MEMORY SYSTEMS

The anatomy of memory: an interactive overview of the parahippocampal–hippocampal network

N. M. van Strien[*||], *N. L. M. Cappaert*[‡||] *and M. P. Witter*[*§]

Abstract | Converging evidence suggests that each parahippocampal and hippocampal subregion contributes uniquely to the encoding, consolidation and retrieval of declarative memories, but their precise roles remain elusive. Current functional thinking does not fully incorporate the intricately connected networks that link these subregions, owing to their organizational complexity; however, such detailed anatomical knowledge is of pivotal importance for comprehending the unique functional contribution of each subregion. We have therefore developed an interactive diagram with the aim to display all of the currently known anatomical connections of the rat parahippocampal–hippocampal network. In this Review, we integrate the existing anatomical knowledge into a concise description of this network and discuss the functional implications of some relatively underexposed connections.

In the more than 100 years since the first explorations of the parahippocampal–hippocampal network by Ramon y Cajal[1], numerous detailed anatomical tract-tracing analyses (BOX 1) have been published. These studies were sparked by the discovery of a prominent relationship between declarative memory and structures in the human medial temporal lobe, in particular the hippocampal formation (HF)[2]; the importance of the parahippocampal region (PHR) for memory was established only later[3]. An increasingly complex picture of the connectivity within and between the HF and the PHR has emerged over the years, and comprehensive knowledge of the PHR–HF network lies at the basis of understanding its functions[4].

The level of anatomical detail at which an experiment must be carried out or results interpreted depends on the questions under investigation. In some instances, the effects of experimental manipulations can be interpreted using connectivity data at an overall network level (without taking the details of local networks into account). Other studies require more detail, but even those studies that benefit from a detailed understanding of the circuitry often do not, for a variety of reasons, take all the known connections into consideration. Sometimes connections are simply overlooked, whereas other times connections are intentionally left out because they seem to have no function and are therefore considered irrelevant for a particular theoretical interpretation. Eventually, such underexposed connections tend to be erased from the common scientific memory. For this Review, we have assembled the extensive anatomical PHR–HF connectivity literature, focusing on all known connections of one frequently used experimental animal: the rat. We introduce a new approach to describe the network connectivity that uses an interactive diagram to display the complete PHR–HF connectivity (see Supplementary information S1 (figure) and Supplementary information S2 (box)). The complex and detailed connectivity patterns in this diagram are made accessible through the ability to switch on and off individual or groups of network connections between cortical layers and/or anatomical areas. The information this diagram provides could prove to be useful at a time when research is moving beyond the functional explanations that can be provided by a PHR–HF circuitry model that contains only a subset of the connections; moreover, it might lead to a re-evaluation of the functional importance of connections that have previously been ignored.

This Review first describes the anatomical concepts that are essential to understanding the PHR–HF circuitry (for an extensive description, see REFS 5–7). Next, it presents an overview of the main PHR–HF circuits as well as of some of the lesser-known aspects of the circuitry, using the interactive diagram (Supplementary information S1 (figure)). Subsequently, it shows how having detailed knowledge of the PHR–HF circuitry can

*Department of Anatomy and Neurosciences, VU University Medical Center, P.O. BOX 7057, 1007 MB Amsterdam, The Netherlands. ‡SILS Center for Neuroscience, University of Amsterdam, 1098 SM Amsterdam, The Netherlands. §Kavli Institute for Systems Neuroscience, and Centre for the Biology of Memory, Department of Neuroscience, Norwegian University of Science and Technology, N-7489 Trondheim, Norway. ||These authors contributed equally to this work. Correspondence to N.M.v.S. e-mail: n.vanstrien@temporal-lobe.com
doi:10.1038/nrn2614

Box 1 | **Neuroanatomical tract-tracing methods**

Most of what is known today about the pathways that connect neurons in different brain regions has been discovered by using neuroanatomical tract-tracing techniques[156]. A tracer is a substance that allows such pathways to be visualized. Tracers can be injected intracellularly to label the dendrites and axons of a neuron. Both autofluorescent dyes (for example, Lucifer yellow and Alexa dyes) and biotin-derived dyes are often used for intracellular labelling, as they can be easily visualized using fluorescent microscopy. Alternatively, a tracer can be injected at a stereotaxically defined extracellular location in the *in vivo* brain. The tracer is taken up by neurons at the injection site and is transported or diffuses within cells. A tracer substance can be transported anterogradely from the soma towards the axon terminals (for example, *Phaseolus vulgaris* leucoagglutinin), retrogradely from the axon terminals towards the soma (for example, Fast Blue), or it can be transported in both directions (for example, horseradish peroxidase). Another tract-tracing method involves creating small lesions and visualizing the resulting degeneration; the labelled connections are generally assessed using light microscopy. Electron microscopy can be used to visualize whether a presynaptic axon contacts a postsynaptic element. This is a very accurate but time-consuming method because only small pieces of tissue can be examined at one time. Alternatively, confocal microscopy allows three-dimensional reconstruction of larger pieces of tissue and can indicate whether pre- and postsynaptic elements are likely to form a synapse. A question of current interest is whether confocal microscopy is reliable enough for indicating such contacts. In order to increase our understanding of the connectivity of the brain and its related function, accurate numbers that provide information about pathways' projection intensity and termination density are needed. To achieve this, techniques using viral tracers[157] and new genetic tools[158] are being developed.

aid one's understanding of some of the functional processes that engage the PHR–HF regions, such as memory formation, spatial navigation and temporal dynamics.

Hippocampal–parahippocampal anatomy

The rat HF is a C-shaped structure that is situated in the caudal part of the brain. Three distinct subregions can be distinguished (FIG. 1): the dentate gyrus (DG), the hippocampus proper (consisting of CA3, CA2 and CA1) and the subiculum. The cortex that forms the HF has a three-layered appearance. The first layer is a deep layer, comprising a mixture of afferent and efferent fibres and interneurons. In the DG this layer is called the hilus, whereas in the CA regions it is referred to as the stratum oriens. Superficial to this polymorph layer is the cell layer, which is composed of principal cells and interneurons. In the DG this layer is called the granule layer, whereas in the CA regions and the subiculum it is referred to as the pyramidal cell layer (stratum pyramidale). The most superficial layer is referred to as the molecular layer (the stratum moleculare) in the DG and the subiculum. In the CA region the molecular layer is subdivided into a number of sublayers. In CA3, three sublayers are distinguished: the stratum lucidum, which receives input from the DG; the stratum radiatum, comprising the apical dendrites of the neurons located in the stratum pyramidale; and, most superficially, the stratum lacunosum-moleculare, comprising the apical tufts of the apical dendrites. The lamination in CA2 and CA1 is similar, with the exception that the stratum lucidum is missing.

The PHR lies adjacent to the HF, bordering the subiculum. It is divided into five subregions: the presubiculum, the parasubiculum, the entorhinal cortex (EC, consisting of medial (MEA) and lateral (LEA) areas), the perirhinal cortex (PER, consisting of Brodmann areas (A) 35 and 36) and the postrhinal cortex (POR). The PHR is generally described as having six layers. The coordinate systems that define position within the HF and the PHR are explained in FIG. 1.

Circuitry of the PHR–HF region

In the interactive diagram (FIG. 2; Supplementary information S1 (figure)) we attempted to display all of the PHR–HF connections that have been reported in the anatomical literature concerning the rat (for references see Supplementary information S3 (table)). The interactive diagram contains almost 1,600 connections, which can be displayed at a customizable level of complexity. This allows easy comparisons between the detailed PHR–HF circuitry illustrated by the diagram and a 'standard' model of this circuitry (FIG. 3), which displays the subset of connections that are currently most often used in the field (based on an analysis of a selection of recent key studies[8–15]).

Connectivity within the PHR. In the standard model (FIG. 3), the projections from the PER and the POR to the EC are often depicted with a topology that emphasizes PER-to-LEA and POR-to-MEA relationships. However, as can be seen in the interactive diagram, the available data indicate (see figure 1a in Supplementary information S4 (figure)) that the POR also projects to the LEA, although quantitatively to a lesser extent than the PER (4.9% versus 15.6%, respectively, of the total cortical input)[16]. Likewise, the PER also projects to the MEA (see figure 1b in Supplementary information S4 (figure)), contributing a level of cortical input equal to that of the POR (7.5%)[16]. Neurons in layers II, III, V and VI of A35 and A36 of the PER project in a convergent way to LEA layers II and III[17], whereas the PER projection to the MEA arises mainly from A36 (REFS 16,17). The POR projection to the LEA arises from layers II, III, V and VI and terminates in layers II and III[16,17]. The POR projection to the MEA originates from the same layers and terminates preferentially in the superficial layers, although some fibres can be seen in the deep layers of the MEA[16,18].

The EC reciprocates the projections from the PER and the POR, as depicted in the standard model. A detailed look at the interactive diagram shows that there are projections from layers III and V of the LEA to all layers of A35 and A36 (REFS 16,17,19), and from the MEA to all layers of A35 (REFS 16,17,20) (see figure 2a in Supplementary information S4 (figure)). The MEA also projects to A36 (REFS 16,21). Both the MEA and the LEA project to the POR, but details of the topography of this connection in the rat are currently not available[16,21,22] (see figure 2b in Supplementary information S4 (figure)).

Traditionally, little attention has been paid to the connections between the PER and the POR, although there is extensive connectivity between these regions. POR layers II and V project to all layers of A35 and A36; POR layer III also projects to A36 (see figure 3a in Supplementary information S4 (figure)). Rostral levels of the POR provide the densest projection to caudal levels of A35 and

Temporal dynamics
Properties of neurons in a network, such as precise spike times and firing rates, that facilitate information transfer.

Convergence
When inputs from different brain regions congregate on to single cells or on to a local network in another region.

