhinal cortex function. *Hippocampus*, 22(10), 1990–1999.
- Nilssen, E. S., Doan, T. P., Nigro, M. J., Ohara, S., & Witter, M. P. (2019). Neurons and networks in the entorhinal cortex: A reappraisal of the lateral and medial entorhinal subdivisions mediating parallel cortical pathways. *Hippocampus*, 29(12), 1–17.
- Norman, G., & Eacott, M. (2004). Impaired object recognition with increasing levels of feature ambiguity in rats with perirhinal cortex lesions. *Behavioural Brain Research*, 148, 79–91. [https://doi.org/10.1016/S0166-4328\(03\)00176-1](https://doi.org/10.1016/S0166-4328(03)00176-1)
- Norman, G., & Eacott, M. J. (2005). Dissociable effects of lesions to the perirhinal cortex and the postrhinal cortex on memory for context and objects in rats. *Behavioral Neuroscience*, 119, 557–566. <https://doi.org/10.1037/0735-7044.119.2.557>
- O'Keefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Research*, 34(1), 171–175. [https://doi.org/10.1016/0006-8993\(71\)90358-1](https://doi.org/10.1016/0006-8993(71)90358-1)
- Olarte-Sánchez, C. M., Amin, E., Warburton, E. C., & Aggleton, J. P. (2015). Perirhinal cortex lesions impair tests of object recognition memory but spare novelty detection. *The European Journal of Neuroscience*, 42(12), 3117–3127. <https://doi.org/10.1111/ejn.13106>
- Olcese, U., Oude Lohuis, M. N., & CMA, P. (2018). Sensory processing across conscious and nonconscious brain states: From single neurons to distributed networks for inferential representation. *Frontiers in Systems Neuroscience*, 12, 49. <https://doi.org/10.3389/fnsys.2018.00049>
- O'Neil, E. B., Barkley, V. A., & Köhler, S. (2013). Representational demands modulate involvement of perirhinal cortex in face processing. *Hippocampus*, 23, 592–605.
- O'Neil, E. B., Protzner, A. B., McCormick, C., McLean, D. A., Poppenk, J., Cate, A. D., & Köhler, S. (2012). Distinct patterns of functional and effective connectivity between perirhinal cortex and other cortical regions in recognition memory and perceptual discrimination. *Cerebral Cortex*, 22, 74–85.
- Otto, T., & Eichenbaum, H. (1992). Complementary roles of the orbital prefrontal cortex and the perirhinal-entorhinal cortices in an odor-guided delayed-nonmatching-to-sample task. *Behavioral Neuroscience*, 106, 762–775.
- Pelletier, J., Apergis, J., & Paré, D. (2004). Low-probability transmission of neocortical and entorhinal impulses through the perirhinal cortex. *Journal of Neurophysiology*, 91, 2079–2089. <https://doi.org/10.1152/jn.01197.2003>
- Pennartz, C. M. A. (1997). Reinforcement learning by Hebbian synapses with adaptive thresholds. *Neuroscience*, 81, 303–319.
- Pennartz, C. M. A. (2015). *The brain's representational power: On consciousness and the integration of modalities* (Vol. 46, pp. 638–639). Cambridge, MA: MIT Press. <https://doi.org/10.1177/0301006616684259>
- Pennartz, C. M. A., Dora, S., Muckli, L., & Lortelje, J. A. M. (2019). Towards a unified view on pathways and functions of neural recurrent processing. *Trends in Neurosciences*, 42, 589–603. <https://doi.org/10.1016/j.tins.2019.07.005>
- Peterson, M. A., & Enns, J. T. (2015). The edge complex: Implicit memory for figure assignment in shape perception. *Perception & Psychophysics*, 67, 727–740.

