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Neurons and networks in the entorhinal cortex: A reappraisal of the lateral and medial entorhinal subdivisions mediating parallel cortical pathways

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Abstract

In this review, we aim to reappraise the organization of intrinsic and extrinsic networks of the entorhinal cortex with a focus on the concept of parallel cortical connectivity streams. The concept of two entorhinal areas, the lateral and medial entorhinal cortex, belonging to two parallel input–output streams mediating the encoding and storage of respectively what and where information hinges on the claim that a major component of their cortical connections is with the perirhinal cortex and postrhinal or parahippocampal cortex in, respectively, rodents or primates. In this scenario, the lateral entorhinal cortex and the perirhinal cortex are connectionally associated and likewise the postrhinal/parahippocampal cortex and the medial entorhinal cortex are partners. In contrast, here we argue that the connectivity matrix emphasizes the potential of substantial integration of cortical information through interactions between the two entorhinal subdivisions and between the perirhinal and postrhinal/parahippocampal cortices, but most importantly through a new observation that the postrhinal/parahippocampal cortex projects to both lateral and medial entorhinal cortex. We suggest that entorhinal inputs provide the hippocampus with high-order complex representations of the external environment, its stability, as well as apparent changes either as an inherent feature of a biological environment or as the result of navigating the environment. This thus indicates that the current connectional model of the parahippocampal region as part of the medial temporal lobe memory system needs to be revised.

KEYWORDS
anatomy, episodic memory, hippocampus, neural network, parahippocampal gyrus

1 | INTRODUCTION

Memory is an important capacity of the brain and has intrigued scientists ever since they started to study the brain. The ability to store and recall information comes of use in a variety of daily behaviors, and the likely most important role is for us to make predictions based on previous experiences. Previous experiences with a high similarity become eventually stored as generalized concepts or schemes, which are being updated with new experiences. The efficacy of our memory system to make accurate predictions about future events depends on the relative robustness of our stored memories. This same robustness, however, provides a potential threat in that memories might become

harder to change and thus our behavior may become guided by concepts that are no longer an adequate representation of the current situation. Research on memory suffers from a comparable threat in that well-established theories might become difficult to adjust to encompass new insights.

The focus on the medial temporal lobe as being critically involved in episodic memory was essentially initiated by the influential paper on patient HM, reporting the devastating anterograde amnesia as the result of bilateral resections of the antero-medial portions of the temporal lobe. The lesions included a substantial part of the hippocampal formation (HF), the amygdala and the parahippocampal region (PHR), in particular the entorhinal cortex (EC) and perirhinal cortex (PER) (Annese et al., 2014; Augustinack et al., 2014; Scoville & Milner, 1957). Irrespective of the fact that the lesions included several different brain structures aside HF bilaterally, the field quickly zoomed in on HF as the likely most critical structure underlying episodic memory (Milner, Squire, & Kandel, 1998). This emphasis on HF was strengthened by a large body of existing data reporting the beautiful morphological simplicity of HF and its intrinsic organization (Blackstad, 1956, 1958; Haug, 1976; Hjorth-Simonsen, 1971; Hjorth-Simonsen & Jeune, 1972; Lorente de Nó, 1934; Ramón y Cajal, 1893), the first description of the spatially modulated "place cell" (O'Keefe, 1976; O'Keefe & Dostrovsky, 1971), the phenomenon of long-term potentiation (Bliss & Lømo, 1973), all culminating in the very influential book in which O'Keefe and Nadel proposed the theory of the hippocampus as a cognitive map (O'Keefe & Nadel, 1978). These authors managed to integrate all these seemingly disparate observations into a coherent theoretical framework organized around the concept of place cells as the cellular basis for representation of space as well as events and experiences associated with space. Although clearly unintended by these two authors at that time, the appealing experimental simplicity of the navigational focus set the scene for a hippocampal-centric hierarchical view of the medial temporal lobe memory system. The latter includes the amygdala and the PHR. Although the amygdala does affect memory functions through influencing consolidation of emotional stimuli (Adolphs, Cahill, Schul, & Babinsky, 1997; Sutherland & McDonald, 1990; Zola-Morgan, Squire, Alvarez-Royo, & Clower, 1991), restricted lesions to the amygdala do not produce appreciable memory impairments (Mishkin, 1978; Sutherland & McDonald, 1990; Zola-Morgan, Squire, & Amaral, 1989). In contrast, PHR with the entorhinal cortex (EC) as a nodal point, eventually became recognized as a player of substance. The latter structure was positioned to mediate the overall reciprocal connections of HF with the cortex (Buzsaki, 1996; Eichenbaum, 2000; Kosel, Van Hoesen, & Rosene, 1982; Squire, Stark, & Clark, 2004).

Ramon y Cajal drew attention to EC or the "sphenoidal cortex"/"angular ganglion" as he initially referred to it (Ramón y Cajal, 1902), describing the massive bundle of entorhinal fibers, perforating the subiculum on its way to HF. This led him to suggest that the functional significance of EC had to be related to that of HF. Subsequent anatomical studies showed that EC provides a main input to HF (Witter, Groenewegen, Lopes da Silva, & Lohman, 1989). A second seminal observation was that in the monkey, HF distributes a main output to deep layers of EC, which in turn originates major projections to adjacent parts of PHR as well as to frontal cortical domains (Kosel et al., 1982; Van Hoesen & Pandya, 1975a; G. Van Hoesen, Pandya, & Butters, 1975; Van Hoesen & Pandya, 1975b). This was later corroborated and further detailed in the monkey (Munoz & Insausti, 2005) and in a number of other species, including rodents (Witter, et al., 1989). Although in subsequent years anatomical studies detailed the connectional organization of PHR, and EC in particular, the role of EC was not really appreciated; the functional attributes of EC remained in the shadow, only to achieve recognition more recently, resulting in a still ongoing explosion of rich and surprising new details. One initial finding contributing to this recognition was that damage to EC results in strong functional impairments in episodic memory (Buckmaster, Eichenbaum, Amaral, Suzuki, & Rapp, 2004; Leonard, Amaral, Squire, & Zola-Morgan, 1995; Meunier, Bachevalier, Mishkin, & Murray, 1993). In addition, the discovery of place fields in area CA1 of HF initiated a discussion on whether these functional properties were the result of internal HF computations or depended on inputs from outside HF. A recent comprehensive review (Moser, Moser, & McNaughton, 2017) summarized this debate in detail and introduced the subsequent discovery of spatially modulated grid cells in the most dorsal part of the medial entorhinal cortex (MEC) in rodents. This and subsequent reports on many functional cell types, all relevant to path-integration-based representation of self-location in MEC, contributed to the current strong interest in the functional attributes of MEC. The discovery of the grid cell further led to a substantial number of studies aiming to describe or model the neuronal networks underlying their specific firing properties (Moser et al., 2017).