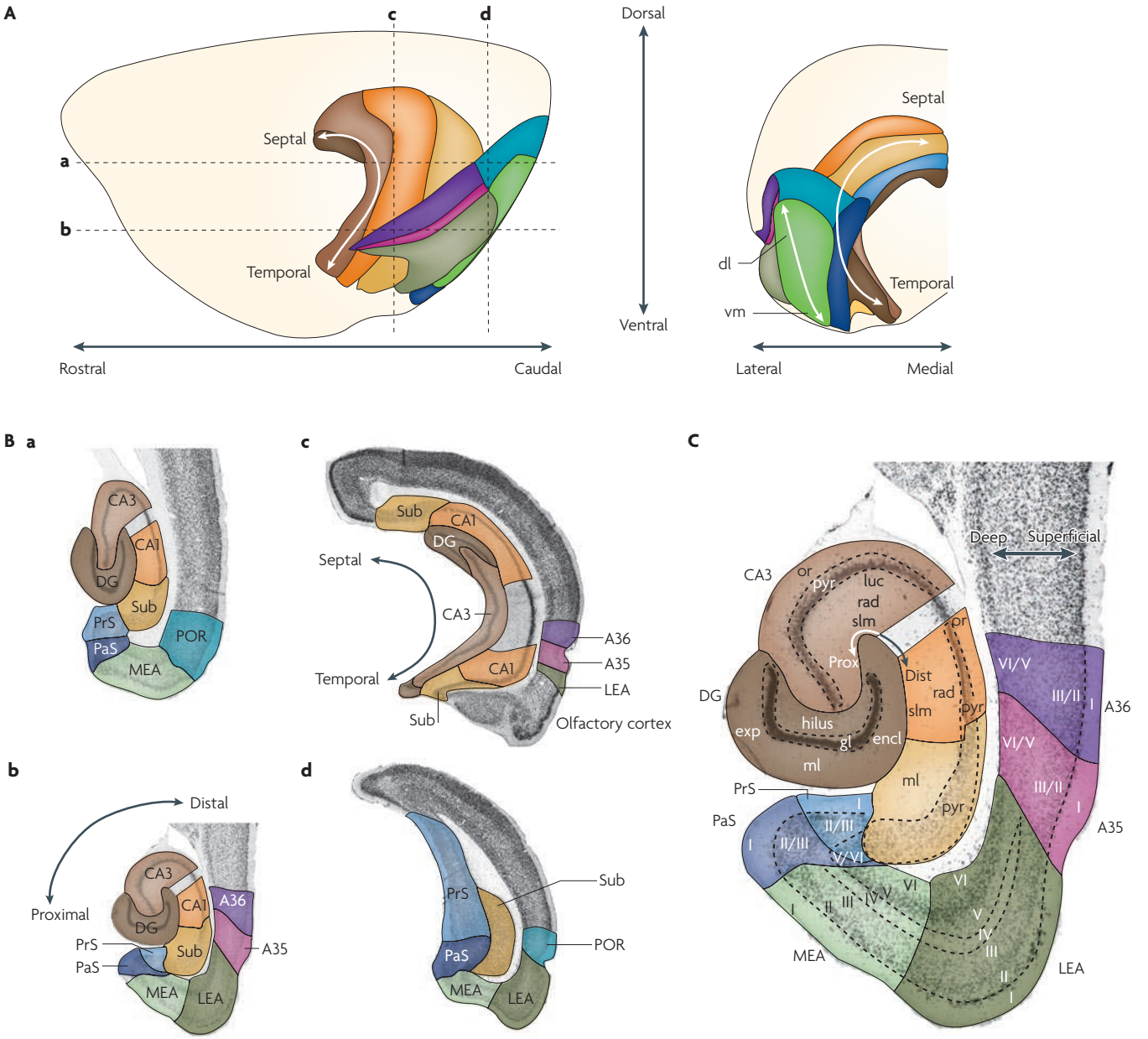

Figure 1 | **Representations of the hippocampal formation and the parahippocampal region in the rat brain.** **A** | Lateral (left panel) and caudal (right panel) views. For orientation in the hippocampal formation (consisting of the dentate gyrus (DG; dark brown), CA3 (medium brown), CA2 (not indicated), CA1 (orange) and the subiculum (Sub; yellow)), three axes are indicated: the long or septotemporal axis (also referred to as the dorsoventral axis); the transverse or proximodistal axis, which runs parallel to the cell layer and starts at the DG; and the radial or superficial-to-deep axis, which is defined as being perpendicular to the transverse axis. In the parahippocampal region (green, blue, pink and purple shaded areas), a similar superficial-to-deep axis is used. Additionally, the presubiculum (PrS; medium blue) and parasubiculum (PaS; dark blue) are described by a septotemporal and proximodistal axis. The entorhinal cortex, which has a lateral (LEA; dark green) and a medial (MEA; light green) aspect, is described by a dorsolateral-to-ventromedial gradient and a rostrocaudal axis. The perirhinal cortex (consisting of Brodmann areas (A) 35 (pink) and 36 (purple)) and the postrhinal cortex (POR; blue-green) share the latter axis with the entorhinal cortex and are additionally defined by a dorsoventral orientation. The dashed lines in the left panel indicate the levels of two horizontal sections (**a**,**b**) and two coronal sections (**c**,**d**), which are shown in part **B**. All subfields of the parahippocampal–hippocampal region are colour-coded in correspondence with the interactive diagram in Supplementary information S1 (figure). A further description of the anatomical features of each subfield is provided in the legend of this supplementary information. **C** | A Nissl-stained horizontal cross section (enlarged from part **Bb**) in which the cortical layers and three-dimensional axes are marked. The Roman numerals indicate cortical layers. CA, cornu ammonis; dist, distal; dl, dorsolateral part of the entorhinal cortex; encl, enclosed blade of the DG; exp, exposed blade of the DG; gl, granule cell layer; luc, stratum lucidum; ml, molecular layer; or, stratum oriens; prox, proximal; pyr, pyramidal cell layer; rad, stratum radiatum; slm, stratum lacunosum-moleculare; vm, ventromedial part of the entorhinal cortex.

Reciprocal connections
Bidirectional, equivalent connections between two areas, networks or neurons.

Perforant pathway
Axons that originate in the superficial layers of the EC and are distributed to all fields of the hippocampus.

A36. Additionally, the POR projection to A36 is stronger than that to A35 (REFS 16,17,23). The PER projection to the POR originates in PER layers II, V and VI[16,17,21,23] (see figure 3b in Supplementary information S4 (figure)). The densest projection connects the rostral PER with the caudal POR[17].

A set of intra-PHR connections that is also underexposed in the standard model is the connections between the EC, the presubiculum and the parasubiculum. The dorsolateral MEA projects to septal levels of the presubiculum and the parasubiculum (see figure 4a in Supplementary information S4 (figure)), whereas the ventromedial MEA projects to the temporal presubiculum and parasubiculum[20,22,24–28] (see figure 4b in Supplementary information S4 (figure)). The LEA also projects to the presubiculum and the parasubiculum, but precise topographical information for this projection is absent[19,20,22,25,29,30]. Both the presubiculum and the parasubiculum send projections to the EC. The septal presubiculum projects to the dorsolateral and intermediate part of the MEA (see figure 5a in Supplementary information S4 (figure)), whereas the temporal presubiculum projects to the ventromedial part of the MEA (see figure 5b in Supplementary information S4 (figure)). The superficial layers of the presubiculum project to the deep layers of the LEA[31] and to layers I, II and III of the MEA[27,32–34]. The deep layers of the presubiculum project to all layers of the MEA and predominantly to the deep layers of the LEA[27,34,35]. A detailed topography for the parasubiculum-to-EC connection has not yet been described, but it is known that all layers of the parasubiculum converge on to layer II of the MEA[21,24,30,32,33,36].

Several other connections have been described that have not been incorporated into the standard model shown in FIG. 3. For example, reciprocal connections between the presubiculum/parasubiculum and the PER/POR have been described[21,23], but details are limited. Other connections, such as the intrinsic connections of the EC, are better anatomically characterized, but they remain outside the scope of most models. For example, the MEA and the LEA are strongly interconnected: cells in layers II, III, V and VI of the MEA project to the superficial layers of the LEA[20,37]; LEA layers II and V project to the superficial layers of the MEA[17,20,29,37], whereas LEA layers III and VI project to superficial and deep layers of the MEA[29,37].

PHR projections to the HF. There is a prominent and topologically arranged circuitry between the PHR and the HF. The EC-to-HF circuitry is known as the perforant pathway (FIG. 3). According to the standard view only EC layer II projects to the entire transverse

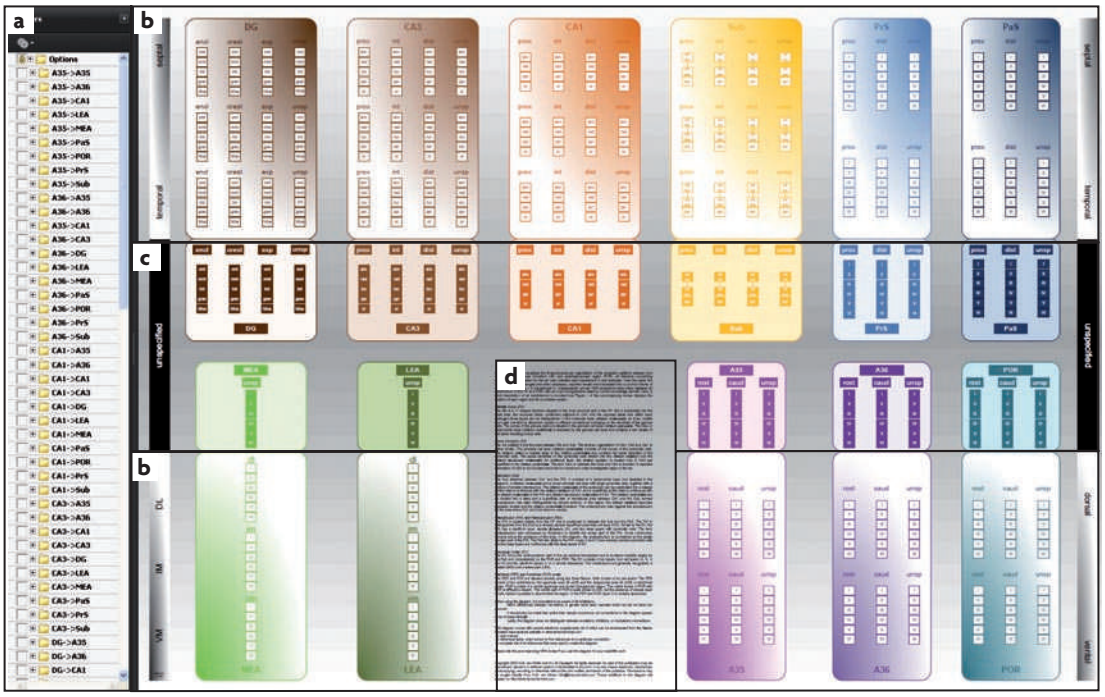

Figure 2 | **Interactive diagram.** The interactive diagram (see Supplementary information S1 (figure)) shows the details of the connectivity in the parahippocampal–hippocampal network, including the topology of the connections. All regions and their three-dimensional axes (for example, the septotemporal axis; see FIG. 1) are included in the diagram. **a** | An alphabetically sorted list of 'from–to' connection groups that can be switched on or off. In front of each group is a + sign. Clicking this expands the list of individual connections that make up the group, allowing one to select connections originating from a specific cortical layer or according to a specific three-dimensional projection pattern (for example, only dorsolateral entorhinal cortex to septal hippocampus connections). **b** | In this area of the diagram the selected connectivity within and between subregions is displayed with full topological detail. **c** | In some cases topological detail is not available; these connections are displayed with a reduced level of topological detail in the centre of the diagram. Connections between diagram elements in parts **b** and **c** also exist. **d** | The diagram legend provides a detailed anatomical description of all subregions. Refer to the diagram manual in Supplementary information S2 (box) for detailed instructions.