- Pezzulo, G., van der Meer, M. A., Lansink, C. S., & Pennartz, C. M. (2014). Internally generated sequences in learning and executing goal-directed behavior. *Trends in Cognitive Sciences*, 18(12), 647–657. <https://doi.org/10.1016/j.tics.2014.06.011>
- Pikkarainen, M., & Pitkänen, A. (2001). Projections from the lateral, basal and accessory basal nuclei of the amygdala to the perirhinal and post-rhinal cortices in rat. *Cerebral Cortex*, 11, 1064–1082. <https://doi.org/10.1093/cercor/11.11.1064>
- Quiroga, R. Q. (2012). Concept cells: The building blocks of declarative memory functions. *Nature Reviews. Neuroscience*, 13(8), 587–597. <https://doi.org/10.1038/nrn3251>
- Ramos Juan, M. J., & Vaquero Joaquín, M. M. (2005). The perirhinal cortex of the rat is necessary for spatial memory retention long after but not soon after learning. *Physiology & Behavior*, 86(1–2), 118–127. <https://doi.org/10.1016/j.physbeh.2005.07.004>
- Ramos, J. (2013). Differential contribution of hippocampus, perirhinal cortex and postrhinal cortex to allocentric spatial memory in the radial maze. *Behavioural Brain Research*, 247, 59–64. <https://doi.org/10.1016/j.bbr.2013.03.017>
- Ramos, J. M. (2014). Essential role of the perirhinal cortex in complex tactual discrimination tasks in rats. *Cerebral Cortex*, 24(8), 2068–2080. <https://doi.org/10.1093/cercor/bht054>
- Ramos, J. M. (2016). Perirhinal cortex supports tactual discrimination tasks with increasing levels of complexity: Retrograde effect. *Neurobiology of Learning and Memory*, 131, 121–130. <https://doi.org/10.1016/j.nlm.2016.03.018>
- Ramos, J. (2017). Perirhinal cortex involvement in allocentric spatial learning in the rat: Evidence from doubly marked tasks. *Hippocampus*, 27, 507–517. <https://doi.org/10.1002/hipo.22707>
- Ranganath, C., & Ritchey, M. (2012). Two cortical systems for memory-guided behaviour. *Nature Reviews. Neuroscience*, 13, 713–726.
- Rao, R. P., & Ballard, D. H. (1999). Predictive coding in the visual cortex: A functional interpretation of some extra-classical receptive-field effects. *Nature Neuroscience*, 2(1), 79–87. <https://doi.org/10.1038/4580>
- Reid, J., Jacklin, D., & Winters, B. (2012). Crossmodal object recognition in rats with and without multimodal object pre-exposure: No effect of hippocampal lesions. *Neurobiology of Learning and Memory*, 98, 311–319. <https://doi.org/10.1016/j.nlm.2012.09.001>
- Ross, D., Sadil, P., Wilson, M., & Cowell, R. (2018). Hippocampal engagement during recall depends on memory content. *Cerebral Cortex*, 28(8), 2685–2698.
- Rubin, R. D., Chesney, S. A., Cohen, N. J., & Gonsalves, B. D. (2013). Using fMR-adaptation to track complex object representations in perirhinal cortex. *Cognitive Neuroscience*, 4, 107–114.
- Rusu, S., & Pennartz, C. M. A. (2020). Learning, memory and consolidation mechanisms for behavioral control in hierarchically organized cortico-basal ganglia systems. *Hippocampus*, 30, 73–98. <https://doi.org/10.1002/hipo.23167>
- Sakai, K., & Miyashita, Y. (1991). Neural organization for the long-term memory of paired associates. *Nature*, 354, 152–155. <https://doi.org/10.1038/354152a0>
- Saksida, L. M., Bussey, T. J., Buckmaster, C. A., & Murray, E. A. (2006). No effect of hippocampal lesions on perirhinal cortex-dependent feature-ambiguous visual discriminations. *Hippocampus*, 16, 421–430. <https://doi.org/10.1002/hipo.20170>
- Saksida, L. M., Bussey, T. J., Buckmaster, C. A., & Murray, E. A. (2007). Impairment and facilitation of transverse patterning after lesions of the perirhinal cortex and hippocampus, respectively. *Cerebral Cortex*, 17, 108–115. <https://doi.org/10.1093/cercor/bhj128>
- Sesack, S. R., Deutch, A. Y., Roth, R. H., & Bunney, B. S. (1989). Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: An anterograde tract-tracing study with *Phaseolus vulgaris* leucoagglutinin. *The Journal of Comparative Neurology*, 290, 213–242.
- Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience*, 27, 279–306.
- Squire, L. R., Wixted, J. T., & Clark, R. E. (2007). Recognition memory and the medial temporal lobe: A new perspective. *Nature Reviews. Neuroscience*, 8, 872–883.
- Staresina, B. P., & Davachi, L. (2008). Selective and shared contributions of the hippocampus and perirhinal cortex to episodic item and associative encoding. *Journal of Cognitive Neuroscience*, 20, 1478–1489.
- Staresina, B. P., & Davachi, L. (2010). Object unitization and associative memory formation are supported by distinct brain regions. *The Journal of Neuroscience*, 30, 9890–9897.