The focus on MEC as the location of the myriad of functional cell types relevant for spatial navigation and spatial memory has enhanced our understanding of the entorhinal-hippocampal interplay and led to an interaction between computational and experimental neuroscience, aiming to identify and study generic circuit motifs underlying spatial perception and navigation. Although very productive, this focus distracted from the fact that there is a nonspatial side to episodic memory. For example, although partial or even complete lesions of MEC do impact the precision and long-term stability of place cells in HF (Brun et al., 2008; Hales et al., 2018), they do not abolish them. Such lesions do impair performance in the water maze of rats, similar to HF-lesions, but do not affect other HF-dependent tasks such as memory for object-location and context (Hales et al., 2018). For an episodic memory, one needs not only to store where the event took place and the position of the observer/participant in an allocentric parametric space, but also what happened and when it happened. This final convergence likely takes place in HF (Eichenbaum, 2017). Anatomical and functional data in rodents, monkeys, and humans suggest that the "What" is represented in the lateral entorhinal cortex (LEC) (Ritchey, Libby, & Ranganath, 2015; M. P. Witter et al., 2000), whereas time was suggested to be mediated through MEC (Eichenbaum, 2017) though more recent data indicated a role for LEC as well (Montchal, Reagh, & Yassa, 2019; Tsao et al., 2018).

It was particularly the knowledge about cortical connectivity that led to the notion of two functionally different portions in EC. The concept of LEC and MEC as entorhinal areas belonging to two parallel

input–output streams mediating the encoding and storage of respectively what and where information is currently well accepted (Eichenbaum, Yonelinas, & Ranganath, 2007; Ritchey et al., 2015). An important component of this concept hinges on the claim that a major component of their cortical connections is with the PER cortex and postrhinal (POR) in rodents, or parahippocampal cortex (PHC) in primates. In this scenario, LEC and PER are connectionally associated and POR and MEC are likewise partners. However, already in the early anatomical studies, there are indications that this connectional dissociation is not as evident as generally portrayed (Burwell & Amaral, 1998a, 1998b; Insausti & Amaral, 2008; Suzuki & Amaral, 1994b). Moreover, several authors emphasized that both PER and POR as well as LEC and MEC are interconnected (Burwell & Amaral, 1998b; Dolorfo & Amaral, 1998; Köhler, 1986, 1988; Lavenex, Suzuki, & Amaral, 2004). Although these interconnections have been included by some authors (Burke et al., 2018; Knierim, Neunuebel, & Deshmukh, 2014; Lisman, 2007; Ranganath & Ritchey, 2012), they have not really surfaced as relevant components in the appraisal of the potential functional roles of LEC and MEC and likewise PER and POR/PHC (cf. Furtak, Ahmed, & Burwell, 2012). So, a reappraisal of the parallel model is considered relevant (Figure 1) to prevent the field from consolidating on an incomplete model of the functional relevance of PHR.

We further need to consider that although the multitude of functionally specialized cell types in MEC is remarkable, many of them express more than one type of information. Such conjunctive neurons are particularly abundant in deeper Layers III and V of MEC, whereas pure grid cells are predominant in Layer II. In the deeper layers of MEC, a majority of the not so numerous grid cells fire conjunctively for position and head direction or speed, and many border cells are direction-selective (Hardcastle, Maheswaranathan, Ganguli, & Giocomo, 2017; Kropff, Carmichael, Moser, & Moser, 2015; Sargolini et al., 2006; Solstad, Boccara, Kropff, Moser, & Moser, 2008). Until recently, very little was known about the local intra—and interlaminar networks in MEC, except for the local network in Layer II, associated with the grid cell phenotype, briefly mentioned earlier. The emergent functional properties of the deeper cells are thus still poorly understood in terms of local architecture and its interactions with input/output connectivity. Even less is known about LEC. Based on the striking difference in functional cell types in LEC and MEC (Deshmukh & Knierim, 2011; Hargreaves, Rao, Lee, & Knierim, 2005; Neunuebel, Yoganarasimha, Rao, & Knierim, 2013; Tsao et al., 2018; Tsao, Moser, & Moser, 2013; Wang et al., 2018) expectations were that local circuits might differ between the two EC subdivisions. This has only recently been studied in detail, and these recent results indicate that the local circuits in LEC and MEC might not be all that
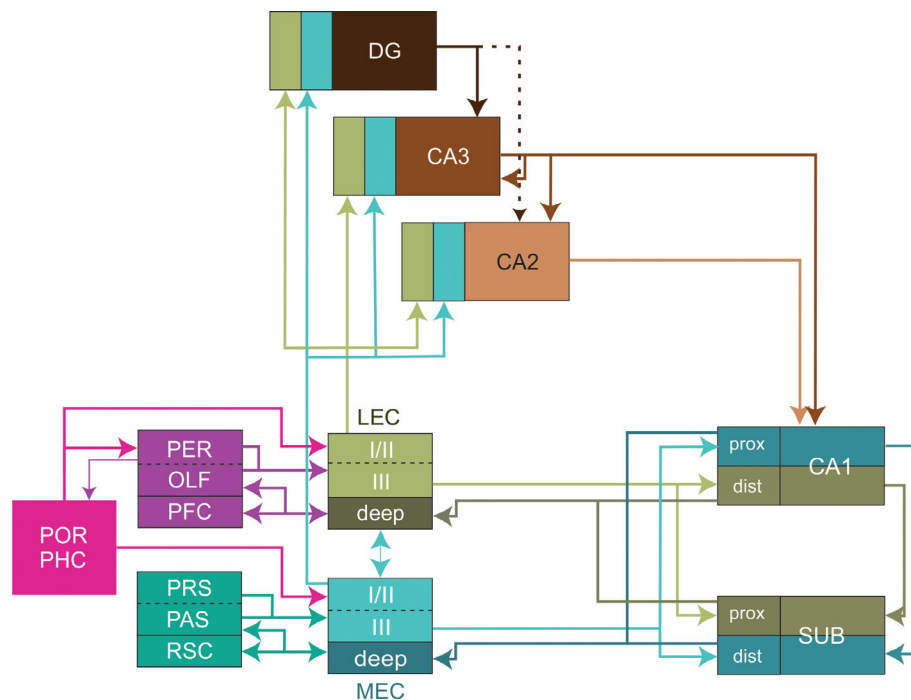

FIGURE 1 Schematic representation of the proposed updated version of the wiring scheme of the parahippocampal-hippocampal system. The lateral and medial entorhinal cortex mediate parallel input streams, conveying integrated representations of two complementary sets of cortical inputs to the hippocampus. The lateral entorhinal cortex (LEC) receives strong inputs from perirhinal (PER), orbitofrontal, medial prefrontal and insular cortices (PFC), and olfactory structures (OLF) including the olfactory bulb and the olfactory or piriform cortex. In contrast, MEC receives main inputs from presubiculum (PRS), parasubiculum (PAS), and retrosplenial cortex (RSC). The postrhinal/parahippocampal cortex (POR/PHC) provides inputs to both MEC and LEC as well as to PER. Dashed dividers in boxes imply that incoming projections distribute to both components of the box. CA3, CA2, CA1, subfields of the hippocampus proper; DG, dentate gyrus; dist, distal part; prox, proximal part [Color figure can be viewed at wileyonlinelibrary.com]

different (Fuchs et al., 2016; Leitner et al., 2016; Nilssen et al., 2018; Ohara et al., 2018).