Divergence
When one brain region sends projections to several different brain regions.

Mossy fibres
The main projection of DG granular cells to CA3; characterized by high concentrations of zinc.

Schaffer collaterals
The axon collaterals of the CA3 pyramidal cells that project to CA1.

extent of the DG. In fact, EC layers III, V and VI also contribute to this projection, although to a lesser extent. The details of the EC-to-DG[19,22,24–26,38–51] and EC-to-CA3[19,20,22,25,29,38,41,42,44,48–50,52] projections might provide clues to their function. For example, in the molecular layer of the DG and the stratum lacunosum-moleculare of CA3, projections from the EC converge on to the apical dendrites of dentate principal cells and interneurons. Specifically, the LEA projects to the outer third of the molecular layer of the DG, and the MEA projects to the middle third of this layer. A similar pattern of convergence[53] is observed in CA3, where the LEA projection terminates in the superficial part of the stratum lacunosum-moleculare and the MEA projection terminates in the deep part of this layer. In addition to convergence, divergence[53] of the EC projections to the DG and CA3 also occurs, as individual layer II cells project to both the DG and CA3 (REFS 48,54).

The organization of the EC projection to CA1 and the subiculum is markedly different from that of the EC-to-DG or EC-to-CA3 projection. The origin of the main projection from the EC to the stratum lacunosum-moleculare of CA1 and the molecular layer of the subiculum lies in layer III although, again, other layers (II, V and VI) contribute to a lesser extent to this projection[20,22,25,26,29,38,41–43,46,49,51,52,55–57]. Another striking feature of this pathway is the difference between the LEA and MEA projections along the transverse axis. The LEA projects to the distal part of CA1 and the proximal subiculum, whereas the MEA projects to the proximal part of CA1 and the distal subiculum[38,49,52]. This segregation suggests that the input from the LEA and the MEA is processed in different parts of CA1 and the subiculum. This idea is supported by the observation that the segregation of the EC input to CA1 and the subiculum is maintained in the intra-HF projection from CA1 to the subiculum (see next subsection).

In addition to this topology along the transverse axis of the HF, there is a topological organization of connections between the dorsolateral–ventromedial axis of the EC and the longitudinal axis of the HF: the dorsolateral parts of the LEA and the MEA project to the septal HF, the intermediate part of the EC projects to intermediate septotemporal levels, and the ventromedial EC projects to the temporal HF[40,58,59]. According to some reports, the actual organization of the perforant pathway is more widespread (see figure 6 in Supplementary information S4 (figure)), such that this topography relates to the densest projections, whereas weaker components show a more divergent distribution along the septotemporal axis[46,50]. Such a broader projection pattern along the septotemporal axis of the HF may affect information processing.

The EC-to-HF projection forms the main PHR connection to the HF. Other PHR subregions have also been observed to project to the HF directly, although less strongly than the EC and most of them are not included in the standard view. Neurons in all layers of the presubiculum and the parasubiculum project to the stratum moleculare of the DG[32,44,60] and the subiculum[24,32,60,61] and to the stratum lacunosum-moleculare of CA3 (REFS 32,44) and CA1 (REFS 32,44,60) (see figures 7a and 7b in Supplementary information S4 (figure)). Another example of underexposed circuitry is the direct projection from the PER and the POR to the HF. Both A35 and A36 have been reported to project to CA1 and the subiculum[23,62]. The POR has been suggested to project to all sub-areas of the HF[23], but another report indicates only direct projections to CA1 and the subiculum[57].

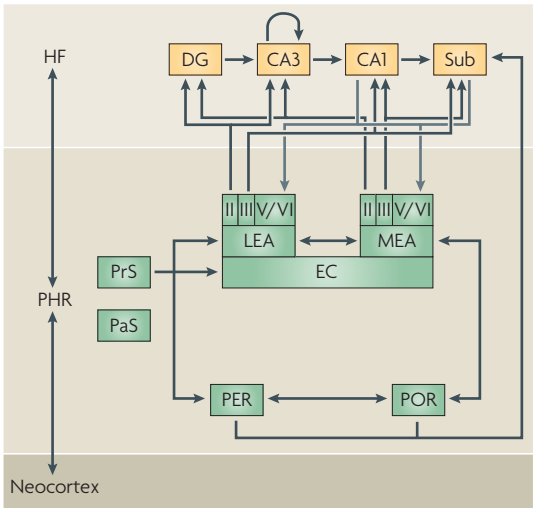

Figure 3 | **The standard view of parahippocampal–hippocampal circuitry.** The standard view that is presented here is based on various circuitry models from recent articles[8–15]. According to this standard view, neocortical projections are aimed at the parahippocampal region (PHR), which in turn provides the main source of input to the hippocampal formation (HF). In the PHR, two parallel projection streams are discerned: the perirhinal cortex (PER) projects to the lateral entorhinal cortex (LEA), and the postrhinal cortex (POR) projects to the medial entorhinal cortex (MEA). The entorhinal cortex (EC) reciprocates the connections from the PER and the POR. Additionally, the EC receives input from the presubiculum (PrS). The EC is the source of the perforant pathway, which projects to all subregions of the hippocampal formation. Entorhinal layer II projects to the dentate gyrus (DG) and CA3, whereas layer III projects to CA1 and the subiculum (Sub). The polysynaptic pathway, an extended version of the traditional trisynaptic pathway, describes a unidirectional route that connects all subregions of the HF sequentially. In short, the DG granule cells give rise to the mossy fibre pathway, which targets CA3. The CA3 Schaffer collaterals project to CA1 and, lastly, CA1 projects to the Sub. Output from the HF arises in CA1 and the Sub and is directed to the PHR, in particular to the deep layers of the EC. The Roman numerals indicate cortical layers.

Connectivity within the HF. In the standard model the first step of the polysynaptic HF pathway (FIG. 3; see also figure 8a in Supplementary information S4 (figure)) is formed by a unidirectional projection from the DG to CA3: the mossy fibres. The Schaffer collaterals, which originate in CA3 and project to CA1, are the next step in the polysynaptic loop. A detailed look at these connections shows an interesting topology along the transverse axis. The distal part of CA3 projects to proximal CA1 and, conversely, the proximal part of CA3 projects to distal

CA1 (REFS 63–65). The topography of the projections that arise from mid-proximodistal portions of CA3 lies between that of these two projection patterns. The last step in the polysynaptic pathway is the projection from CA1 to the subiculum. The proximal part of the CA1 pyramidal cell layer projects to the distal subiculum, whereas the distal CA1 projects to the proximal part of the subiculum[52,66–69].

In contrast to what is depicted in the standard model, there are several backprojections in the HF. Pyramidal cells in CA3 project back to the hilus and the inner molecular layer of the DG[64,70–74], and all septotemporal levels have this backprojection (see figure 8b in Supplementary information S4 (figure)). The strongest backprojection originates in the temporal levels of CA3 and projects to the temporal part of the DG[71]. Again contrasting the standard idea of unidirectionality, a backprojection from CA1 to CA3 has also been reported; this backprojection most likely arises from inhibitory neurons in the stratum radiatum and stratum oriens of CA1 and projects to the same layers in CA3 (REFS 64,66,67,75) (see figure 8b in Supplementary information S4 (figure)). A backprojection from the subiculum to CA1 has also been reported (see figure 8b in Supplementary information S4 (figure)). This backprojection arises from neurons in the stratum pyramidale of the subiculum and projects to all layers of CA1 (REFS 32,76). Currently, it is not known whether this backprojection is of an excitatory or an inhibitory nature.

Recurrent collaterals of the CA3 region[63,64,70–73,77–81] are well acknowledged in the literature (FIG. 3), and they have been described in the other HF subregions as well (see figure 9 in Supplementary information S4 (figure); these intrinsic recurrent networks are less extensive and are also less investigated in terms of their anatomy and function (see the 'Functional implications' section). In the polymorphic layer of the DG, each granule cell establishes contact with the proximal dendrites of several mossy cells, which return excitatory synapses to granule cell dendrites in the molecular layer[47,64,65,70,80,82–85]. CA1 has recurrent loops that are restricted to one septotemporal level[66,69,75,76,79,86]. In the subiculum, principal cells extend axon collaterals to a substantial part of the subiculum that lies ventral to the site of origin; these collaterals terminate on pyramidal cells and interneurons[32,76,87,88].

HF projections to the PHR. The HF output to the PHR arises from CA1 and the subiculum and, according to the standard view, terminates primarily in the deep layers of the EC. In contrast to this view, several authors have reported direct projections from CA1 (REFS 72,75) and the subiculum[32,89,90] to the superficial layers of both the LEA and the MEA.