- Staresina, B. P., Duncan, K. D., & Davachi, L. (2011). Perirhinal and parahippocampal cortices differentially contribute to later recollection of object- and scene-related event details. *The Journal of Neuroscience*, 31, 8739–8747.
- Stark, C. E. L., & Squire, L. R. (2000). Intact visual perceptual discrimination in humans in the absence of perirhinal cortex. *Learning & Memory*, 7, 273–278.
- Struckmeier, O., Tiwari, K., Dora, S., Pearson, M. J., Bohte, S. M., Pennartz, C. M., & Kyrki, V. (2019). MuPNet: Multi-modal predictive coding network for place recognition by unsupervised learning of joint visuo-tactile latent representations. *arXiv preprint*. <http://arxiv.org/abs/1909.07201>
- Suzuki, W., & Amaral, D. (1994). Perirhinal and parahippocampal cortices of the macaque monkey: Cortical afferents. *The Journal of Comparative Neurology*, 350, 497–533. <https://doi.org/10.1002/cne.903500402>
- Suzuki, W. A., & Naya, Y. (2014). The perirhinal cortex. *Annual Review of Neuroscience*, 37(1), 39–53. <https://doi.org/10.1146/annurev-neuro-071013-014207>
- Taylor, K. I., Moss, H. E., Stamatakis, E. A., & Tyler, L. K. (2006). Binding crossmodal object features in perirhinal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 103, 8239–8244.
- Taylor, K. I., Stamatakis, E. A., & Tyler, L. K. (2009). Crossmodal integration of object features: Voxel-based correlations in brain-damaged patients. *Brain*, 132, 671–683.
- Taylor, K. I., & Probst, A. (2008). Anatomic localization of the transentorhinal region of the perirhinal cortex. *Neurobiology of Aging*, 29(10), 1591–1596. <https://doi.org/10.1016/j.neurobiolaging.2007.03.024>
- Tomás Pereira, I., Agster, K. L., & Burwell, R. D. (2016). Subcortical connections of the perirhinal, postrhinal, and entorhinal cortices of the rat. I. Afferents. *Hippocampus*, 26(9), 1189–1212. <https://doi.org/10.1002/hipo.22603>
- Treves, A., & Rolls, E. T. (1992). Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. *Hippocampus*, 2(2), 189–199. <https://doi.org/10.1002/hipo.450020209>
- Tsao, A., Moser, M. B., & Moser, E. I. (2013). Traces of experience in the lateral entorhinal cortex. *Current Biology*, 23(5), 399–405. <https://doi.org/10.1016/j.cub.2013.01.036>
- Tyler, L. K., Stamatakis, E. A., Bright, P., Acres, K., Abdallah, S., Rodd, J. M., & Moss, H. E. (2004). Processing objects at different levels of specificity. *Journal of Cognitive Neuroscience*, 16, 351–362.
- Unal, G., John, A.-S., & Paré, D. (2012). Associative properties of the perirhinal network. *Cerebral Cortex*, 22, 1318–1332. <https://doi.org/10.1093/cercor/bhr212>
- van Strien, N. M., Cappaert, N. L., & Witter, M. P. (2009). The anatomy of memory: An interactive overview of the parahippocampal-hippocampal network. *Nature Reviews. Neuroscience*, 10(4), 272–282. <https://doi.org/10.1038/nrn2614>
- van Wingerden, M., Vinck, M., Lankelma, J. V., & Pennartz, C. M. A. (2010b). Theta-band phase-locking of orbitofrontal neurons during reward expectancy. *The Journal of Neuroscience*, 30, 7078–7087.
- von Linstow Roloff, E., Muller, R. U., & Brown, M. W. (2016). Finding and not finding rat perirhinal neuronal responses to novelty. *Hippocampus*, 26, 1021–1032. <https://doi.org/10.1002/hipo.22584>

- Wais, P. E. (2008). fMRI signals associated with memory strength in the medial temporal lobes: A meta-analysis. *Neuropsychologia*, *46*, 3185–3196.
- Wang, W.-C., Lazzara, M. M., Ranganath, C., Knight, R. T., & Yonelinas, A. P. (2010). The medial temporal lobe supports conceptual implicit memory. *Neuron*, *68*, 835–842.
- Wang, W., Ranganath, C., & Yonelinas, A. P. (2014). Activity reductions in perirhinal cortex predict conceptual priming and familiarity-based recognition. *Neuropsychologia*, *52*, 19–26.