In this review, we aim to relate the organization of local networks to what is known about cortical inputs and their postsynaptic targets, with a focus on the concept of parallel cortical connectivity streams. Although this review is dominated by rodent data, we aim to integrate relevant primate data. We will argue that EC, changed from being insignificant into possibly one of the most important characters in the tale of the medial temporal lobe. Moreover, instead of considering LEC and MEC as mediating segregated parallel input pathways to HF, the network structure emphasizes the potential of substantial integration of cortical information through interactions between LEC and MEC. Integration is likely reflected in the complex conjunctive properties of neurons seen throughout EC, and more in particular in LEC (Deshmukh & Knierim, 2011; Naya & Suzuki, 2011; Suzuki, Miller, & Desimone, 1997; Tsao et al., 2013; Wang et al., 2018). We therefore feel the need to revise the current parallel model where the medial and lateral entorhinal cortex provide parallel input streams to HF into one where EC is considered as an area allowing for integration of two or even more parallel cortical streams (Yoo & Lee, 2017), providing HF with high-order complex representations of the external environment, its stability, as well as apparent changes either as an inherent feature of a biological environment or as the result of navigating the environment.

1.1 | The entorhinal cortex comprises two subdivisions

EC can be best defined based on its projections to the hippocampus, which target neurons in all main hippocampal subdivisions. Although EC projections to some of the HF fields, particularly those to CA1 and subiculum are paralleled by projections from PER and POR, the EC projections to DG are currently considered a unique projection, identifying EC (Cappaert, Van Strien, & Witter, 2014; Witter, Doan, Jacobsen, Nilssen, & Ohara, 2017). EC is associated with the rhinal sulcus and in many if not all mammalian species, EC is characterized by a regular six-layered structure with a neuron-sparse superficial Layer I and a similarly neuron-sparse Layer IV in the center, sandwiched between Layer III and Layer V. In the posteromedially positioned MEC, all layers are clearly demarcated and show a relatively homogeneous distribution of neurons. The opposite, anterolateral part, LEC, has a less stringent laminar structure, and the overall distribution of neurons is less homogeneous. Note that there is generally an area in between these extremes and in particular this intermediate area has been subdivided differently in various species. It is a common observation that the cytoarchitectonically based subdivision of this intermediate area is increasingly complex in primates (Amaral, Insausti, & Cowan, 1987; Insausti, Tunon, Sobreviela, Insausti, & Gonzalo, 1995; Krimer, Hyde, Herman, & Saunders, 1997). A detailed description and comparison of all subdivisional schemes that have been proposed is beyond the scope of the review but has been covered in several papers in detail (Insausti, Munoz-Lopez, Insausti, & Artacho-Perula, 2017; Witter, Groenewegen, et al., 1989). For this review we will use LEC and MEC as indications for two areas, irrespective of species, for which most functional data

are available, including in humans (Maass, Berron, Libby, Ranganath, & Duzel, 2015; Montchal et al., 2019; Navarro Schroder, Haak, Zaragoza Jimenez, Beckmann, & Doeller, 2015). Moreover, in a recent comparative review on the distribution of chemically defined neurons and neuropil, we have argued that these are best described as a gradient related to the distance from the rhinal/collateral sulcus and not related to any of the traditional cytoarchitectural subdivisions (Kobro-Flatmoen & Witter, 2019).

In most if not all studied nonprimate species, the organization of the EC projection to DG, originating from reelin expressing neurons in Layer II of both LEC and MEC, supports the subdivision of EC into two subareas, whereby LEC targets dendritic compartments located distally to those targeted by MEC fibers (Hjorth-Simonsen, 1972; Hjorth-Simonsen & Jeune, 1972; Witter, 2007; Witter et al., 2017). Whereas axons from LEC terminate in the outer one-third of the DG molecular layer, those from MEC terminate in the middle one-third. This spatial segregation is less evident in the monkey (Witter & Amaral, 1991; Witter, Van Hoesen, & Amaral, 1989). Irrespective of these anatomical differences, it is likely that in all species the projections from all parts of EC, irrespective of the number of subdivisions recognized by various authors, converge onto single neurons in DG and likely this holds true for CA3 and CA2 as well. In rodents and monkeys, entorhinal Layer III projections to CA1 and subiculum show a strikingly different organization from those arising from Layer II in that axons from LEC target neuronal populations different from those targeted by projections from MEC (Naber, Lopes da Silva, & Witter, 2001; van Groen, Miettinen, & Kadish, 2003; Witter & Amaral, 1991). Fibers from LEC innervate a part of CA1 close to the subiculum and the directly adjacent portion of the subiculum, whereas fibers from MEC terminate in the CA1 part adjacent to CA2 and in the subicular part adjacent to the presubiculum. The return projections to Layer V of EC from CA1 and subiculum follow a similar topographical organization, thus creating segregated anatomical connectivity loops between LEC and MEC on the one hand and discrete portions of CA1 and subiculum on the other hand (Tamamaki & Nojyo, 1995; Witter, 1993).

Further data in support of a dissociation between the two EC subdivisions come from recent gene expression studies. Embryonic gene expression patterns in mice indicate that the two subdivisions of EC originate from two different pallial structures. Whereas MEC originates in close association with HF, LEC has its origin in a specific dorsoposterior part of the cortical anlage. Interestingly, these genetically defined subdivisions of EC were also recognized in birds and reptiles (Medina, Abellan, & Desfilis, 2017). In line with this is a report that LEC and MEC in adult mice show strikingly different enhancer-expression profiles (Blankvoort, Witter, Noonan, Cotney & Kentros, 2018).

1.2 | Emergent functional cell types

1.2.1 | MEC

In MEC, most if not all of the functionally defined neuron types seem to relate to coding aspects of space or navigation relevant to path-

integration-based representation of self-location. One finds at least two types of spatially modulated cells types, grid cells, which have multiple equidistant firing fields organized in a hexagonal pattern (Fyhn, Molden, Witter, Moser, & Moser, 2004; Hafting, Fyhn, Molden, Moser, & Moser, 2005), as well as spatially modulated nongrid cells (Miao, Cao, Moser, & Moser, 2017; Rowland et al., 2018). Grid cells have been reported in rats (Hafting et al., 2005), mice (Fyhn, Hafting, Witter, Moser, & Moser, 2008), bats (Yartsev, Witter, & Ulanovsky, 2011), and nonhuman primates (Killian, Jutras, & Buffalo, 2012). Periodic, grid-like signals have been identified also in the human EC (Doeller, Barry, & Burgess, 2010; J. Jacobs & Lee, 2016). Grid cells coexist in MEC with other functionally defined cell types that code for the heading of the animal (head-direction cells), for speed (speed cells), environmental borders (border cells), or the distance and angle to objects (object-vector cells) (Høydal, Skytøen, Moser, & Moser, 2018; Kropff et al., 2015; Sargolini et al., 2006; Solstad et al., 2008). MEC is thus best considered as a cortical structure capable of computations underpinning path integration, an idiotetic navigation strategy in which the animal uses self-motion cues to track its current position relative to an arbitrary reference location (Buzsaki & Moser, 2013; Moser et al., 2017).