There are reciprocal connections between the EC and CA1/the subiculum. The CA1–to–EC projection is organized such that the septotemporal axis of the HF is mapped topologically on to the dorsolateral–ventromedial axis of the EC, comparable to the organization of the strongest EC-to-HF projection[52,72,75]. The transverse output organization also mimics the input — that is, the proximal part of CA1 projects to the MEA (see figure 10a in Supplementary information S4 (figure)) and the distal part of CA1 projects to the LEA[49,52] (see figure 10b in Supplementary information S4 (figure)). The subiculum-to-EC projections have a similar topography along the long[89,91] and transverse axes[49,88,89,91,92], although they seem to be less sharply defined. Moreover, along the transverse axis the organization is opposite to that of the CA1-to-EC connections: the proximal subiculum sends a stronger projection to the LEA and the distal subiculum sends a stronger projection to the MEA, again in line with the overall organization of the EC projections to the subiculum.

Although the CA1/subiculum-to-EC projections form the main part of the HF output to the PHR, other connections to the PHR also exist. For example, CA3 (REFS 24,44,72,78), CA1 (REFS 24,31,44,69,75) and the subiculum[24,31,32,88,89,91,92] all project to the presubiculum and the parasubiculum (see figure 11 in Supplementary information S4 (figure)). The projection from the subiculum to the presubiculum is the best described of these. It follows a septotemporal gradient, such that the septal part of the subiculum projects to the septal presubiculum[31,88,89,91] and the temporal part of the subiculum projects to the temporal presubiculum[24,91]. A projection from the subiculum to the parasubiculum exists, but no detailed information about it is known[24,32,89]. Finally, CA1 and the subiculum project to both the PER and the POR, although no detailed information about the organization of this projection is currently available[21,23].

Functional implications

In the preceding section we compared the details of the PHR–HF circuitry to the standard view, highlighting several underexposed connections. To provide a functional perspective on some of these connections, we now discuss them in the context of three topics that have long been associated with the HF: memory formation, navigation and temporal dynamics.

Memory formation. The first example of how increased knowledge of connections in the PHR and the HF might change our views on the memory function of the HF concerns the idea that the HF is the region in which different types of information are associated in memory. By contrast, the EC is generally defined as a simple input–output structure that keeps the incoming information flows separate by way of two parallel pathways (FIG. 3): the PER-to-LEA-to-HF pathway conveys non-spatial information about external stimuli, whereas the POR-to-MEA-to-HF pathway conveys spatial information[18].

However, there are four arguments that support the notion that, rather than being a simple input–output structure, the EC has a role in more complex associations. First, anatomical evidence shows that PER and POR projections to the EC overlap (see the 'Circuitry' section). Second, there is an extensive network in the EC that reciprocally connects the LEA and the MEA[17,20,29,37]. These first two anatomical characteristics suggest that non-spatial information in the LEA and spatial information in the MEA can become associated at the level of the EC, which is supported by the observation that the LEA

is involved in odour–place associations[93]. Third, deep and superficial layers of the EC are also anatomically interconnected[20,26,29,37,94], and this connection is likely to explain the observation that the firing characteristics of cells in all layers of the MEA have a clear correlation across layers during the performance of spatial tasks[95]. Fourth, according to the classical view (FIG. 3), the superficial EC layers are the input layers to the HF, whereas the deep layers receive hippocampally processed information that they convey back to the cortex. However, the anatomical data summarized in this Review show projections from the deep layers of the EC to the HF, consistent with the finding that activation of the deep layers of the EC is sufficient to activate the DG[96]. Additionally, the HF projects to both deep and superficial EC layers (see the 'Circuitry' section).

We therefore propose that the notion that the EC is a simple, laminated input–output structure needs revision: information becomes integrated before it enters the HF. This suggests that both the HF and the EC associate information that is relevant to memory. As the same types of information are processed by the two structures, the question remains how their functions compare. One way to view the distinctive roles of the regions is that the EC holds a more universal memory representation of the associated information, whereas the HF is involved in processing details of this information through processes such as pattern separation and pattern completion. The observation that activity in the HF increases when a person is recalling details from memory supports the proposal that the HF has a role in processing detailed information[97]. The idea that the EC processes information at an earlier and more generic level than the HF (in which detailed information is processed) corresponds to the idea that the EC holds a universal map that is important to the HF in navigation, as discussed below.

Associative networks and, in particular, the auto-associative network of CA3 have been proposed to be essential for encoding and storing episodic memories[98,99]. The recurrent connections in this area can be theoretically arranged into a number of discrete patterns of activation, called stable states or attractors, and the synaptic strengths of the recurrent connections determine the stable states of this network[98]. Incoming information presumably directs the network into one of its stable states, thus enabling pattern completion[100]. Although the CA3 recurrent network is currently thought to be the most elaborate in the HF, CA1, the DG hilus region and the subiculum also contain recurrent collateral networks (see figure 9 in Supplementary information S4 (figure)) and are likely to exhibit computational characteristics comparable to those of the CA3 recurrent network. One striking feature of the CA1 recurrent network that emerges from the diagram is that the recurrent loops are restricted to one septotemporal level (see figure 9 in Supplementary information S4 (figure)). For example, the input to the septal CA1 from CA3 arises from both septal and intermediate levels of CA3, whereas the input to the temporal CA1 arises from the temporal and intermediate CA3. This input is then processed independently in both the septal and the temporal CA1. It would be interesting to know whether there is also regional specificity of CA1 recurrents along the transverse axis, as the MEA and the LEA project preferentially to different proximodistal regions of CA1 (see the 'PHR projections to the HF' subsection). Preliminary data from recordings in the septal CA1 are in line with this idea and show that cells at different transverse positions have different firing characteristics[101] that are related to the type of information provided by the MEA or LEA inputs (spatial and non-spatial, respectively). We propose that CA1 is divided into subdomains along the combination of the septotemporal and proximodistal axes, and that each subdomain independently processes different, specific combinations of information originating from different input areas. In theory, each of these subdomains would thus be able to encode and store unique input patterns, which may be instrumental in discriminating subtle differences in input cues and may aid pattern separation and completion. This prediction awaits further experimental data, such as detailed recordings along both axes in freely behaving animals.

Navigation. Different types of spatial information, discussed below, are represented in the PHR–HF circuitry, and the circuitry may facilitate the exchange of these different types of information in order to make navigation through an environment possible. The same circuitry may mediate the formation of memories for the spatial position of behaviourally relevant cues. Place cells, which encode place fields, provide essential information for navigation. They are found in CA1 (REF. 102) and CA3 (REF. 103), but cells with similar functional properties have been found in the subiculum[104–106], the septal presubiculum[107] and the parasubiculum[108,109]. In the HF, the size of a place field is related to the septotemporal position of the place cells: place cells in the septal HF have the smallest place fields, at intermediate septotemporal levels place fields are twice as big[110] and in the temporal HF they become even larger[103,110,111]. Place field size can be interpreted as a measure of spatial scale, indicating that environments might be represented at different spatial resolutions along the septotemporal axis of the HF.

A large number of non-overlapping, unique spatial representations of the environment are stored in the rather limited network of the HF, which creates a storage problem. It has been argued that in order to solve this problem the HF might make use of a universal map, presumably located outside the HF[102,112,113], that can be applied across environments. Based on the strong reciprocal connectivity between the EC and the HF, the EC (in particular the MEA) was considered a likely candidate for the location of this map, as this area was shown to receive predominantly visuospatial information from the POR[16]. Indeed, a disruption of the monosynaptic information flow from MEA layer III to CA1 affected long-term spatial-memory performance[114] and impaired place cell firing in CA1 (REF. 115). However, initial recordings in the EC did not reveal cells with a striking spatially modulated firing pattern[116,117], probably because these recordings did not cover the most dorsolateral portion of the MEA. The dorsolateral MEA was predicted to contain such cells because it is reciprocally connected both to the septal hippocampus (see the 'Circuitry' section), in which place cells are

Auto-associative network
A network of neurons with axon collaterals that terminate on dendrites of the parent cell.

Place cells
Principal neurons in the hippocampus and parahippocampus that fire whenever an animal is in a specific location in an environment (corresponding to the cell's 'place field').

most conspicuous, and to visuospatial cortical domains — for example, the POR[17,18]. Subsequent recordings in the dorsolateral part of the MEA indeed revealed grid cells[118]. Like place cells, grid cells show a gradual increase in grid field size from the dorsolateral MEA towards the ventromedial MEA[119] and, because of the predominant topology of the perforant path, the grid cells with the smallest grid field scale in the dorsolateral MEA connect to the place cells in the septal HF with the smallest place field scale. Similarly, the grid cells with the largest grid field scale in the ventromedial MEA connect to the place cells in the temporal HF with the largest place field scale.

Head-direction cells are a third class of cells involved in navigation. Head-direction cells were first discovered in the septal presubiculum[109,120], but directionally tuned cells have also been observed in the EC[95], the anterior and lateral dorsal thalamic nuclei[121–123], the lateral mammillary nucleus[124], the retrosplenial cortex[125] and the striatum[126]. This indicates that the directional signal is probably computed in brain networks outside the HF. The head-direction information from the mammillary bodies is crucial for place and grid cell functioning[124], and head-direction information from the presubiculum is important, although not indispensable, for the functional characteristics of place fields in CA1 (REF. 127). As the septal presubiculum also projects to other HF subregions, we propose that the firing properties of neurons in the DG, CA3 and the subiculum might also be affected by presubiculum lesions.

What more can the details of the circuitry tell us about the space-related functional properties of the network? A first hypothesis is that information from the head-direction system may enter the HF through at least two different routes. One route projects from the presubiculum directly to the HF and a second route runs indirectly to the HF through the projections from layers II and III of the EC. In order to decide which of these routes provides the predominant directional input to the HF, the reported effects of presubiculum lesions on CA1 place cell firing[107] should be compared with the effect of presubiculum lesions on the spatial-firing properties of MEA neurons. If MEA neuron firing is not affected by such lesions, the direct route from the presubiculum to CA1 is more likely to be the predominant input pathway for directional information to the HF. However, if the firing properties of MEA neurons do change as a result of presubiculum lesions, the CA1 firing properties after a presubiculum lesion should be compared with the CA1 firing properties after a selective MEA lesion[115] and after a combined presubiculum and MEA lesion.