- Wiig, K., & Bilkey, D. (1994). The effects of perirhinal cortical lesions on spatial reference memory in the rat. *Behavioural Brain Research*, *63*, 101–109. [https://doi.org/10.1016/0166-4328\(94\)90055-8](https://doi.org/10.1016/0166-4328(94)90055-8)
- Willems, J. G. P., Wadman, W. J., & Cappaert, N. L. M. (2016). Distinct spatiotemporal activation patterns of the perirhinal-entorhinal network in response to cortical and amygdala input. *Frontiers in Neural Circuits*, *10*, 44. <https://doi.org/10.3389/fncir.2016.00044>
- Winters, B., & Reid, J. (2010). A distributed cortical representation underlies crossmodal object recognition in rats. *The Journal of Neuroscience*, *30*, 6253–6261. <https://doi.org/10.1523/JNEUROSCI.6073-09.2010>
- Witter, M. P., & Groenewegen, H. J. (1986). Connections of the parahippocampal cortex in the cat. III. Cortical and thalamic efferents. *Journal of Comparative Neurology*, *252*(1), 1–31. <https://doi.org/10.1002/cne.902520102>
- Witter, M., Wouterlood, F., Naber, P., & Haeflten, T. (2000). Anatomical organization of the parahippocampal-hippocampal network. *Annals of the New York Academy of Sciences*, *911*, 1–24. <https://doi.org/10.1111/j.1749-6632.2000.tb06716.x>
- Witter, M. P., Naber, P., van Haeflten, T., Machielsen, W., Rombouts, S., Barkhof, F., ... Lopes da Silva, F. (2000). Cortico-hippocampal communication by way of parallel parahippocampal-subicular pathways. *Hippocampus*, *10*, 398–410. [https://doi.org/10.1002/1098-1063\(2000\)10:4<398::AID-HIPO6>3.0.CO;2-K](https://doi.org/10.1002/1098-1063(2000)10:4<398::AID-HIPO6>3.0.CO;2-K)
- Wright, P., Randall, B., Clarke, A., & Tyler, L. K. (2015). The perirhinal cortex and conceptual processing: Effects of feature-based statistics following damage to the anterior temporal lobes. *Neuropsychologia*, *76*, 192–207.
- Yoganarasimha, D., Rao, G., & Knierim, J. J. (2011). Lateral entorhinal neurons are not spatially selective in cue-rich environments. *Hippocampus*, *21*(12), 1363–1374. <https://doi.org/10.1002/hipo.20839>
- Young, B., Otto, T., Fox, G., & Eichenbaum, H. (1997). Memory representation within the parahippocampal region. *The Journal of Neuroscience*, *17*, 5183–5195.
- Zeithamova, D., Manthuruthil, C., & Preston, A. R. (2016). Repetition suppression in the medial temporal lobe and midbrain is altered by event overlap. *Hippocampus*, *26*, 1464–1477.
- Zhu, X. O., & Brown, M. W. (1995). Changes in neuronal activity related to the repetition and relative familiarity of visual stimuli in rhinal and adjacent cortex of the anaesthetised rat. *Brain Research*, *689*, 101–110. [https://doi.org/10.1016/0006-8993\(95\)00550-A](https://doi.org/10.1016/0006-8993(95)00550-A)
- Zhu, X. O., Brown, M. W., McCabe, B. J., & Aggleton, J. P. (1995). Effects of the novelty or familiarity of visual stimuli on the expression of the immediate early gene c-fos in rat brain. *Neuroscience*, *69*, 82.
- Zhu, X., McCabe, B. J., Aggleton, J., & Brown, M. (1997). Differential activation of the rat hippocampus and perirhinal cortex by novel visual stimuli and a novel environment. *Neuroscience Letters*, *229*, 141–143. [https://doi.org/10.1016/S0304-3940\(97\)00437-0](https://doi.org/10.1016/S0304-3940(97)00437-0)
- Zhuo, J., Fan, L., Liu, Y., Zhang, Y., Yu, C., & Jiang, T. (2016). Connectivity profiles reveal a transition subarea in the parahippocampal region that integrates the anterior temporal–posterior medial systems. *The Journal of Neuroscience*, *36*, 2782–2829. [https://doi.org/10.1016/0306-4522\(95\)00320-1](https://doi.org/10.1016/0306-4522(95)00320-1)

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