The complement of cortical relationships of MEC seems to match this overall presence of functional neuron-types. Main inputs to MEC originate from presubiculum and parasubiculum (Caballero-Bleda & Witter, 1993; Köhler, 1985; Room & Groenewegen, 1986; Shipley, 1975; van Groen & Wyss, 1990a, 1990b). Likewise, in rodents, cats, and monkeys, the retrosplenial cortex projects densely to MEC (Burwell & Amaral, 1998a; Jones & Witter, 2007; Kobayashi & Amaral, 2007; Room & Groenewegen, 1986). Additional inputs to MEC originate in visual association areas of the occipital cortex in the rat (Burwell & Amaral, 1998a; Kerr, Agster, Furtak, & Burwell, 2007), whereas these areas in monkeys primarily target PHC (Van Hoesen, 1982; Van Hoesen, Pandya, & Butters, 1972), and might thus influence MEC activity only indirectly. Projections from parietal cortex to MEC are weak to absent in all species studied; likely parietal cortex projects to PER and POR/PHC instead (Burwell & Amaral, 1998a; Kerr et al., 2007; Olsen, Ohara, Iijima, & Witter, 2017).

A final input that was historically specifically associated with MEC, a notion refuted in this paper, originates in POR in rodents and the cat or PHC as the likely homologous area in the monkey is referred to (Burwell, Witter, & Amaral, 1995). This notion of POR/PHC preferred connectivity with MEC seems in line with recent resting state connectional studies in humans (Maass et al., 2015; Navarro Schroder et al., 2015). However, a reanalysis of the available data has made us to reconsider this notion (Doan, Donate Lagartos, Nilssen, & Witter, 2018). As it turns out, in the monkey, the largest subdivision of PHC (area TF) sends projections that cover almost the entire AP axis of EC, showing an oblique distribution from caudomedial to rostrolateral, thus interacting with neurons in both MEC and LEC. Interestingly, the TF projections show an increasing density more rostrally in close association with the collateral sulcus (Insausti & Amaral, 2008; Suzuki & Amaral, 1994b). A reanalysis of the three main rodent studies (Burwell & Amaral, 1998a, 1998b; Naber, Caballero-Bleda, Jorritsma-

Byham, & Witter, 1997) and analysis of own additional anterograde tracing material in mice and rats led to a comparable conclusion that POR in the rat projects to both LEC and MEC. These analyses indicate that, in rodents at least, these projections do not differ much in anatomical strength, in line with quantitative retrograde data indicating that POR provide 7% of cortical input to MEC and 5% to LEC (Burwell & Amaral, 1998a). Like in the monkey, the projections from POR in the rat preferentially target more lateral and central parts of EC (Doan et al., 2018).

1.2.2 | Lateral entorhinal cortex

Functional descriptions of neurons in LEC are unfortunately less detailed and less numerous. It is clear that space does not represent a main correlate. In the rodent, grid cells have not been recorded in LEC and spatially modulated cells are scarce (Hargreaves et al., 2005; Yoganarasimha, Rao, & Knierim, 2011). Across cortical layers, LEC contains a low number of neurons that show emerging spatially confined firing fields, resembling hippocampal place fields, following the exposure to objects. These neurons signal either the current or previous locations of the introduced objects, that is, some represent a memory for object location or show spatial firing not associated to current or past object presence, but these cells seem to require objects present in the environment (Deshmukh & Knierim, 2011; Tsao et al., 2013). Similar physiological responses have been reported in upstream connected areas, including PER (Burke et al., 2012; Deshmukh, Johnson, & Knierim, 2012). Likewise, in the monkey EC, cells that responded specifically to the visual presentation of objects or their spatial location have been reported. Furthermore, a number of cells displayed sustained activity after the removal of the visual stimulus, indicating that object features, or locations were maintained in memory (Suzuki et al., 1997), thus strongly resembling neurons in LEC in the rat (Tsao et al., 2013). Whereas such object-in-place neurons are found preferentially in the anterior parts of EC, likely thus in LEC, place-selective neurons were more equally distributed along the anteroposterior extent of EC, thus likely such cells are common to both LEC and MEC (Suzuki et al., 1997).

Neurons in LEC are also involved in olfactory processing, as witnessed by the modulation of LEC neuronal activity by olfactory stimuli in rats (Leitner et al., 2016; Xu & Wilson, 2012; Young, Otto, Fox, & Eichenbaum, 1997). Such a role of LEC is in line with data from studies in rats, guinea pigs, and cats demonstrating that olfactory information to HF is mediated by way of LEC (Biella & de Curtis, 2000; Boeijinga & van Groen, 1984; Habets, Lopes da Silva, & Mollevanger, 1980; Schwerdtfeger, Buhl, & Germroth, 1990; Van Groen, Lopes da Silva, & Wadman, 1987; R. C. Wilson & Steward, 1978). The importance of the LEC in olfactory memory processes is indicated by observations of altered behavior in olfactory-dependent tasks following electrolytic damage of the LEC. Such interventions in rats have been shown to result in olfactory anterograde amnesia (Staubli, Fraser, Kessler, & Lynch, 1986; Staubli, Ivy, & Lynch, 1984), but also facilitation of olfactory recognition abilities (Otto, Schottler, Staubli, Eichenbaum, & Lynch, 1991; Wirth, Ferry, & Di Scala, 1998).

These effects are in line with the important role of LEC in olfactory associate learning (Ferry, Ferreira, Traissard, & Majchrzak, 2006; Igarashi, Lu, Colgin, Moser, & Moser, 2014). For example, coherence in the slow gamma range (20–40 Hz) between LEC and distal CA1 has been demonstrated during successful odor–place associations in an associative learning task. This coherence suggests a state of synchronized activity likely mediating information transfer between LEC and the HF during odor learning or facilitating the use of retrieved olfactory memory from HF to fine-tune olfactory discrimination (Colgin, 2016). Interestingly, for similar trials, such coherence was not observed between MEC and CA1 (Igarashi et al., 2014). Note that during spatial navigation MEC and CA1 showed coherence in the high gamma range (Colgin & Moser, 2010).

Like for MEC, also for LEC the accompaniment of cortical relationships seems to match this overall presence of functional neurontypes. Evoked odor responses in LEC are in agreement with extensive axonal projections to LEC from the piriform cortex and the olfactory bulb, reported in several species including mice, rat, cat, and monkey (Boeijinga & van Groen, 1984; Burwell & Amaral, 1998a; Haberly & Price, 1977; Insausti, Amaral, & Cowan, 1987; Kerr et al., 2007; Kosel, Van Hoesen, & West, 1981; Room, Groenewegen, & Lohman, 1984; Shipley & Adamek, 1984; G. W. Van Hoesen et al., 1972; Wouterlood, Mugnaini, & Nederlof, 1985; Wouterlood & Nederlof, 1983). Note that the projection from the olfactory bulb in monkeys is restricted to more rostral areas of LEC (Insausti et al., 1987).

Representation of objects likely reflect LEC's prominent input from PER, which only provide weak input to MEC (Burwell & Amaral, 1998b; Suzuki & Amaral, 1994b). PER is involved in discrimination between novel and familiar objects both in rodents and primates, and its activity reflects the integration of multimodal sensory aspects of objects, items, or events (Brown, 2008; Buckley & Gaffan, 2006; Bussey & Saksida, 2005, 2007; Bussey, Saksida, & Murray, 2006; Kealy & Commins, 2011; Naya, 2016; Taylor, Moss, Stamatakis, & Tyler, 2006).

1.3 | Neurons and networks in MEC and LEC are remarkably similar

The EC comprises six cortical layers, four of which contain the main populations of neurons, Layers II, III, V, and VI. The molecular Layer I contains only a low number of interneurons, and Layer IV or the lamina dissecans as it is often referred to, also contains very low numbers of neurons. Here we focus on the networks of Layers II, III, and V, because for the remaining layers, detailed connectional data for both entorhinal subdivisions are lacking.

1.3.1 | Layer II

Principal cells in Layer II of LEC and MEC come in at least two chemical types, calbindin- and reelin-expressing cells. In MEC, stellate cells make up most of the principal neurons and they are typically reelin-positive and calbindin-negative. The main counterparts in Layer II of MEC are the calbindin-positive pyramidal neurons. In LEC, a comparable subdivision has been reported with fan and multipolar neurons forming a substantial part of the reelin-positive principal cells and pyramidal neurons corresponding largely to calbindin-positive neurons (for review see Kobro-Flatmoen & Witter, 2019; Witter et al., 2017). In MEC, these two main principal cell types can also be distinguished based on their electrophysiological profiles. Stellate cells have a prominent sag potential, resonance, and membrane oscillations, whereas in the pyramidal neurons these properties are absent (Canto & Witter, 2012b; Fuchs et al., 2016). Note that the typical stellate properties are most pronounced in medially located neurons and become less apparent in more laterally positioned neurons. This gradient continues into LEC, such that in LEC medially positioned stellate/multipolar neurons share some of these properties with adjacent MEC stellate cells (Canto & Witter, 2012b). In lateral LEC, more subtle electrophysiological differences between the two chemically and morphologically defined neuron classes have been reported (Leitner et al., 2016; Tahvildari & Alonso, 2005) though this is not supported by others (Canto & Witter, 2012a; Desikan, Koser, Neitz, & Monyer, 2018).

Reelin-positive neurons in Layer II of both LEC and MEC give rise to the projections to DG, and likely also to CA3 and CA2. Likewise, calbindin-positive neurons show connectional motifs in both LEC and MEC that are very similar, in that they contribute to a wide range of extrinsic projections including hippocampal field CA1, many if not all of EC extrahippocampal target areas as well as commissural projections (Fuchs et al., 2016; Kitamura et al., 2014; Leitner et al., 2016; Varga, Lee, & Soltesz, 2010). Interestingly, recent data in rodents show that almost 50% of Layer II calbindin-positive neurons originate local excitatory projections, with MEC neurons projecting within MEC and sending projections to LEC, whereas the local LEC calbindin-positive projections predominantly distribute within LEC (Ohara et al., 2016; Figure 2).

The local circuits of principal cells in Layer II of MEC have been probed extensively and all data indicate that individual stellate reelin-positive cells lack monosynaptic connections with other principal cells, and the same is the common connectivity pattern between pyramidal calbindin-positive neurons. However, pyramidal neurons do have a relatively strong connection with stellate neurons (Fuchs et al., 2016; Winterer et al., 2017). Communication among neurons of the same class occurs through an intermediate inhibitory interneuron, in a mechanism by which activation of one or more principal neurons evokes disynaptic inhibitory currents in neighboring principal neurons (Couey et al., 2013; Fuchs et al., 2016; Pastoll, Solanka, van Rossum, & Nolan, 2013). The functional disynaptic link that illustrates the core principle of the stellate reelin-positive microcircuit is mediated by a single type of inhibitory neuron, the PV positive fast spiking cell (Armstrong, Szabadics, Tamas, & Soltesz, 2011; Fuchs et al., 2016; Varga et al., 2010) and in case of grid cells in Layer II the same has been reported (Buetfering, Allen, & Monyer, 2014). In case of calbindin-positive pyramidal cells, the interneuron in between belongs to the heterogeneous $5HT_{3A}$ expressing population of interneurons (Fuchs et al., 2016). In a recent study, the Layer II network in LEC was analyzed, showing that very similar connectivity motifs are present.
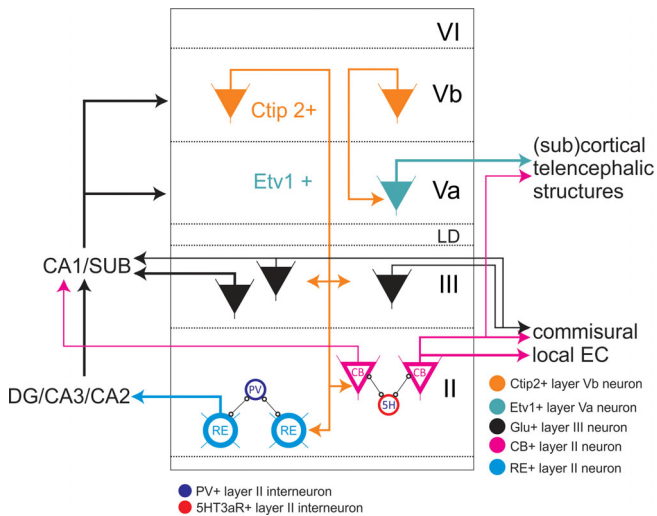
FIGURE 2   Summary of shared neuron types and local circuit motifs of the lateral and medial entorhinal cortex. Because very little to nothing is known concerning Layer VI, no neurons and circuits are indicated. In Layer II, we show the two types of principal neurons, reelin (RE) and calbindin (CB) positive, and their specific local connectivity to parvalbumin (PV) and 5HT3a-receptor (5H) expressing interneurons, respectively. Also shown are the main projections to hippocampal fields and intrinsic and commissural projections. Not included is the observation that these two populations of principal cells do communicate through a separate class of pyramidal neurons. In Layer III, about 40% of the neurons projecting to CA1 and subiculum do give rise to commissural collaterals. Pyramidal cells in Layer III show a relatively strong developed local excitatory network (not indicated). In Layer V, we indicate that VB neurons project to Va as well as to Layers II and III. Note that although data indicate that the superficially projecting Layer Vb neurons also project to Laver Va, conclusive evidence for that is still lacking, so we have depicted as if these respective projections originate from different principal neurons. Inputs to layers and identified neurons therein are not indicated since they differ between LEC and MEC. CA3, CA2, CA1 subfields of the hippocampus proper; CB, calbindin-positive neuron; DG, dentate gyrus; EC, entorhinal cortex; LD, lamina dissecans; RE, reelin-positive neuron [Color figure can be viewed at wileyonlinelibrary.com]

Like in MEC, principal neurons in LEC lack monosynaptic connectivity among members of their own class, showing a preferred disynaptic connectivity mediated by interneurons (Nilssen et al., 2018). Note that the prevalent types of interneurons mediating disynaptic inhibitory connectivity between principal neurons in LEC are partially different from those in MEC. A detailed analysis of the diverse population of interneurons in EC is not yet available and the relevance of these interneuronal differences is not yet fully understood.

1.3.2 | Layer III

Layer III in both LEC and MEC comprises a homogenous population of spiny excitatory pyramidal neurons, multipolar neurons, and interneurons (Germroth, Schwerdtfeger, & Buhl, 1989; Gloveli, Schmitz,

Empson, Dugladze, & Heinemann, 1997; Köhler & Chan-Palay, 1983; Wouterlood & Pothuizen, 2000; Wouterlood, van Denderen, van Haeften, & Witter, 2000). The pyramidal and multipolar neurons are the source of the projections to CA1 and subiculum (Canto & Witter, 2012a, 2012b; Germroth et al., 1989; Tahvildari & Alonso, 2005; Tang et al., 2015). Layer III neurons also project contralaterally to the hippocampus and EC (Steward & Scoville, 1976), with about 40% of the Layer III hippocampal projecting cells in MEC sending collaterals to the contralateral MEC (Tang et al., 2015).

The microcircuits of Layer III seem markedly different from those seen in Layer II, showing higher connection probability between principal neurons (Dhillon & Jones, 2000; Kloosterman, Van Haeften, Witter, & Lopes Da Silva, 2003; Tang et al., 2015; van der Linden & Lopes da Silva, 1998). Neurons in Layer III, like those in Layer II, are main recipients of the local deep-to-superficial projections, which predominantly originate from neurons in Layer V (Kloosterman et al., 2003; Ohara et al., 2018; van Haeften, Baks-Te Bulte, Goede, Wouterlood, & Witter, 2003). Currently, no correlations have been reported between morphology, connectional profile, and electrophysiological in vitro and in vivo properties (Canto & Witter, 2012a, 2012b; Tang et al., 2015) (Figure 2).

1.3.3 | Layer V

Layer V is commonly subdivided into a Layer Va and Vb (Amaral et al., 1987; Boccara et al., 2015; Canto & Witter, 2012a, 2012b; Hamam, Amaral, & Alonso, 2002; Hamam, Kennedy, Alonso, & Amaral, 2000). In mice and rats, the expression pattern of the transcription factors Etv1 and Ctip2 provides for the differentiation between the two sublayers Va and Vb, respectively. This organization prevails across the whole mediolateral and dorsoventral extent of EC. In both MEC and LEC, Layer Va cells are the major output neurons projecting to diverse cortical and subcortical structures (Kosel et al., 1982; Ohara et al., 2018; Ramsden, Surmeli, McDonagh, & Nolan, 2015; Surmeli et al., 2015; Swanson & Köhler, 1986; G. W. van Hoesen, 1982). Surprisingly, Layer Vb cells are selectively targeted by the outputs from the hippocampus, originating in CA1 and subiculum (Surmeli et al., 2015), though this is apparently only true for projections originating from dorsal levels of subiculum and CA1; increasingly more ventral levels apparently innervate neurons in both Layer Va and Vb (Egorov, Lorenz, Rozov, & Draguhn, 2017; Ohara and Witter, unpublished data). Layer Vb neurons in both LEC and MEC innervate Layer Va as well as Layers II and III (Ohara et al., 2018), corroborating older data that neurons in Layer Vb issue superficially directed axon collaterals (Canto & Witter, 2012a, 2012b; Hamam et al., 2000; Hamam et al., 2002). Preliminary in vitro single cell recordings indicate that the effective connectivity to Layer III neurons is higher than the connectivity to Layer II (Ohara and Witter, unpublished data). Layer Vb neurons, but not Layer Va neurons, are also targeted by projections originating from reelin neurons in Layer II of MEC (Surmeli et al., 2015). Layer V is also innervated by cortical projections from frontal and cingular domains, including the anterior cingular cortex (Area 24) in case of LEC and retrosplenial cortex (Area 29 and 30) in case of

MEC. Projections from the retrosplenial cortex target, among others, spiny pyramidal neurons that issue axons to superficial layers (Czajkowski et al., 2013).

In conclusion, neuron types, local circuit motifs, and the laminar origin and termination of outputs and inputs respectively, in MEC and LEC are strikingly similar (Figure 2). This seems somewhat counterintuitive to the striking functional differences described earlier, and reports that LEC and MEC develop from different parts of the pallium (Medina et al., 2017). As concisely and eloquently reviewed by Desfilis and colleagues (Desfilis, Abellan, Sentandreu, & Medina, 2018), MEC shares its embryological pallial origin with HF, whereas LEC shares its origin with PER, orbitofrontal, and insular domains of the cortex. The latter are cortical structures with which LEC selectively is connected and that are also strongly interconnected as argued earlier. Data on the origin of POR are currently lacking. Both LEC and MEC share an input from the olfactory or piriform cortex, but the connections with the olfactory bulb are almost exclusive with LEC. Comparable patterns can be found in case of the presumed homologous regions in lizards and chicken (Desfilis et al., 2018). Interestingly, LEC and MEC also differ with respect to the sequential developmental origin of the different layers, in that LEC follows the "neocortical" inside-out pattern, whereas in MEC, like in HF, the developmental gradient is such that outside layers, that is, Layer II in case of MEC, develop first. This latter observation is supported by developmental data recently reported in the mouse (Donato, Jacobsen, Moser, & Moser, 2017). The latter authors not only reported that neurons in MEC Layer II are the first to mature, but that interfering with the maturation of these early developing Layer II MEC neurons postpones the subsequent maturation of all neurons in LEC. This suggests that MEC layer II neurons already in early stages of development directly influence the development of LEC.

One way for such a developmental influence to take place is through the presence of projections from MEC to LEC. Though long-ranging intrinsic connections may already be partially present in the postnatally developing brain (O'Reilly et al., 2015), they are quite extensive in adults; note that in the monkey the long-range extent does not cover the total AP axis of EC but seems to indicate that the connectional hub is formed by the central portion of EC (Chrobak & Amaral, 2007; Dolorfo & Amaral, 1998; Köhler, 1986, 1988; Witter, Room, Groenewegen, & Lohman, 1986). It would be of interest to know whether similar connections exist in the reptilian brain. Comparable long-range projections exist between PER and POR in rats (Burwell & Amaral, 1998b) and PER and PHC in monkeys (Lavenex et al., 2004). Similar to what was noted above for intrinsic EC connections in the monkey, the caudal part of PER, located centrally along the AP axis of PER/PHC is the main hub for these long-range connections. The overall patterns of origin and terminal distributions of these projections supports the conjecture that POR/PHC projections to PER are of the feedforward type whereas the reverse projections fit more the patterns of feedback projections (Barbas & Rempel-Clower, 1997).

These observations, taken together with the data described above that the projections of POR/PHC are not restricted to MEC but also target LEC, makes it relevant to ask the question what these posterior parts of PHR contribute functionally to PHR and thus to HF. To address this question, it is worthwhile to summarize the cortical input patterns described earlier by emphasizing that the widespread projections from POR/PHC to both MEC and LEC is the exception to the rule because most cortical afferents to LEC and MEC, like those to PER and POR/PHC, are selective for one or the other.

1.4 | Connectional and functional position of POR/PHC

Inputs from POR/PHC and PER in monkeys give rise to 60% of the cortical input to the EC (Insausti et al., 1987; Insausti & Amaral, 2008). This percentage includes the temporal polar cortex, which is considered part of the perirhinal cortex, likely specific for primates (Insausti et al., 1987). Within the primate PHC, there are two main subdivisions, TH and TF, where TF is further subdivided into lateral and medial components. Whereas area TH receives mainly auditory input from the superior temporal gyrus but weak or no direct visual input, both subdivisions of area TF receives strong visual inputs from areas TEO and V4, as well as from the retrosplenial cortex and the dorsal bank of the superior temporal sulcus. The lateral part of TF receives additional inputs from posterior parietal areas (Suzuki & Amaral, 1994a). In the rat, approximately 13% of the total cortical inputs to EC originate in PER and POR (Kerr et al., 2007). In case of POR, 40% of its cortical inputs originate in visual areas, 7% in posterior parietal cortex, and 16% in temporal association cortex; inputs from auditory, somatosensory, olfactory as well as frontal areas including insular, orbitofrontal, and medial prefrontal areas are negligible (Burwell & Amaral, 1998a; Furtak, Wei, Agster, & Burwell, 2007). Note that these input patterns are very different from those reported for PER (see later). In line with these prominent cortical inputs, which are largely reciprocated, POR is typically portrayed as providing visuospatial information to EC. This is supported by reports in humans that the PHC supports spatial perception in real time (Epstein, Parker, & Feiler, 2007), though there are also strong data both in rats and primates that POR/PHC is particularly relevant in relation to processing contextual associations (Aminoff, Gronau, & Bar, 2007; Furtak et al., 2012). In many instances the data relate to object-in-space/location or object-in-context associations (Bohbot et al., 1998; Hayes, Nadel, & Ryan, 2007; Maguire, Frith, Burgess, Donnett, & O'Keefe, 1998). Data in rats are sparser, but single cells responses of neurons in POR indicate that around 30% of POR cells showed object-location conjunctive encoding (Furtak et al., 2012). The latter authors suggested that POR combines object and pattern information from PER with incoming contextual and spatial information from retrosplenial and posterior parietal cortices to represent specific environmental contexts. This is in line with results of lesion studies in rats, showing that POR processes information about objects in relation to place or context (Gaffan, Healey, & Eacott, 2004; Norman & Eacott, 2005). Furtak and colleagues (Furtak et al., 2012) further reported that neuronal responses in POR show evidence of reflecting changes in context, or responses that relate to egocentric coding, which they relate to inputs

from parietal cortex, as well as. The latter is reminiscent of recent reports of egocentric coding in LEC (Wang et al., 2018; see also below) whereas the former is suggested to be associated with the strong connectivity from PER to POR. Based on these additional neuronal properties, they suggest that POR monitors the context for changes and updates the representation of the context accordingly. This updated representation would be a subsequent input to downstream areas, such as PER, EC, and HF. This suggestion seems to conflict somewhat with data indicating that PHC in humans is more active in response to stationary, spatially defining objects than to spatially ambiguous objects (Mullally & Maguire, 2011).

An alternative proposal, which we prefer to entertain, might be that changes in object/contextual or spatial relationships are perceived in downstream areas, such as PER, and fed back to the POR network to allow for an update of the contextual representation as to secure stability. This fits with the laminar pattern of projections between PER and POR/PHC (Lavenex et al., 2004). Interestingly, the proposition that POR plays a critical role in providing a stable representation of object-place associations is in line with very recent data showing that POR receives information from the superior colliculus, via its connections to LP (Beltramo & Scanziani, 2019; Bennett et al., 2019), which might provide an unconscious representation of self-movement related changes in the perceived position of objects. It further fits with the recent suggestion that both LEC and MEC may process visual context information, likely thus derived from POR, but that both use this information in a completely different functional way, related to the appropriate motor output (Yoo & Lee, 2017). Based on this notion one could predict that silencing of visual inputs to POR or silencing POR itself might change the representation of the context and thus will induce place cell remapping the hippocampus.

1.5 | Connectional and functional position of the PER/LEC interface

Neurons in LEC are responsive to objects-in-position associations, likely without discriminating between the nature of the object (Deshmukh & Knierim, 2011; Tsao et al., 2013). However, neurons and networks in LEC code beyond this by incorporating representations of context, because LEC is critically involved in complex object-context associations binding together information relating to objects, places, and contexts (Scaplen, Ramesh, Nadvar, Ahmed, & Burwell, 2017; Wilson et al., 2013; Wilson, Watanabe, Milner, & Ainge, 2013). Recent electrophysiological studies provide data suggesting that distinct contextual features of experiences are represented in LEC both at the single-cell and population level (Pilkiw et al., 2017; Tsao et al., 2018). Further analysis of LEC ensemble activity indicated a shift of population states according to the temporal progression of the experimental event. These data suggest that the activity of LEC populations carries a representation of time, brought about by the encoding of sequences of ongoing events. Although comparable data have been obtained in the anterolateral parts of the monkey and human EC (Montchal et al., 2019; Naya & Suzuki, 2011), the representation of incremental timing information, based on the sequence of ongoing

events is weaker in EC compared to that in PER and HF (Naya & Suzuki, 2011). Likewise, although LEC neurons can integrate item and time information (Naya & Suzuki, 2011) conjunctive item neurons seem to be a more prevalent type in monkey LEC (Naya, Chen, Yang, & Suzuki, 2017).

Neurons and networks in the lateral part of LEC may embed other features to these already complex representations, including olfactory and salience percepts. The proposition that LEC neurons code for high order associations is in line with recent observations, indicating that individual principal cells in Layer II of LEC receive convergent inputs from PER, POR, MEC, olfactory piriform cortex, and from contralateral LEC Doan, Nilssen, & Witter, 2016). It is worth reiterating that the connectivity motif in Layer II in LEC is comparable to that of Layer II in MEC (Nilssen et al., 2018). We thus proposed that neurons in Layer II of LEC may show hexagonal, or at least regularly repeating, firing patterns along dimensions defined by their inputs (Nilssen et al., 2018). In contrast to the pure spatial representation observed in MEC, periodic patterns might arise in LEC to represent complex features of the context as part of a particular episode (Bellmund, Gardenfors, Moser, & Doeller, 2018; Constantinescu, O'Reilly, & Behrens, 2016). In this view, the inputs from POR and MEC provide LEC with relevant information to act as an integrative hub between what has been referred to as an egocentric representation of a context with the allocentric representation of self-position in that context (Wang et al., 2018; Yoo & Lee, 2017).

Here we emphasize the relevance of the PER/LEC interface. As argued earlier, multimodal representations of objects depend on perirhinal networks and PER also plays a relevant role in novelty-familiarity discriminations. Such functions likely reflect the variety of inputs targeting PER. Interestingly, PER shares most of these inputs with the strongly reciprocally connected directly adjacent lateral parts of LEC. These inputs include dense inputs from insular, orbitofrontal cortex, anterior cingulate cortex, temporal association cortex, as well as from the lateral and basal amygdala. In rats, additional inputs originate from the medial prefrontal prelimbic and infralimbic cortex, although these projections do target MEC and POR as well, be it with a lesser density of termination (Burwell & Amaral, 1998a; Insausti et al., 1987; Jones & Witter, 2007; Kerr et al., 2007; Kondo & Witter, 2014; Krettek & Price, 1977; Mathiasen, Hansen, & Witter, 2015; Mohedano-Moriano et al., 2007; Pitkanen, Kelly, & Amaral, 2002; Room & Groenewegen, 1986; Stefanacci & Amaral, 2000; Suzuki & Amaral, 1994a; Van Hoesen & Pandya, 1975a; Van Hoesen et al., 1975; Van Hoesen, 1982; Van Hoesen et al., 1972; Vaudano, Legg, & Glickstein, 1991; Vertes, 2004). Many of these forebrain areas play a role in coding of information concerning the salience or the reinforcing value of a particular context or elements in that context (Dixon, Thiruchselvam, Todd, & Christoff, 2017; Ritchey, Wang, Yonelinas, & Ranganath, 2018; Wallis, 2007). This would enable the PER/LEC interface to evaluate sensory cues not only as part of a particular context or episode but add information about the current emotional value of individual elements of the context or the context as a whole. Note that the frontal cortical inputs mainly, though not exclusively, target deeper layers of the PER/LEC interface and thus are in a

potential position to influence the main cortical output stream, mediated by the deep EC layers. Irrespective, we argued that deep entorhinal circuits also influence superficial circuits, so likely these frontal inputs have a role to play in modifying sensory representations in the superficial input network of PER/LEC as well. Of course, the lateral amygdala input might be the most relevant, because it terminates densely in superficial layers and it shares this superficial termination with olfactory inputs and those from higher order temporal sensory association cortex (Pitkanen et al., 2002; Pitkanen, Pikkarainen, Nurminen, & Ylinen, 2000).

In line with this shared input, we propose that it is the PER/LEC interface that provides the optimal substrate to detect changes in the context. This proposition is strengthened by an additional unique transmission property in this network. Connectivity from PER to adjacent LEC is governed by a striking inhibitory gating (de Curtis & Pare, 2004). This "wall of inhibition" is overcome by the convergence in time and space of at least two coincident inputs (Samarth, Ball, Unal, Pare, & Nair, 2017). These could be coincident inputs from temporal cortex or PER with lateral amygdala (Kajiwara, Takashima, Mimura, Witter, & Iijima, 2003; R. Paz, Pelletier, Bauer, & Pare, 2006; Pelletier, Apergis-Schoute, & Pare, 2005), mPFC and PER (Rony Paz, Bauer, & Pare, 2007), or insular cortex and amygdala (Willems, Wadman, & Cappaert, 2016). Coincident changes in sensory and saliency inputs would thus allow activation of LEC where neurons are capable of coding such changes over time. As already proposed, POR/PHC inputs would provide a stable representation of the current context, allowing the PER/LEC interface to detect relevant changes in the context over time, in line with the aforedescribed sequence coding that apparently occurs in the network. Subsequent transmission of salient changes in these contextual features would then result in updating HF representations of an episode. At the same time PER projections to POR and LEC projections to MEC would provide feedback information allowing these networks to incorporate these changes into their updated stable representations.

1.6 | Conclusions and future perspectives

We started this review with the concept of parallel pathways connecting HF with the cortical mantle and that there might be subdivisions of EC mediating such parallel pathways, because EC forms a major cortical input and output hub for HF. A key element in the development of this notion was the conceived preferred connectivity of PER with LEC and PHC/POR with MEC. Of likely similar influence was the notion of a hierarchical organization of the parallel streams culminating in the final convergence at the level of the networks in HF. We have argued that this conceived preferred connectivity in case of POR/PHC is incorrect. POR/PHC contributes to both pathways, providing both MEC and PER/LEC with what we propose is a continuously stable representation of context.

We support earlier suggestions that convergence takes place at multiple levels in the EC-HF memory system and provide new evidence, integrated in already existing data that this happens predominantly in LEC. In addition, we conclude that the connectional

differences between LEC and MEC strongly support the concept of functional differences. Whereas the PER/LEC interface provides the hippocampus with a highly integrated, multidimensional representation of sensory information, including changes over time, constituting the content of an episodic memory, MEC provides the position of the subject, coded in an allocentric space (Eichenbaum et al., 2007; Lisman, 2007).

Contrary to previous expectations, all data concerning the intrinsic network motifs of LEC and MEC point to a striking overall similarity, notwithstanding that subtle differences in interneuron contributions may exist. The delicate role, undoubtedly played by interneurons, will be important to refine our understanding of information coding in the two subdivisions of EC. Our current knowledge leads to the intriguing conclusion that two embryologically different parts of the cortex, that even follow different developmental schemes, inside-out, versus outside-in, eventually result in two similar and strongly interconnected areas, which independently cannot fully support hippocampal functions. The shared network motifs of LEC and MEC suggest that HF requires an input that uses a particular "language" that originates from these network motifs. The developmental dependence of LEC on MEC input (Donato et al., 2017) supports the notion that the hippocampal anlage shapes its LEC input system to represent evolutionary new, more complex sensory and higher order stimuli, and communicates with HF using the same network dependent language to communicate with HF as the developmentally HF-associated-MEC system. It would be of interest to study this conjecture experimentally. One approach might be to use the reptilian brain as a simple model comparing olfactory and spatial representations in the likely homologues of LEC and MEC, which, like in the mammalian brain, project to all subdivisions of HF (Desfilis et al., 2018). Understanding this coding principle might be relevant, because olfaction has been proposed as a universal system among the sensory systems to mediate navigation and memory formation (L. F. Jacobs, Arter, Cook, & Sulloway, 2015). A second, very relevant and promising approach would be to pursue computational modeling of the output of such a network motif and study how HF responses depend on this input by systematically perturbing the input language. A similar argument can be made for the functional relevance of the hippocampal output network mediated by EC deep layers, which is still grossly understudied.

CONFLICT OF INTERESTS

The authors declare no potential conflict of interest.

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