Another prediction based on the PHR–HF network characteristics is that the place-specific firing of CA1 should be stronger at its proximal end than at its distal end, as the MEA preferentially projects to the proximal portion of CA1 and place-specific firing in CA1 strongly depends on the direct input from the MEA[115,128,129]. By contrast, the preferential LEA-to-CA1 projection pattern predicts that non-spatial information about external stimuli is processed in the distal CA1. Preliminary data show that the firing of cells in the proximal (MEA-recipient) CA1 is indeed significantly more affected by spatial information than the firing of cells in the distal CA1 (REF. 101). A similar type of prediction can be made for the subiculum, as the LEA projects to the proximal part of the subiculum and the MEA projects to its distal part. On the basis of this topology, the most prominent place cells are expected to be found in the distal subiculum. One study found subtle differences in the spatial properties of cells in the proximal versus the distal subiculum[104]. There are several explanations for why the difference was only small, but the best explanation is probably the extensive but underexposed and not very well studied intrinsic recurrent network in the subiculum[130].

Temporal dynamics. Some of the underexposed PHR–HF connections are likely to be involved in the temporal synchronization of neuronal firing between brain areas. Synchronized firing is essential for the coordination of spatially distributed networks and is generally achieved through neuronal oscillations. By synchronizing excitatory periods across regions, oscillations may facilitate the transfer of information in the PHR–HF network[131]. Furthermore, oscillations promote coincident firing among cells, which is likely to be important for inducing synaptic plasticity (for example, see REF. 132) and memory consolidation[133]. One of the prerequisites for the occurrence of oscillations is the interaction between excitatory glutamatergic neurons and inhibitory GABA (γ-aminobutyric acid)-ergic interneurons[134]. Different classes of GABAergic neurons can be characterized in the hippocampus according to their distinct firing patterns during behaviourally relevant oscillations such as theta oscillations, gamma oscillations and sharp wave ripples[135–138]; projections from these interneurons to different targets synchronize the firing of large numbers of pyramidal cells[135]. Although most research on GABAergic cells is carried out on interneurons that project locally in one sub-area, recent evidence showed the existence of long-range GABAergic projection neurons that cross the sub-area border and are involved in the coordination of spike timing across sub-areas[139].

Although most tract-tracing studies do not reveal whether a projection is excitatory or inhibitory, an indication of the excitatory or inhibitory nature of a connection can be derived from the layers of origin and termination. For example, the CA1-to-CA3 backprojections discussed in the 'Circuitry' section arise not from the (excitatory) glutamatergic principal cell layer, but mainly from neurons located in the stratum oriens of CA1 (REFS 64,66,67,75), and project to the stratum radiatum and stratum oriens of CA3. An *in vivo* labelling study showed the same locus of origin and termination for CA1 GABAergic neurons projecting to CA3 (REFS 77,140–142). Also, in the stratum radiatum of CA1, cells project to the DG and the subiculum. GABAergic cells have been reported to reside in the CA1 stratum radiatum with axons that radiate to the molecular layer of the DG and the subiculum[143].

Because the layer of origin of these CA1 neurons seems to be a reliable predictor of GABAergic connections, it is likely that other projections that do not start

Grid cells
Neurons in the entorhinal cortex that fire strongly when an animal is at one of several specific locations in an environment and that are organized in a grid-like fashion.

Head-direction cells
Neurons that fire only when the animal's head points in a specific direction in an environment.

Mammillary bodies
A pair of nuclei in the hypothalamus, strongly connected to the HF and the anterior complex of the thalamus, that are involved in recognition memory.

Theta oscillations
Rhythmical changes at 5–12 Hz in network activity, as observed in the electroencephalogram, characteristic of the hippocampal network communicating with various cortical and subcortical networks in the brain.

Gamma oscillations
Rhythmical oscillations of 25–70 Hz observed in the electroencephalogram.

Ripple oscillations
Short-lasting bursts of field oscillations (~140–200 Hz) in the mammalian hippocampus and parahippocampus that occur during rest or slow-wave sleep.

in the principal cell layer are also GABAergic. This can be used to discover the existence of other inhibitory projections. In the interactive diagram (see Supplementary information S1 (figure)) one can observe that, in the hippocampus, cells in the hilus of the DG project to CA1. There are also reports of projections from the HF to the PHR that do not start in the principal cell layer of the HF: cells in the molecular layer of the subiculum project to the parasubiculum, the presubiculum and the POR. Moreover, cells in the stratum oriens and the stratum radiatum of CA1 and the molecular layer of the subiculum project to the LEA and the MEA. We suggest that these connections indeed originate from long-range GABAergic neurons, and are capable of functionally coupling the PHR–HF subregions and coordinate oscillations over the entire PHR–HF network.

Conclusions and future directions

Comprehensive knowledge of the organization of the PHR–HF connectivity is of pivotal importance for elucidating PHR–HF function. Such detailed knowledge of PHR–HF circuits will help us to understand how these circuits are engaged in spatial processing and temporal dynamics, as well as in other functions that have been associated with the region, such as episodic memory[144], crossmodal memory[145], recollection and recognition[146], memory for the temporal order of events[147–150] and visual perception of conjunctions[151]. Moreover, the PHR and HF are implicated in various disorders, such as Alzheimer's disease[152], epilepsy[153], schizophrenia[154] and depression[155]. Knowing the changes in connection patterns within and between these regions may help us to understand the underlying mechanisms of these PHR–HF-related disorders and consequently enhance the possibilities for treating them. This Review and the complementary knowledge base may facilitate the study of altered connectivity in animal models for diseases that involve the PHR and HF.

Although topological information is available in the interactive diagram for a large number of connections, increasing the knowledge base of PHR–HF connectivity is an important requirement for future functional understanding of these regions. Although currently all connections in the interactive diagram are displayed as if they are of equal density, we aim for future versions of the diagram (which will be available on our website) to differentiate between strong and weak connections. Unfortunately, connectional density is often not reported quantitatively in the anatomical literature, and even when it is reported it is a subjective observation that is difficult to compare between studies. Second, we aim to incorporate *in vivo* and *in vitro* electrophysiological data into future versions of this knowledge base so that it will contain information about the excitatory or inhibitory role of connections. Third, the current version of the diagram displays only the layers of origin and termination, but each region and layer consists of several cell types. We aim for future versions of the diagram to contain a description of pre- and postsynaptic cell types. Implementing these improvements requires extensive fundamental research into the cytoarchitectonic and connectional properties of the region, but this investment will have a tremendous impact on advancing our functional understanding.

An ever-increasing amount of anatomical knowledge brings with it several difficulties. One consequence of the overwhelming number of reported connections is that attention focuses on a selection of the connections whereas others fall into disuse, especially those for which the functional relevance is not entirely clear, such as some of the recurrent collaterals in the HF subregions. A knowledge base such as the one presented in this Review can help to prevent the loss of valuable knowledge and inspire creative minds to come up with new solutions for outstanding problems in the field.

1. Ramón y Cajal, S. Estructura del asta de Ammon y fascia dentata. *Anales de la Sociedad Española de Historia Natural* **22**, 53–126 (1893).
2. Scoville, W. B. & Milner, B. Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* **20**, 11–21 (1957).
3. Zola-Morgan, S., Squire, L. R., Amaral, D. G. & Suzuki, W. A. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. *J. Neurosci.* **9**, 4355–4370 (1989).
4. Crick, F. & Koch, C. A framework for consciousness. *Nature Neurosci.* **6**, 119–126 (2003).
5. Amaral, D. G. & Lavenex, P. in *The Hippocampus Book* (eds Andersen, P., Morris, R., Amaral, D. G., Bliss, T. & O'Keefe, J.) 37–114 (Oxford Univ. Press, New York, 2007).
6. Witter, M. P. & Amaral, D. G. in *The Rat Nervous System* 3rd edn (ed. Paxinos, G.) 637–703 (Elsevier Academic Press, San Diego, 2004).
This book chapter gives an extensive description of cells and projections in the HF and the PHR.
7. Burwell, R. D. & Witter, M. P. in *The Parahippocampal Region: Organization and Role in Cognitive Function* (eds Witter, M. P. & Wouterlood, F. G.) 35–60 (Oxford Univ. Press, New York, 2002).
8. Bird, C. M. & Burgess, N. The hippocampus and memory: insights from spatial processing. *Nature Rev. Neurosci.* **9**, 182–194 (2008).
This paper provides a comprehensive summary of arguments that support the thesis that studies on the role of the rodent hippocampus in navigation bear on our understanding of memory.
9. Brown, M. W. & Aggleton, J. P. Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nature Rev. Neurosci.* **2**, 51–61 (2001).
10. Bussey, T. J. & Saksida, L. M. Memory, perception, and the ventral visual-perirhinal-hippocampal stream: thinking outside of the boxes. *Hippocampus* **17**, 898–908 (2007).
This paper provides a critical but stimulating perspective on the idea that the medial temporal lobe system is involved only in memory, with special emphasis on the functions of the perirhinal cortex.
11. Eichenbaum, H. A cortical-hippocampal system for declarative memory. *Nature Rev. Neurosci.* **1**, 41–50 (2000).
12. Eichenbaum, H., Yonelinas, A. P. & Ranganath, C. The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.* **30**, 123–152 (2007).
This paper reviews current concepts of how familiarity and recollection memory are supported by regions in the medial temporal lobe and proposes that there is a distinction between recollection and familiarity in specific regions of the medial temporal lobe.
13. Hasselmo, M. E., Fransen, E., Dickson, C. & Alonso, A. A. Computational modeling of entorhinal cortex. *Ann. NY Acad. Sci.* **911**, 418–446 (2000).
14. Martin, S. J. & Clark, R. E. The rodent hippocampus and spatial memory: from synapses to systems. *Cell. Mol. Life Sci.* **64**, 401–431 (2007).
15. Squire, L. R., Stark, C. E. & Clark, R. E. The medial temporal lobe. *Annu. Rev. Neurosci.* **27**, 279–306 (2004).
16. Burwell, R. D. & Amaral, D. G. Cortical afferents of the perirhinal, postrhinal, and entorhinal cortices of the rat. *J. Comp. Neurol.* **398**, 179–205 (1998).
17. Burwell, R. D. & Amaral, D. G. Perirhinal and postrhinal cortices of the rat: interconnectivity and connections with the entorhinal cortex. *J. Comp. Neurol.* **391**, 293–321 (1998).
18. Naber, P. A., Caballero-Bleda, M., Jorritsma-Byham, B. & Witter, M. P. Parallel input to the hippocampal memory system through peri- and postrhinal cortices. *Neuroreport* **8**, 2617–2621 (1997).
19. Swanson, L. W. & Kohler, C. Anatomical evidence for direct projections from the entorhinal area to the entire cortical mantle in the rat. *J. Neurosci.* **6**, 3010–3023 (1986).
20. Kohler, C. Intrinsic connections of the retrohippocampal region in the rat brain. II. The medial entorhinal area. *J. Comp. Neurol.* **246**, 149–169 (1986).
21. Deacon, T. W., Eichenbaum, H., Rosenberg, P. & Eckmann, K. W. Afferent connections of the perirhinal cortex in the rat. *J. Comp. Neurol.* **220**, 168–190 (1983).
22. Kerr, K. M., Agster, K. L., Furtak, S. C. & Burwell, R. D. Functional neuroanatomy of the parahippocampal region: the lateral and medial entorhinal areas. *Hippocampus* **17**, 697–708 (2007).
23. Furtak, S. C., Wei, S. M., Agster, K. L. & Burwell, R. D. Functional neuroanatomy of the parahippocampal region in the rat: the perirhinal and postrhinal cortices. *Hippocampus* **17**, 709–722 (2007).
24. van Groen, T. & Wyss, J. M. The connections of presubiculum and parasubiculum in the rat. *Brain Res.* **518**, 227–243 (1990).

25. Wyss, J. M. An autoradiographic study of the efferent connections of the entorhinal cortex in the rat. *J. Comp. Neurol.* **199**, 495–512 (1981).
26. Lingenhohl, K. & Finch, D. M. Morphological characterization of rat entorhinal neurons *in vivo*: soma-dendritic structure and axonal domains. *Exp. Brain Res.* **84**, 57–74 (1991).
27. Honda, Y. & Ishizuka, N. Organization of connectivity of the rat presubiculum: I. Efferent projections to the medial entorhinal cortex. *J. Comp. Neurol.* **473**, 463–484 (2004).
28. Van Haeften, T., Wouterlood, F. G., Jorritsma-Byham, B. & Witter, M. P. GABAergic presubicular projections to the medial entorhinal cortex of the rat. *J. Neurosci.* **17**, 862–874 (1997).
29. Kohler, C. Intrinsic connections of the retrohippocampal region in the rat brain: III. The lateral entorhinal area. *J. Comp. Neurol.* **271**, 208–228 (1988).
30. Segal, M. Afferents to the entorhinal cortex of the rat studied by the method of retrograde transport of horseradish peroxidase. *Exp. Neurol.* **57**, 750–765 (1977).
31. van Groen, T. & Wyss, J. M. The postsubicular cortex in the rat: characterization of the fourth region of the subicular cortex and its connections. *Brain Res.* **529**, 165–177 (1990).
32. Kohler, C. Intrinsic projections of the retrohippocampal region in the rat brain. I. The subicular complex. *J. Comp. Neurol.* **236**, 504–522 (1985).
33. Caballero-Bleda, M. & Witter, M. P. Regional and laminar organization of projections from the presubiculum and parasubiculum to the entorhinal cortex: an anterograde tracing study in the rat. *J. Comp. Neurol.* **328**, 115–129 (1993).
34. Honda, Y., Umitsu, Y. & Ishizuka, N. Organization of connectivity of the rat presubiculum: II. Associational and commissural connections. *J. Comp. Neurol.* **506**, 640–658 (2008).
35. Van Haeften, T., Wouterlood, F. G. & Witter, M. P. Presubicular input to the dendrites of layer-V entorhinal neurons in the rat. *Ann. NY Acad. Sci.* **911**, 471–473 (2000).
36. Kohler, C., Shipley, M. T., Srebro, B. & Harkmark, W. Some retrohippocampal afferents to the entorhinal cortex. Cells of origin as studied by the HRP method in the rat and mouse. *Neurosci. Lett.* **10**, 115–120 (1978).
37. Dolorfo, C. L. & Amaral, D. G. Entorhinal cortex of the rat: organization of intrinsic connections. *J. Comp. Neurol.* **398**, 49–82 (1998).
38. Baks-Te-Bulte, L., Wouterlood, F. G., Vinkenoog, M. & Witter, M. P. Entorhinal projections terminate onto principal neurons and interneurons in the subiculum: a quantitative electron microscopical analysis in the rat. *Neuroscience* **136**, 729–739 (2005).
39. Deller, T., Martinez, A., Nitsch, R. & Frotscher, M. A novel entorhinal projection to the rat dentate gyrus: direct innervation of proximal dendrites and cell bodies of granule cells and GABAergic neurons. *J. Neurosci.* **16**, 3322–3333 (1996).
This paper described an underexposed projection from the deep layers of the EC to the DG, which should fundamentally alter our concept of the EC (see also reference 96).
40. Dolorfo, C. L. & Amaral, D. G. Entorhinal cortex of the rat: topographic organization of the cells of origin of the perforant path projection to the dentate gyrus. *J. Comp. Neurol.* **398**, 25–48 (1998).
41. Hjorth-Simonsen, A. Projection of the lateral part of the entorhinal area to the hippocampus and fascia dentata. *J. Comp. Neurol.* **146**, 219–232 (1972).
42. Kajiwara, R. *et al.* Convergence of entorhinal and CA3 inputs onto pyramidal neurons and interneurons in hippocampal area CA1 - An anatomical study in the rat. *Hippocampus* **18**, 266–280 (2007).
43. Kohler, C. A projection from the deep layers of the entorhinal area to the hippocampal formation in the rat brain. *Neurosci. Lett.* **56**, 13–19 (1985).
44. Nafstad, P. H. An electron microscope study on the termination of the perforant path fibres in the hippocampus and the fascia dentata. Z. *Zellforsch. Mikrosk. Anat.* **76**, 532–542 (1967).
45. Ruth, R. E., Collier, T. J. & Routtenberg, A. Topography between the entorhinal cortex and the dentate septotemporal axis in rats: I. Medial and intermediate entorhinal projecting cells. *J. Comp. Neurol.* **209**, 69–78 (1982).
46. Ruth, R. E., Collier, T. J. & Routtenberg, A. Topographical relationship between the entorhinal cortex and the septotemporal axis of the dentate gyrus in rats: II. Cells projecting from lateral entorhinal subdivisions. *J. Comp. Neurol.* **270**, 506–516 (1988).
47. Segal, M. & Landis, S. Afferents to the hippocampus of the rat studied with the method of retrograde transport of horseradish peroxidase. *Brain Res.* **78**, 1–15 (1974).
48. Steward, O. Topographic organization of the projections from the entorhinal area to the hippocampal formation of the rat. *J. Comp. Neurol.* **167**, 285–314 (1976).
49. Tamamaki, N. & Nojyo, Y. Preservation of topography in the connections between the subiculum, field CA1, and the entorhinal cortex in rats. *J. Comp. Neurol.* **353**, 379–390 (1995).
50. Tamamaki, N. Organization of the entorhinal projection to the rat dentate gyrus revealed by Dil anterograde labeling. *Exp. Brain Res.* **116**, 250–258 (1997).
51. Witter, M. P., Griffioen, A. W., Jorritsma-Byham, B. & Krijnen, J. L. Entorhinal projections to the hippocampal CA1 region in the rat: an underestimated pathway. *Neurosci. Lett.* **85**, 193–198 (1988).
52. Naber, P. A., Lopes da Silva, F. H. & Witter, M. P. 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 (2001).
53. Sporns, O. & Tononi, G. in *Handbook of Brain Connectivity* (eds Jirsa, V. K. & McIntosh, A. R.) 117–147 (Springer, Berlin, 2007).
In this book chapter the authors clearly explain segregation and integration and describe a method for quantifying structural connection patterns as global measures of brain dynamics.
54. Tamamaki, N. & Nojyo, Y. Projection of the entorhinal layer II neurons in the rat as revealed by intracellular pressure-injection of neurobiotin. *Hippocampus* **3**, 471–480 (1993).
55. Braak, H. On the structure of the human archicortex. I. The cornu ammonis. A Golgi and pigmentarchitectonic study. *Cell Tissue Res.* **152**, 349–383 (1974).
56. Honda, Y., Umitsu, Y. & Ishizuka, N. Topographic projections of perforant path from entorhinal area to CA1 and subiculum in the rat. *Neurosci. Res.* **24** (Suppl.), S101 (2000).
57. Naber, P. A., Witter, M. P. & Lopes da Silva, F. H. Evidence for a direct projection from the postrhinal cortex to the subiculum in the rat. *Hippocampus* **11**, 105–117 (2001).
58. Witter, M. P. & Groenewegen, H. J. Laminar origin and septotemporal distribution of entorhinal and perirhinal projections to the hippocampus in the cat. *J. Comp. Neurol.* **224**, 371–385 (1984).
59. Witter, M. P. A survey of the anatomy of the hippocampal formation, with emphasis on the septotemporal organization of its intrinsic and extrinsic connections. *Adv. Exp. Med. Biol.* **203**, 67–82 (1986).
60. Witter, M. P., Holtrop, R. & van de Loosdrecht, A. A. Direct projections from the periallocortical subicular complex to the fascia dentata in the rat. *Neurosci. Res. Commun.* **2**, 61–68 (1988).
61. Beckstead, R. M. Afferent connections of the entorhinal area in the rat as demonstrated by retrograde cell-labeling with horseradish peroxidase. *Brain Res.* **152**, 249–264 (1978).
62. Kosel, K. C., Van Hoesen, G. W. & Rosene, D. L. A direct projection from the perirhinal cortex (area 35) to the subiculum in the rat. *Brain Res.* **269**, 347–351 (1983).
63. Ishizuka, N., Weber, J. & Amaral, D. G. Organization of intrahippocampal projections originating from CA3 pyramidal cells in the rat. *J. Comp. Neurol.* **295**, 580–623 (1990).
64. Laurberg, S. Commissural and intrinsic connections of the rat hippocampus. *J. Comp. Neurol.* **184**, 685–708 (1979).
65. Laurberg, S. & Sorensen, K. E. Associational and commissural collaterals of neurons in the hippocampal formation (hilus fasciae dentatae and subfield CA3). *Brain Res.* **212**, 287–300 (1981).
66. Amaral, D. G., Dolorfo, C. & varez-Royo, P. Organization of CA1 projections to the subiculum: a PHA-L analysis in the rat. *Hippocampus* **1**, 415–435 (1991).
67. Swanson, L. W., Sawchenko, P. E. & Cowan, W. M. Evidence for collateral projections by neurons in Ammon's horn, the dentate gyrus, and the subiculum: a multiple retrograde labeling study in the rat. *J. Neurosci.* **1**, 548–559 (1981).
68. Tamamaki, N. & Nojyo, Y. Disposition of the slab-like modules formed by axon branches originating from single CA1 pyramidal neurons in the rat hippocampus. *J. Comp. Neurol.* **291**, 509–519 (1990).
69. van Groen, T. & Wyss, J. M. Extrinsic projections from area CA1 of the rat hippocampus: olfactory, cortical, subcortical, and bilateral hippocampal formation projections. *J. Comp. Neurol.* **302**, 515–528 (1990).
70. Buckmaster, P. S., Strowbridge, B. W. & Schwartzkroin, P. A. A comparison of rat hippocampal mossy cells and CA3c pyramidal cells. *J. Neurophysiol.* **70**, 1281–1299 (1993).
71. Li, X. G., Somogyi, P., Ylinen, A. & Buzsaki, G. The hippocampal CA3 network: an *in vivo* intracellular labeling study. *J. Comp. Neurol.* **339**, 181–208 (1994).
72. Swanson, L. W., Wyss, J. M. & Cowan, W. M. An autoradiographic study of the organization of intrahippocampal association pathways in the rat. *J. Comp. Neurol.* **181**, 681–715 (1978).
73. Wittner, L., Henze, D. A., Zaborszky, L. & Buzsaki, G. Hippocampal CA3 pyramidal cells selectively innervate aspiny interneurons. *Eur. J. Neurosci.* **24**, 1286–1298 (2006).
74. Wittner, L., Henze, D. A., Zaborszky, L. & Buzsaki, G. Three-dimensional reconstruction of the axon arbor of a CA3 pyramidal cell recorded and filled *in vivo*. *Brain Struct. Funct.* **212**, 75–83 (2007).
75. Cenquizca, L. A. & Swanson, L. W. Spatial organization of direct hippocampal field CA1 axonal projections to the rest of the cerebral cortex. *Brain Res. Rev.* **56**, 1–26 (2007).
76. Finch, D. M., Nowlin, N. L. & Babb, T. L. Demonstration of axonal projections of neurons in the rat hippocampus and subiculum by intracellular injection of HRP. *Brain Res.* **271**, 201–216 (1983).
77. Sik, A., Tamamaki, N. & Freund, T. F. Complete axon arborization of a single CA3 pyramidal cell in the rat hippocampus, and its relationship with postsynaptic parvalbumin-containing interneurons. *Eur. J. Neurosci.* **5**, 1719–1728 (1993).
78. Siddiqui, A. H. & Joseph, S. A. CA3 axonal sprouting in kainate-induced chronic epilepsy. *Brain Res.* **1066**, 129–146 (2005).
79. Hjorth-Simonsen, A. Some intrinsic connections of the hippocampus in the rat: an experimental analysis. *J. Comp. Neurol.* **147**, 145–161 (1973).
80. Van, G. T. & Wyss, J. M. Species differences in hippocampal commissural connections: studies in rat, guinea pig, rabbit, and cat. *J. Comp. Neurol.* **267**, 322–334 (1988).
81. Lorente de Nó, R. Studies on the structure of the cerebral cortex. II. Continuation of the study of the ammonic system. *J. Psychol. Neurol.* **46**, 113–177 (1934).
82. Claiborne, B. J., Amaral, D. G. & Cowan, W. M. A light and electron microscopic analysis of the mossy fibers of the rat dentate gyrus. *J. Comp. Neurol.* **246**, 435–458 (1986).
83. Frotscher, M., Seress, L., Schwerdtfeger, W. K. & Buhl, E. The mossy cells of the fascia dentata: a comparative study of their fine structure and synaptic connections in rodents and primates. *J. Comp. Neurol.* **312**, 145–163 (1991).
84. Deller, T., Nitsch, R. & Frotscher, M. Heterogeneity of the commissural projection to the rat dentate gyrus: a *Phaseolus vulgaris* leucoagglutinin tracing study. *Neuroscience* **75**, 111–121 (1996).
85. Swanson, L. W. & Cowan, W. M. An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. *J. Comp. Neurol.* **172**, 49–84 (1977).
86. Finch, D. M. & Babb, T. L. Demonstration of caudally directed hippocampal efferents in the rat by intracellular injection of horseradish peroxidase. *Brain Res.* **214**, 405–410 (1981).
87. Harris, E., Witter, M. P., Weinstein, G. & Stewart, M. Intrinsic connectivity of the rat subiculum: I. Dendritic morphology and patterns of axonal arborization by pyramidal neurons. *J. Comp. Neurol.* **435**, 490–505 (2001).
88. Witter, M. P., Ostendorf, R. H. & Groenewegen, H. J. Heterogeneity in the dorsal subiculum of the rat. Distinct neuronal zones project to different cortical and subcortical targets. *Eur. J. Neurosci.* **2**, 718–725 (1990).
89. Kloosterman, F., Witter, M. P. & Van Haeften, T. Topographical and laminar organization of subicular projections to the parahippocampal region of the rat. *J. Comp. Neurol.* **455**, 156–171 (2003).
90. Van Haeften, T., Jorritsma-Byham, B. & Witter, M. P. Quantitative morphological analysis of subicular terminals in the rat entorhinal cortex. *Hippocampus* **5**, 452–459 (1995).
91. Naber, P. A. & Witter, M. P. Subicular efferents are organized mostly as parallel projections: a double-labeling, retrograde-tracing study in the rat. *J. Comp. Neurol.* **393**, 284–297 (1998).

92. Honda, Y., Umitsu, Y. & Ishizuka, N. Efferent projections of the subiculum to the retrohippocampal and retrosplenial cortices of the rat. *Neurosci. Res.* **22** (Suppl.), S265 (1999).
93. Mayeaux, D. J. & Johnston, R. E. Discrimination of social odors and their locations: role of lateral entorhinal area. *Physiol. Behav.* **82**, 653–662 (2004).
94. Van Haeften, T., Baks-Te-Bulte, L., Goede, P. H., Wouterlood, F. G. & Witter, M. P. Morphological and numerical analysis of synaptic interactions between neurons in deep and superficial layers of the entorhinal cortex of the rat. *Hippocampus* **13**, 943–952 (2003).
95. Sargolini, F. *et al.* Conjunctive representation of position, direction, and velocity in entorhinal cortex. *Science* **312**, 758–762 (2006).
This study provided evidence that information on location, direction and distance is integrated and updated in the grid cell network during navigation.
96. Koganezawa, N. *et al.* Significance of the deep layers of entorhinal cortex for transfer of both perirhinal and amygdala inputs to the hippocampus. *Neurosci. Res.* **61**, 172–181 (2008).
97. Viskontas, I. V., Carr, V. A., Engel, S. A. & Knowlton, B. J. The neural correlates of recollection: hippocampal activation declines as episodic memory fades. *Hippocampus* **19**, 265–272 (2008).
98. Rolls, E. T. An attractor network in the hippocampus: theory and neurophysiology. *Learn. Mem.* **14**, 714–731 (2007).
This paper provided a clear definition of the characteristic features of attractor networks and summarized data in support of the view that the hippocampus comprises an attractor network relevant for fast and efficient encoding and retrieval of trial-unique memories.
99. Nakazawa, K. *et al.* Requirement for hippocampal CA3 NMDA receptors in associative memory recall. *Science* **297**, 211–218 (2002).
100. Gold, A. E. & Kesner, R. P. The role of the CA3 subregion of the dorsal hippocampus in spatial pattern completion in the rat. *Hippocampus* **15**, 808–814 (2005).
101. McNaughton, B. L. *et al.* Distinct characteristics of CA1 place cells correlated with medial or lateral entorhinal cortex layer III input. *Society for Neuroscience Abstract* 391.3 (2008).
102. O'Keefe, J. Place units in the hippocampus of the freely moving rat. *Exp. Neurol.* **51**, 78–109 (1976).
103. Kjelstrup, K. B. *et al.* Finite scale of spatial representation in the hippocampus. *Science* **321**, 140–143 (2008).
104. Sharp, P. E. & Green, C. Spatial correlates of firing patterns of single cells in the subiculum of the freely moving rat. *J. Neurosci.* **14**, 2339–2356 (1994).
105. Sharp, P. E. Subicular cells generate similar spatial firing patterns in two geometrically and visually distinctive environments: comparison with hippocampal place cells. *Behav. Brain Res.* **85**, 71–92 (1997).
106. Sharp, P. E. Subicular place cells expand or contract their spatial firing pattern to fit the size of the environment in an open field but not in the presence of barriers: comparison with hippocampal place cells. *Behav. Neurosci.* **113**, 643–662 (1999).
107. Sharp, P. E. Multiple spatial/behavioral correlates for cells in the rat postsubiculum: multiple regression analysis and comparison to other hippocampal areas. *Cereb. Cortex* **6**, 238–259 (1996).
108. O'Keefe, J. in *The Hippocampus Book* (eds Andersen, P., Morris, R., Amaral, D. G., Bliss, T. & O'Keefe, J.) 475–579 (Oxford Univ. Press, New York, 2007).
109. Taube, J. S. Place cells recorded in the parasubiculum of freely moving rats. *Hippocampus* **5**, 569–583 (1995).
110. Jung, M. W., Wiener, S. I. & McNaughton, B. L. Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat. *J. Neurosci.* **14**, 7347–7356 (1994).
111. Maurer, A. P., Vanrhoads, S. R., Sutherland, G. R., Lipa, P. & McNaughton, B. L. Self-motion and the origin of differential spatial scaling along the septo-temporal axis of the hippocampus. *Hippocampus* **15**, 841–852 (2005).
112. Touretzky, D. S. & Redish, A. D. Theory of rodent navigation based on interacting representations of space. *Hippocampus* **6**, 247–270 (1996).
113. Sharp, P. E. Complimentary roles for hippocampal versus subicular/entorhinal place cells in coding place, context, and events. *Hippocampus* **9**, 432–443 (1999).
114. Remondes, M. & Schuman, E. M. Role for a cortical input to hippocampal area CA1 in the consolidation of a long-term memory. *Nature* **431**, 699–703 (2004).
115. Brun, V. H. *et al.* Impaired spatial representation in CA1 after lesion of direct input from entorhinal cortex. *Neuron* **57**, 290–302 (2008).
116. Quirk, G. J., Muller, R. U., Kubie, J. L. & Ranck, J. B. Jr. The positional firing properties of medial entorhinal neurons: description and comparison with hippocampal place cells. *J. Neurosci.* **12**, 1945–1963 (1992).
117. Frank, L. M., Brown, E. N. & Wilson, M. Trajectory encoding in the hippocampus and entorhinal cortex. *Neuron* **27**, 169–178 (2000).
118. Fyhn, M., Molden, S., Witter, M. P., Moser, E. I. & Moser, M. B. Spatial representation in the entorhinal cortex. *Science* **305**, 1258–1264 (2004).
119. Brun, V. H. *et al.* Progressive increase in grid scale from dorsal to ventral medial entorhinal cortex. *Hippocampus* **18**, 1200–1212 (2008).
120. Taube, J. S., Muller, R. U. & Ranck, J. B. Jr. Head-direction cells recorded from the postsubiculum in freely moving rats. II. Effects of environmental manipulations. *J. Neurosci.* **10**, 436–447 (1990).
121. Mizumori, S. J. & Williams, J. D. Directionally selective mnemonic properties of neurons in the lateral dorsal nucleus of the thalamus of rats. *J. Neurosci.* **13**, 4015–4028 (1993).
122. Taube, J. S. Head direction cells recorded in the anterior thalamic nuclei of freely moving rats. *J. Neurosci.* **15**, 70–86 (1995).
123. Stackman, R. W. & Taube, J. S. Firing properties of head direction cells in the rat anterior thalamic nucleus: dependence on vestibular input. *J. Neurosci.* **17**, 4349–4358 (1997).
124. Sharp, P. E. & Koester, K. Lesions of the mammillary body region severely disrupt the cortical head direction, but not place cell signal. *Hippocampus* **18**, 766–784 (2008).
This study provides evidence that the mammillary bodies provide important information for the head-direction cells but not for the place cells in the hippocampus.
125. Chen, L. L., Lin, L. H., Green, E. J., Barnes, C. A. & McNaughton, B. L. Head-direction cells in the rat posterior cortex. I. Anatomical distribution and behavioral modulation. *Exp. Brain Res.* **101**, 8–23 (1994).
126. Wiener, S. I. Spatial and behavioral correlates of striatal neurons in rats performing a self-initiated navigation task. *J. Neurosci.* **13**, 3802–3817 (1993).
127. Calton, J. L. *et al.* Hippocampal place cell instability after lesions of the head direction cell network. *J. Neurosci.* **23**, 9719–9731 (2003).
128. McNaughton, B. L., Barnes, C. A., Meltzer, J. & Sutherland, R. J. Hippocampal granule cells are necessary for normal spatial learning but not for spatially-selective pyramidal cell discharge. *Exp. Brain Res.* **76**, 485–496 (1989).
129. Brun, V. H. *et al.* Place cells and place recognition maintained by direct entorhinal-hippocampal circuitry. *Science* **296**, 2243–2246 (2002).
130. Witter, M. P. Connections of the subiculum of the rat: topography in relation to columnar and laminar organization. *Behav. Brain Res.* **174**, 251–264 (2006).
131. Buzsaki, G. & Draguhn, A. Neuronal oscillations in cortical networks. *Science* **304**, 1926–1929 (2004).
132. Levy, W. B. & Steward, O. Synapses as associative memory elements in the hippocampal formation. *Brain Res.* **175**, 233–245 (1979).
133. Wilson, M. A. & McNaughton, B. L. Reactivation of hippocampal ensemble memories during sleep. *Science* **265**, 676–679 (1994).
134. Mann, E. O. & Paulsen, O. Role of GABAergic inhibition in hippocampal network oscillations. *Trends Neurosci.* **30**, 343–349 (2007).
This paper reviews the mechanism by which GABAergic interneurons control the spike timing of other neurons and synchronize network activity.
135. Cobb, S. R., Buhl, E. H., Halasy, K., Paulsen, O. & Somogyi, P. Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature* **378**, 75–78 (1995).
136. Klausberger, T. *et al.* Brain-state- and cell-type-specific firing of hippocampal interneurons *in vivo*. *Nature* **421**, 844–848 (2003).
137. Klausberger, T. *et al.* Spike timing of dendrite-targeting bistratified cells during hippocampal network oscillations *in vivo*. *Nature Neurosci.* **7**, 41–47 (2004).
138. Tukker, J. J., Fuentealba, P., Hartwich, K., Somogyi, P. & Klausberger, T. Cell type-specific tuning of hippocampal interneuron firing during gamma oscillations *in vivo*. *J. Neurosci.* **27**, 8184–8189 (2007).
139. Jinno, S. *et al.* Neuronal diversity in GABAergic long-range projections from the hippocampus. *J. Neurosci.* **27**, 8790–8804 (2007).
This paper provides evidence that particular long-range GABAergic projection neurons are important for coordinating oscillation across brain areas.
140. Gulyas, A. I., Hajos, N., Katona, I. & Freund, T. F. Interneurons are the local targets of hippocampal inhibitory cells which project to the medial septum. *Eur. J. Neurosci.* **17**, 1861–1872 (2003).
141. Losonczy, A., Zhang, L., Shigemoto, R., Somogyi, P. & Nusser, Z. Cell type dependence and variability in the short-term plasticity of EPSCs in identified mouse hippocampal interneurones. *J. Physiol.* **542**, 193–210 (2002).
142. Sik, A., Penttonen, M., Ylinen, A. & Buzsaki, G. Hippocampal CA1 interneurons: an *in vivo* intracellular labeling study. *J. Neurosci.* **15**, 6651–6665 (1995).
143. Vida, I., Halasy, K., Szinyei, C., Somogyi, P. & Buhl, E. H. Unitary IPSPs evoked by interneurons at the stratum radiatum-stratum lacunosum-moleculare border in the CA1 area of the rat hippocampus *in vitro*. *J. Physiol.* **506**, 755–773 (1998).
144. Tulving, E. in *Organization of Memory* (eds Tulving, E. & Donaldson, W.) 381–403 (Academic, New York, 1972).
145. Goulet, S. & Murray, E. A. Neural substrates of crossmodal association memory in monkeys: the amygdala versus the anterior rhinal cortex. *Behav. Neurosci.* **115**, 271–284 (2001).
146. Mayes, A., Montaldi, D. & Migo, E. Associative memory and the medial temporal lobes. *Trends Cogn. Sci.* **11**, 126–135 (2007).
147. Manns, J. R., Howard, M. W. & Eichenbaum, H. Gradual changes in hippocampal activity support remembering the order of events. *Neuron* **56**, 530–540 (2007).
148. Fortin, N. J., Agster, K. L. & Eichenbaum, H. B. Critical role of the hippocampus in memory for sequences of events. *Nature Neurosci.* **5**, 458–462 (2002).
149. Kesner, R. P., Gilbert, P. E. & Barua, L. A. The role of the hippocampus in memory for the temporal order of a sequence of odors. *Behav. Neurosci.* **116**, 286–290 (2002).
150. Lisman, J. E. Relating hippocampal circuitry to function: recall of memory sequences by reciprocal dentate-CA3 interactions. *Neuron* **22**, 233–242 (1999).
151. Bussey, T. J., Saksida, L. M. & Murray, E. A. The perceptual-mnemonic/feature conjunction model of perirhinal cortex function. *Q. J. Exp. Psychol. B* **58**, 269–282 (2005).
152. Braak, H. & Braak, E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol.* **82**, 239–259 (1991).
153. McCormick, D. A. & Contreras, D. On the cellular and network bases of epileptic seizures. *Annu. Rev. Physiol.* **63**, 815–846 (2001).
154. Honea, R., Crow, T. J., Passingham, D. & Mackay, C. E. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am. J. Psychiatry* **162**, 2233–2245 (2005).
155. Campbell, S. & MacQueen, G. The role of the hippocampus in the pathophysiology of major depression. *J. Psychiatry Neurosci.* **29**, 417–426 (2004).
156. Zaborszky, L., Wouterlood, F. G. & Lanciego, J. L. *Neuroanatomical Tract-Tracing: Molecules, Neurons, and Systems* (Springer, 2006).
This book provides excellent guidance on tract-tracing methods.
157. Wickersham, I. R., Finke, S., Conzelmann, K. K. & Callaway, E. M. Retrograde neuronal tracing with a deletion-mutant rabies virus. *Nature Methods* **4**, 47–49 (2007).
158. Luo, L., Callaway, E. M. & Svoboda, K. Genetic dissection of neural circuits. *Neuron* **57**, 634–660 (2008).
This paper showed that a genetic approach can be an additional tool, next to anatomical and physiological methods, for constructing circuit diagrams.

Acknowledgements
The authors would like to thank E. Moser and L. Colgin for providing helpful comments on an earlier version of this article. N.L.M.C. acknowledges a personal grant from the Netherlands Organization for scientific research (NWO) — grant number 903-47-074.

FURTHER INFORMATION
Authors' homepage: www.temporal-lobe.com

SUPPLEMENTARY INFORMATION
See online article: S1 (figure) | S2 (box) | S3 (table) | S4 (box)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF