3.03 Anatomy of the Hippocampus and the Declarative Memory System

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3.03.1 Introduction

3.03.1.1 A Short History of the Anatomy of Declarative Memory

A half century ago, Scoville and Milner (1957) described profound memory loss following bilateral medial temporal lobe resection in the landmark patient HM. In the following years, scientists studying memory and the brain narrowed in on the hippocampus as the critical structure for everyday memory for facts and events. In the past two decades, however, we have come full circle: It is now apparent that the cortical areas surrounding the hippocampal formation also play critical roles in memory. Today, it is generally accepted that the hippocampal formation and the nearby parahippocampal region together are necessary for human declarative memory, but many questions remain concerning the functional diversity of structures within the so-called declarative memory system. To what extent can the function of hippocampal and parahippocampal substructures be dissociated? How discrete are such functions? How do these structures interact to permit encoding, storage, consolidation, and retrieval of representations of facts and events? What additional cognitive functions might be supported? Understanding the structure and connectivity of these regions is necessary for generating and testing sound hypotheses about the neurobiology of memory.

3.03.1.2 Overview of the Hippocampal System

3.03.1.2.1 Nomenclature

The structures that are the topic of this chapter have variously been termed the medial temporal lobe memory system (Squire and Zola-Morgan, 1991), the hippocampal memory system (Eichenbaum et al., 1994), and the hippocampal region (Witter and Amaral, 2004). The terms hippocampal region or hippocampal system have the advantage that the terminology translates effectively from humans to animal models of human memory, including rodents.
These regions are thought to support a type of memory that has been variously called episodic memory, declarative memory, or autobiographical memory. For research on memory using animal models, the terms episodic or episodic-like memory may be most appropriate.

The hippocampal system comprises the hippocampal formation and the parahippocampal region (Figure 1). The hippocampal formation includes the dentate gyrus, the hippocampus proper (fields CA1, CA2, and CA3), and the subiculum (Figure 2). The primary criterion for inclusion in the hippocampal formation is the trilaminar character of the structures. In addition, the included structures are connected by largely unilateral pathways beginning with the dentate gyrus granule cell input to the CA3 (Figure 3). CA3 pyramidal cells, in turn, provide a unidirectional input to the CA1. Finally, CA1 projects to the subiculum. Because corticocortical connections in the brain are overwhelmingly reciprocal, such a multisynaptic, unidirectional circuit is unique. In contrast, the entorhinal cortex projects to all portions of the hippocampal formation. The connectivity and laminar structure of the entorhinal cortex differentiate it from hippocampal formation structures. The dentate gyrus, hippocampus proper, and subiculum are therefore collectively referred to as the hippocampal formation (Figure 3, structures shown in yellow), and the entorhinal cortex is considered part of the parahippocampal region.

The parahippocampal region, also called the retrohippocampal region, includes the perirhinal, postrhinal (or parahippocampal), entorhinal, presubiculum, and parasubiculum cortices (Figure 1). The postrhinal cortex in the rodent brain is considered the homolog of the primate PH (see text for details). In the monkey and the rat brain, the parasubiculum (ParaS) is interposed between the entorhinal and POR/PH (arrows). The pre- and parasubiculum, which are components of the parahippocampal region, are not shown (but see Figure 2). Abbreviations: cs, collateral sulcus; rs, rhinal sulcus; DG, dentate gyrus; D, dorsal; L, lateral; M, medial; ParaS, parasubiculum; PreS, presubiculum; S, septal; Sub, subiculum; T, temporal; V, ventral.

Figure 1  Comparative views of the hippocampal system for the human (left), monkey (middle), and rat (right). The upper panel shows the relevant structures in lateral views of the human brain (a), the monkey brain (b), and the rodent brain (c). The lower panel shows unfolded maps of the relevant cortical structures for the human brain (d), the monkey brain (e), and the rodent brain (f). Shown for the human and monkey brain are unfolded layer IV maps of the perirhinal (PER) areas 35 and 36, parahippocampal (PH) areas TF and TH, and entorhinal cortex (EC). Figures adapted from Burwell RD, Witter MP, and Amaral DG (1995) The perirhinal and postrhinal cortices of the rat: A review of the neuroanatomical literature and comparison with findings from the monkey brain. *Hippocampus* 5: 390–408; Insausti R, Tuhon T, Sobreviela T, Insausti AM, and Gonsalo LM (1995) The human entorhinal cortex: A cytoarchitectonic analysis. *J. Comp. Neurol.* 355: 171–198. Shown for the rodent brain are unfolded surface maps of the PER areas 35 and 36, the postrhinal cortex (POR), and the lateral and medial entorhinal areas (LEA and MEA). The rodent POR is the homolog of the primate PH (see text for details). In the monkey and the rat brain, the parasubiculum (ParaS) is interposed between the entorhinal and POR/PH (arrows). The pre- and parasubiculum, which are components of the parahippocampal region, are not shown (but see Figure 2). Abbreviations: cs, collateral sulcus; rs, rhinal sulcus; DG, dentate gyrus; D, dorsal; L, lateral; M, medial; ParaS, parasubiculum; PreS, presubiculum; S, septal; Sub, subiculum; T, temporal; V, ventral.
Figure 2  Comparative views of the hippocampal formation with the pre- and parasubiculum. (a) Coronal sections of the human brain (a), monkey brain (b), and rat brain (c) showing the cellular layers of the hippocampal formation structures: the dentate gyrus (green), CA3 (blue), CA2 (purple), CA1 (red), and the subiculum (yellow). (d) An unfolded map of the rodent hippocampal formation. Rodent schematics adapted from Burwell RD and Witter MP (2002) Basic anatomy of the parahippocampal region in monkeys and rats. In: Witter MP and Wouterlood FG (eds.) The Parahippocampal Region, Organization and Role in Cognitive Functions. London: Oxford University Press. The presubiculum (light orange) and parasubiculum (dark orange) are also shown at two rostrocaudal levels in panels (e) and (f). Also shown are perirhinal areas 36 and 35 (panels (c) and (e)), the lateral and medial entorhinal areas (LEA and MEA, panels (e) and (f)), and the postrhinal cortex (POR, panel (f)). Abbreviations: DG, dentate gyrus; D, dorsal; L, lateral; M, medial; ParaS, parasubiculum; PreS, presubiculum; S, septal; Sub, subiculum; T, temporal; V, ventral.
homolog of the parahippocampal cortex in the primate brain. The perirhinal and postrhinal cortices are the major recipients of cortical afferents, and they project heavily to entorhinal cortex. The entorhinal cortex and the pre- and parasubiculum also receive direct cortical inputs. The entorhinal cortex projects directly to all components of the hippocampal formation and all other components of the parahippocampal region (Figure 3). The entorhinal connections with CA1, the subiculum, and all other parahippocampal structures are reciprocal.

One practical problem in the comparative anatomy of these structures is the confusing use of the term parahippocampal. In the rodent brain, the term has only one use (i.e., in the phrase ‘parahippocampal region’). In the human and monkey brains, the term is used in two additional ways. First is the parahippocampal cortex, a cortical region in the medial temporal lobe that is a component of the parahippocampal region (and is the homolog of the rodent postrhinal cortex). Second, the parahippocampal gyrus is the fold or gyrus that contains a large portion of the entorhinal, perirhinal, and parahippocampal cortices.

There are also discrepancies in the terminology for the perirhinal cortex. In Brodmann’s (1909) nomenclature, which includes verbal and numeric terms, the verbal term for area 35 was perirhinal, and the verbal term for area 36 was ectorhinal. Although Brodmann defined area 36 as a very narrow strip of cortex that did not include the temporal pole, other classic studies, which reported more detailed cytoarchitectonic analyses of these regions, included the temporal pole in area 36 (von Economo, 1929; Von Bonin and Bailey, 1947). There was no designation in Brodmann’s nomenclature for the caudally located region we now call the parahippocampal cortex (reviewed in Suzuki and Amaral, 2003b).

Using a different nomenclature, von Economo and Koskinas named the rostral perirhinal/ectorhinal region areas TG and TGa and the caudal (parahippocampal) region areas TF and TH. In modern terminology, the term perirhinal cortex was used to designate the combined areas 35 and 36 (Amaral et al., 1987) or 35a and 35b (Van Hoesen and Pandya, 1975). In the latter nomenclature, area 36 was termed TL.

Currently, the most commonly used nomenclature for memory research in the primate brain is perirhinal cortex comprising areas 35 and 36. Burwell and colleagues (Burwell et al., 1995; Burwell, 2001) adapted that nomenclature for use in the rodent brain. The term ectorhinal is no longer in use except in rodent brain atlases. Thus, within a comparative framework for experimental neuroscience, it seems reasonable to adhere to the nomenclature of perirhinal cortex as designating the combined areas 35 and 36 for both the rodent and primate brains.

**3.03.1.2.2 Location of the hippocampal system structures**

The focus of this chapter is the rat hippocampal system about which we have the most detailed anatomical information, but it is worth noting that there are surprising similarities and interesting differences between these structures in the rodent and the primate brains. The upper panel of Figure 1 shows that the hippocampus is C-shaped and relatively larger in the rodent brain (Figure 1(c)). The dorsal or septal portion of the region is associated with the fimbria-fornix and the septal nuclei. The ventral or temporal portion of the structure is associated with the temporal cortices. The hippocampus is relatively smaller in the primate brain (Figure 1(b)). The structure is still shaped like a C, though shallower and rotated.

- **Figure 3** Simplified schematic of the hippocampal system. The schematic includes the hippocampal formation (structures in yellow) and the parahippocampal region (structures in red, blue, green, and orange). The hippocampal formation comprises three-layered structures characterized by largely unidirectional connections, whereas the parahippocampal region comprises six-layered cortices characterized by reciprocal connections. Note that the perirhinal and postrhinal cortices (PER and POR) have reciprocal connections with CA1 and the subiculum. Abbreviations: DG, dentate gyrus; EC, entorhinal cortex; LEA, lateral entorhinal area; MEA, medial entorhinal area; ParaS, parasubiculum; PER, perirhinal cortex; PH, parahippocampal cortex in the primate brain; POR, postrhinal cortex in the rodent brain; PreS, presubiculum; subiculum (SUB).
about 90° clockwise, such that the opening is pointing upward. In the primate brain, the rostral hippocampus is associated with the temporal cortices, and the caudal hippocampus is associated with the septal nuclei. Accordingly, for cross-species comparisons, the best terminology for the long axis of the hippocampus is the term septotemporal.

In the human brain, the rhinal sulcus is relatively small and is associated with only the most rostral portion of the perirhinal cortex. The collateral sulcus forms the lateral border of the parahippocampal gyrus (Figure 1). As in the monkey brain, the entorhinal, perirhinal, and parahippocampal cortices occupy the parahippocampal gyrus and the temporal pole. The perirhinal cortex occupies the temporal pole and continues caudally. The entorhinal cortex lies in the medial portion of the anterior parahippocampal gyrus and is bordered rostrally and laterally by the perirhinal cortex. The parahippocampal cortex forms the caudal border of the perirhinal cortex.

In the monkey brain, which is less gyrencephalic (smoother) than the human brain and more gyrencephalic than the rat brain, the rhinal sulcus is associated with the full extent of the perirhinal cortex. Area 35 is a narrow band of agranular cortex that occupies the fundus and the lateral bank of the rhinal sulcus. Area 36 is a larger strip of dysgranular cortex located lateral to area 35 and including the temporal pole (Figure 1). All but the most rostral part of the lateral border of area 36 is shared with area TE of inferotemporal cortex. The rostrolateral border is formed by the superior temporal gyrus. Suzuki and Amaral (2003a) extended the border of area 36 rostrally and septrally to include the medial half of the temporal pole on cytoarchitectonic and connectional grounds. The monkey parahippocampal cortex, comprising areas TH and TF, is located caudal to the perirhinal and entorhinal cortices (Figure 1). Area TH is larger than area TF and is located adjacent to area TH. Area TH is a thin strip of largely agranular cortex medially adjacent to area TF. The parahippocampal cortex is bordered rostrally by the entorhinal and perirhinal cortices, laterally by TE, medially by the para- and presubiculum, and caudally by visual area V4.

In the rodent brain, the rhinal sulcus, or fissure as it is sometimes called, is the only prominent sulcus (Figure 1). It extends along the entire lateral surface of the brain, though it is quite shallow in its caudal extent. The region is bordered rostrally by the insular cortex. Insular cortex is classically defined as the region overlying the claustrum. The transition from insular cortex to the perirhinal cortex occurs when claustral cells underlying layer VI of the cortex are no longer visible. The perirhinal cortex comprises two cytoarchitectonically distinct strips of cortex, areas 35 and 36. Area 36 lies dorsally adjacent to area 35. The entorhinal cortex provides the ventral border of area 35. The dorsal border of area 36 is formed by secondary somatosensory cortex, rostrally, secondary auditory cortex at midrostrocaudal levels, and ventral temporal association cortex at caudal levels. The postrhinal cortex is located caudal to perirhinal cortex and provides the caudal border. It lies ventral to the ventral temporal area and dorsal to the medial entorhinal cortex (Figure 2).

3.03.1.2.3 Cross-species comparisons: Human, monkey, and rodent

A comparative analysis of the unfolded maps of the human, monkey, and rat brains shows that the spatial relationships of the perirhinal, parahippocampal/postrhinal, and entorhinal cortices are similar (Figure 1). Aside from the obvious differences in scale, the relative size differences are also interesting. Studies in rats, monkeys, and humans suggest that the perirhinal cortex accounts for roughly 3% of the cortical surface area, suggesting that the region scales linearly with cortical surface area. Also, in all three species, the surface area of the perirhinal cortex is roughly twice that of the postrhinal/parahippocampal cortex. Therefore, postrhinal/parahippocampal cortex also appears to scale linearly with brain size. The relative size of the entorhinal cortex, however, differs dramatically across species. In the rat brain, its surface area is more than three times that of the perirhinal cortex, but in the primate brain, entorhinal cortex is considerably smaller than the perirhinal cortex.

The homology of the rodent postrhinal cortex with the primate parahippocampal cortex is based on the structural and connectional similarities. In rodents and primates, the region receives substantial input from visual associational, retrosplenial, and posterior parietal cortices. Subcortical connections are also similar. For example, the rat postrhinal cortex is strongly and reciprocally connected with the lateral posterior nucleus of the thalamus (LPO). Likewise, the monkey parahippocampal cortex is connected with the pulvinar, the homolog of the lateral preoptic area (LPO) in the rodent.

In human, monkey, and rat, the entorhinal cortex is a six-layered cortex characterized by a cell sparse layer (lamina dissecans) separating the deep and
superficial layers. The medial part of the entorhinal area is, structurally, more highly differentiated as compared to the lateral part, and the lamina dissecans is more evident. It should be noted that in the rat, the medial entorhinal area is more caudal and ventral, whereas the lateral entorhinal area is more rostral and dorsal (Figure 1(c) and 1(f)). In both rat and monkey, the intrinsic connectivity of the entorhinal cortex appears to be organized into intrinsic bands of interconnectivity that form discrete associative networks. In the rat, these bands of intrinsic connectivity project to different levels of the dentate gyrus, suggesting a functional topography. There is evidence that a similar topography exists for the monkey.

All hippocampal formation structures observed in the human brain are also present in the monkey and rat brains (Figure 2). The absolute size of the hippocampal formation is largest in the human brain and smallest in the rodent brain, though the structure is relatively larger in the rodent brain. As previously mentioned, the hippocampus is situated differently in different species. In the human and monkey brains, it is as if the hippocampal formation has swung down and forward, such that rostral hippocampus in the primate brain is comparable to ventral hippocampus in the rodent brain. Similarly, caudal hippocampus in the primate brain is comparable to dorsal hippocampus in the rodent brain. For ease of comparative analysis, it is most efficient to use the terms septal and temporal to describe the long axis because these terms can be applied similarly across all species. The septotemporal axis in the rodent hippocampus is equivalent to dorsoventral axis, and the septotemporal axis in the primate hippocampus is equivalent to the caudorostral axis.

### 3.03.2 The Parahippocampal Region

#### 3.03.2.1 The Postrhinal Cortex

The postrhinal cortex is located near the caudal pole of the rat brain, caudal to the perirhinal cortex, dorsal to the rhinal sulcus and to the medial entorhinal area (Figure 1(c)). Usually the postrhinal cortex arises at the caudal limit of the angular bundle when subicular cells are no longer present in coronal sections (Figure 4(a)). At this level, postrhinal cortex is characterized by the presence of ectopic layer II cells at the perirhinal–postrhinal border near the ventral border with the medial entorhinal cortex (Figure 4(b), arrow). Moving caudally, the postrhinal cortex rises dorsally above the caudal extension of the rhinal fissure and wraps obliquely around the

![Figure 4](Location and photomicrograph of the postrhinal cortex (POR). (a) Drawing of a coronal section of the rat brain at the level of the rostral limit of the postrhinal cortex. (b) Nissl-stained coronal section showing the septal and temporal subregions of the POR (PORd and PORv, respectively). Layers are labeled I–VI. The septal subregion has a more differentiated laminar pattern. The ventral subregion is characterized by ectopic layer II cells (arrow) that appear near the rostral border with area 36. Abbreviations: ab, angular bundle.)
caudal pole of the brain. Visual association cortex, which forms the dorsal border of postrhinal cortex, has a more differentiated laminar pattern and a broader layer IV. The precise location of the dorsal border is difficult to distinguish cytoarchitectonically. A convenient landmark, however, is provided by the parasubiculum. The dorsal border of the postrhinal cortex on the lateral surface tends to be at the same dorsoventral level as the parasubiculum on the medial surface. The medial entorhinal cortex borders the postrhinal cortex ventrally and is easily distinguished by the large layer II cells and distinct laminar look of the cortex.

The cell layers of the postrhinal cortex have a homogeneous look because the packing density of cells is similar across layers (Figure 4(b)). In coronal sections, there is a broadening of the deep layers, which is due to the conformation of the region at the caudal pole of the brain (Figure 4). In sagittal sections, however, layers II–III, V, and VI each occupy about one-third of the cortical depth. The region can be subdivided into dorsal and ventral subdivisions based on cytoarchitectonic features. In general, the dorsal subregion has a more organized and radial appearance. The primary difference between the two subdivisions is that the dorsal portion has a distinguishable granule cell layer IV. Another difference is that layer V of the dorsal subregion is slightly narrower than in the ventral subdivision.

Retrograde tract tracing studies show that three-quarters of postrhinal afferentation arise in neocortex. The remainder is roughly evenly divided between subcortical and hippocampal afferents. The neocortical connections of the postrhinal cortex distinguish it from the nearby perirhinal cortex, in that cortical input to the postrhinal cortex is strongly dominated by visual and visuospatial inputs. In terms of sensory input, the postrhinal cortex receives almost a third of its total input from visual association regions. The strongest associational input arises in the posterior parietal cortex. Dorsal retrosplenial cortex also provides a strong projection. The input from frontal association areas largely arises in ventrolateral orbital frontal cortex. A strong input arises in the caudal and ventral temporal area, which is itself strongly interconnected with visual association cortices. For the most part, all cortical connections are equally reciprocated. The exception is that the postrhinal cortex projects strongly to the perirhinal cortex, but the return projection is substantially weaker.

The subcortical afferents are dominated by the thalamic inputs, which arise predominantly in the lateral posterior nucleus of the thalamus. That projection is reciprocal. There is also input from the anteromedial dorsal thalamic group and the intralaminar nucleus of the thalamus. The input from the amygdala is very small and is mainly from the lateral and basolateral nuclei. The postrhinal cortex also projects back to the lateral and basolateral amygdala nuclei. The inputs from the septum are also relatively small and are dominated by the medial septum.

The postrhinal cortex projects strongly to the medial entorhinal cortex, particularly to the lateral band. The entorhinal projection is weakly reciprocal. Postrhinal cortex has strong reciprocal connections with the septal presubiculum and the parasubiculum. In addition to these parahippocampal connections, there are strong direct connections with the hippocampus. The postrhinal cortex projects directly to the septal CA1 and subiculum, and both projections are returned. Connections with the temporal hippocampus are modest.

3.03.2.2 The Perirhinal Cortex

The perirhinal cortex arises at the caudal limit of the insular cortex and can be distinguished from insular cortex by the absence of the underlying claustrum. It is bordered dorsally by temporal association regions, ventrally by piriform and entorhinal cortex, and caudally by the postrhinal cortex. For most of its rostrocaudal extent, the perirhinal cortex includes the fundus and both banks of the rhinal sulcus (Figure 1(f)). At its caudal limit, the region rises dorsal to the fundus. A signature feature of the perirhinal cortex in the rodent and monkey brains is the presence of large heart-shaped cells in deep layer V that appear in both area 36 and area 35 (Figure 5).

Perirhinal area 36 is located dorsal to the rhinal sulcus. Although the region has a more prominent laminar structure dorsally than ventrally, area 36 is generally described as dysgranular cortex. The dorsal border of area 36 is best discerned by characteristics of the granular cell layer, layer IV. Area 36 has a fairly rudimentary layer IV as compared to the discrete granular layer of the dorsally adjacent neocortical areas. Another feature of the region is the patchy layer II in which medium-sized cells are organized in clumps or patches. The organization of layer V cells into lines gives the region a radial look, especially dorsally. Layer VI has a bilaminar appearance in that the cells in the deep portion of the layer
are smaller, darker, and more densely packed than the cells in the superficial portion of the layer.

Area 35 is generally characterized by a broad layer I. Layers II and III tend to blend together (Figure 5). The region lacks a layer IV and is thus considered agranular cortex. Layer V of area 35 has a disorganized look as compared to the radial appearance in area 36. As in area 36, layer VI has a bilaminar appearance. A general characteristic of area 35 is the organization of its cells into an arcing formation that spans all layers. This feature is most evident below the rhinal sulcus. The entorhinal cortex forms most of the ventral border and can be distinguished from ventral area 35 by the medium to large darkly staining stellate cells of layer II and by the appearance of the lamina dissecans, a cell-sparse area between layers III and V.

The input to the perirhinal cortex is roughly evenly divided between cortical and subcortical structures. The perirhinal cortex receives input from nearly all unimodal and polymodal associational regions of neocortex, but there are subregional differences. For example, area 36 receives roughly equal input from olfactory, auditory, visual and visuospatial, and sensorimotor regions, whereas area 35 is dominated by olfactory input from piriform cortex. There are also subregional similarities and differences in polymodal association input. Area 36 receives the largest cortical input from temporal association regions followed by insular and frontal regions. In contrast, area 35 receives the larger input from insular cortex followed by temporal association and frontal regions. Of course, there is also a heavy intrinsic input from area 36. Areas 36 and 35 each receive only small inputs from posterior associational regions. As would be expected, these associational connections are largely reciprocal.

Perirhinal areas 36 and 35 are also differentiated by subcortical connections. The strongest subcortical connections of area 36 are with the amygdala. The afferent input arises largely in the lateral nucleus, but the basolateral and basomedial nuclei also provide substantial inputs. Substantial thalamic input arises largely in the dorsolateral group and in the reticular thalamic nucleus. In contrast, area 35 receives its strongest subcortical afferents from olfactory structures, primarily from the endopiriform nucleus, but also from the piriform transition area. Other substantial inputs arise in the amygdala, the midline and lateral thalamic groups, and the medial geniculate nucleus of the thalamus.

Like the postrhinal cortex, the perirhinal cortex projects strongly to the lateral entorhinal cortex. The projection arises in area 35 and terminates most heavily in the so-called lateral band of the entorhinal cortex (see following). The entorhinal projection is weakly reciprocated. Area 36 is weakly connected with hippocampal and subicular structures, although these connections may be functionally important. Area 35 receives input back from the septal presubiculum. The strongest projection back to area 35 arises in temporal CA1, but it also receives input from temporal subiculum and presubiculum. Other smaller inputs arise in septal CA1 and the parasubiculum.

3.03.2.3 Entorhinal Cortex

The entorhinal cortex is of considerable interest in memory research. Not only does it provide the major conduit for sensory information to the hippocampal
formation, but a number of recent discoveries also suggest that the region may make unique contributions to the processing of spatial information. The entorhinal cortex is a relatively large and complicated structure, and its connections are topographically organized. Thus, understanding the areal differences in entorhinal structure could provide insight into its role in memory.

In rats and other animals, the entorhinal cortex has been divided into two subdivisions roughly equivalent to modern definitions of the lateral and medial entorhinal areas (LEA and MEA, Figure 1(f) (Brodman, 1909; Krieg, 1946). The LEA (Figure 5, top) is perhaps most easily distinguished from the MEA (Figure 5, bottom) by differences in layer II. LEA has a very clumpy layer II as compared to the more homogeneous layer II of the MEA. The sparsely populated layer IV, also called the lamina dissecans, is considered a landmark feature of the entorhinal cortex, but there are subregional differences. In general, the LEA exhibits a less prominent lamina dissecans as compared to the MEA (compare Figure 5).

Some time ago, the monkey entorhinal cortex was further subdivided on the basis of structural and connectional criteria (Van Hoesen and Pandya, 1975; Amaral et al., 1987). The rat entorhinal cortex has now been subdivided into six fields according to similar criteria (Figure 6(a)) (Insausti et al., 1997). The LEA comprises four fields: the dorsal lateral entorhinal field (DLE), the dorsal intermediate entorhinal field (DIE), the amygdalo-entorhinal transitional field (AE), and the ventral intermediate entorhinal field (VIE). Each field has unique connectional and/or structural characteristics. The medial entorhinal area (MEA) is subdivided into a caudal field (CE) and a medial field (ME). Medially, the MEA is bordered by the parasubiculum. The MEA border with the parasubiculum is marked by a layer II that thickens into a characteristic club-shaped formation.

The intrinsic connections of the entorhinal cortex are organized in a rostrocaudal manner, such that the cells located in each of three bands of the entorhinal area are highly interconnected but do not project outside the band of origin (Figure 6(b)) (Dolorfo and Amaral, 1998). Interestingly, each band of intrinsic connectivity spans the MEA and LEA. An important recent discovery about these regions has to do with the relationship of these bands of intrinsic connectivity with the perforant pathway, the entorhinal projection to the dentate gyrus. Briefly, the lateral band projects to the septal half of the dentate gyrus, whereas the intermediate and medial bands project to the third and fourth septotemporal quarters, respectively (Figure 6(c)). This connectional topography suggests that functional diversity within the entorhinal cortex may be in register with functional diversity in the hippocampus.

The entorhinal cortex is strongly connected with other parahippocampal region structures. Perirhinal

**Figure 6** Unfolded maps of the entorhinal cortex and the target of the perforant pathway, the dentate gyrus. (a) Unfolded map of the rodent entorhinal cortex showing the LEA in light green and the MEA in dark green. Further parcellation of each subregion is noted by black lines (Insausti et al., 1997). (b) Unfolded map of the rodent entorhinal cortex showing the lateral (LB) in dark green, the intermediate band (IB) in medium green, and medial band (MB) in pale green. (c) The unfolded dentate gyrus, color coded to denote the terminations of the perforant pathway. The entorhinal LB projects to the septal half of the dentate gyrus, the IB projects to the third quarter, and the MB projects to the temporal quarter. Abbreviations: AE, amygdalo-entorhinal transitional field; CE, caudal entorhinal field; D, dorsal; DLE, dorsal lateral entorhinal field; DIE, dorsal intermediate entorhinal field; L, lateral; M, medial; ME, medial entorhinal field; S, septal; T, temporal; V, ventral.
input arises largely in area 35 and terminates preferentially to the lateral band of the LEA. The postrhinal input arises in all portions of the region and terminates primarily in the lateral band of the MEA. There is a heavy return projection to perirhinal cortex that arises in all layers and all portions of the entorhinal cortex, though the strongest projection arises in the lateral band. Strong inputs originate from the pre- and parasubiculum. The parasubiculum targets the entire entorhinal cortex, septal presubiculum projects more heavily to the MEA, and temporal presubiculum projects more heavily to the LEA. The entorhinal cortex provides modest reciprocal connections with the pre- and parasubiculum (Witter and Amaral, 2004).

The entorhinal cortex has neocortical connections, through weaker than perirhinal and postrhinal cortices. The LEA receives very strong input from the piriform and agranular insular cortices. Medial and orbital frontal regions provide a strong projection. Input from the cingulate, parietal, and occipital cortices is relatively weak. There is little differentiation across the lateral to medial bands. Piriform cortex also projects to the MEA, but the projection terminates in the lateral and intermediate bands. In contrast, the lateral band receives moderate to strong projections from frontal, cingulate, parietal, and occipital cortices. Projections to the medial frontal and olfactory structures tend to arise in the intermediate and medial bands. A very narrow strip of the entorhinal cortex that is positioned closest to the rhinal fissure gives rise to the major projections to other cortical areas, including the lateral frontal, temporal, parietal, cingulate, and occipital cortices.

The entorhinal cortex has widespread connections with subcortical structures, and it is possible that the subcortical afferents are as influential as the cortical afferents. Strong projections arise in claustrum, olfactory structures, the amygdala, and dorsal thalamus. The olfactory input arises in the endopiriform nucleus and the piriform transition area and is stronger to the LEA than the MEA. The dorsal thalamic input arises primarily in the midline thalamic nuclei and is stronger to MEA than to LEA. The LEA and MEA receive input from septal nuclei, though the inputs are relatively small. The amygdala input arises in all nuclei except the central nucleus and amygdalohippocampal area and is stronger to LEA than MEA. In addition, the entorhinal cortex projects to all amygdaloid structures except the nucleus of the lateral olfactory tract and the central nucleus (Pikkarainen and Pitkanen, 1999).

The entorhinal cortex projects to all hippocampal formation structures including the dentate gyrus, fields CA3, CA2, and CA1 of the hippocampus proper, and the subiculum (reviewed in Witter and Amaral, 2004). The entorhinal projections to the dentate gyrus, CA3, and CA2 originate in layer II of the entorhinal cortex. The terminations of the layer II projections exhibit a radial topography in that the LEA terminates in the outer DG molecular layer, whereas the MEA projects to the middle DG molecular layer (Figure 7). The projections to CA1 and the subiculum originate in layer III. The terminations of the layer III projections
exhibit a transverse topography such that the LEA projects to distal CA1 and proximal subiculum, and the MEA projects to the proximal CA1 and distal subiculum. The organization of the CA1 and subicular projections back to deep layers of the LEA and MEA roughly reciprocates the forward projections.

3.03.2.4 Presubiculum

The presubiculum is bordered dorsally by retrosplenial cortex, medially by the subiculum, and ventrolaterally by the parasubiculum (Figures 2(e), 2(f), and 8(a)). Areas 48 and 27 according to Brodmann (1909) are both included in the presubiculum. Area 48, the most dorsal extension of the presubiculum, is sometimes called the postsubiculum. Because the presubiculum and this dorsal component exhibit considerable cytoarchitectonic similarities, it may be more appropriate to designate the area collectively with a single term.

Layer II of the six-layered presubiculum is thick and contains small, densely packed, and darkly staining pyramidal cells (Figure 8(b)). Cells in layer III are even smaller, round, and also darkly staining. Whereas cells in layer II tend to form clusters, cells in layer III have a more homogeneous look. Layer III is separated from the deep layers by a narrow, sparsely populated gap that is continuous with the lamina dissecans of the parasubicular cortex. Deep to this cell-sparse gap are two layers. Layer V is very thin and contains pyramidal cells. Layer VI is slightly thicker and contains a mixture of cell types.

As it turns out, acetylcholinesterase (AChE) is an excellent marker for the presubiculum. Layer II stains moderately darkly (Figure 8(c)). Deep to layer II is a dark band that contains layers III, the cell-sparse gap, and layer V. Layer VI is moderately to lightly stained in AChE preparations. AChE is also a good marker for the parasubiculum.

The presubiculum has extensive associational, commissural, and hippocampal parahippocampal connections (Witter and Amaral, 2004). The septal and temporal parts of the presubiculum are highly interconnected. Connections with the contralateral presubiculum are also extensive, though commissural connectivity may be stronger ventrally than dorsally. The presubiculum provides a weak input to the dentate gyrus and all fields of the hippocampus proper. It is reciprocally connected with the subiculum. The presubiculum projects to superficial layers of the subiculum. The projection to the septal subiculum is moderately strong, and the temporally directed projection is relatively weak. The input from the subiculum terminates in layer I.

Regarding parahippocampal connectivity, the presubiculum projects to superficial layers of the

![Figure 8](image_url)  
**Figure 8** Photomicrographs of the presubiculum (PreS) and parasubiculum (ParaS). (a) Drawing of a coronal section of the rat brain at the level of the angular bundle (ab). The inset designates the areas shown in panels (b) and (c). (b) Nissl-stained coronal section showing the PreS and ParaS. Layer II is outlined for the PreS, and the combined layer II/III is outlined for ParaS. (c) Adjacent section stained for acetylcholinesterase (AChE). AChE provides an excellent marker for these regions.
parasubiculum, but the connections with the entorhinal cortex are by far the strongest. The presubicularentorhinal projection is bilateral, largely directed to medial entorhinal cortex, and almost exclusively terminates in layer III. Septal presubiculum projects much more heavily to the MEA than the LEA, but temporal presubiculum projects heavily to both entorhinal divisions. Septal presubiculum also provides a moderately heavy input to the posrithral cortex. The dorsal extension (Brodmann’s area 48, sometimes termed the postsubiculum) projects massively to postrithral cortex. Temporal presubiculum projects heavily to the LEA and the MEA and moderately heavily to perirhinal areas 36 and 35. Septal presubiculum receives heavy input from postrithral cortex and a moderately heavy input from the MEA portion of the lateral band. Temporal presubiculum receives a very heavy input from the MEA portion of the medial band, weak input from the LEA, and virtually nothing from the perirhinal and postrithral cortices.

The heaviest neocortical input to the presubiculum arises in the granular retrosplenial cortex, but weaker inputs arise in prelimbic cortex, dorsomedial prefrontal areas, and the anterior cingulate cortex (Witter and Amaral, 2004). The primary subcortical inputs are from the dorsal thalamus, specifically, the anteroventral, the anterodorsal, and the laterodorsal nuclei. The presubiculum receives subcortical input from the thalamus, primarily the anterior thalamic nuclei including the anteroventral, anterodorsal, and laterodorsal nuclei. A massive return projection targets the same nuclei. There is also a strong cholinergic input arising from septal nuclei. Finally, the presubiculum has reciprocal connections with the mamillary nuclei of the hypothalamus.

3.03.2.5 The Parasubiculum

For most of its rostrocaudal extent, the parasubiculum is bordered by presubiculum dorsally and the medial entorhinal area ventrally (Figure 2(e) and 2(f)). At more caudal levels, the parasubiculum is interposed between the postrithral cortex and the medial entorhinal area. A broad, combined layer II/III contains large, densely packed, moderately darkly staining pyramidal cells. This layer is separated from the deep layers by a broad lamina dissecans. Layers V and VI can be distinguished from one another and tend to run continuously with deep layers of the medial entorhinal area. In AChE preparations, layers I and II/III are darkly stained (Figure 8(c)). The lamina dissecans and layer V are lightly stained, and layer V is moderately darkly stained.

The parasubiculum has associational connections that project dorsally and ventrally. The ventral projections are heavier and more extensive than the dorsal ones. Commissural projections terminate in layers I and III of the contralateral homotopic region.

The hippocampal input to the parasubiculum arises mainly in the subiculum and terminates in layer I and superficial layer II. There are also return projections to the hippocampal formation. The structure projects directly to the molecular layer of the dentate gyrus. This is especially interesting given that the parasubiculum receives strong inputs from anterior thalamic nuclei. As has been previously noted, the anterior thalamic projection to the parasubiculum provides a pathway by which the anterior thalamus can affect hippocampal processing of incoming information at very early stages.

Like the presubiculum, the parasubiculum exhibits substantial connections with other parahippocampal structures. The parasubiculum projects selectively to layer II of the entorhinal cortex. The entorhinal projection is much heavier to MEA than to the LEA. Interestingly, the parasubiculum projection to POR is even heavier than that to the MEA. Parahippocampal inputs arise mainly from the MEA, with the medial band providing the heaviest return projection. There is also a modest presubiculum input.

Extrinsic connections of the parasubiculum are few. The only neocortical afferents arise in retrosplenial cortex and visual cortex, and these inputs are quite weak. Other than the input from the anterior thalamus, the only other subcortical afferents arise in the amygdala from the lateral, basal, and accessory basal nuclei.

3.03.3 The Hippocampal Formation

The structures of the hippocampal formation are grouped together partly because of the sequential activation pattern that was identified several decades ago. The entorhinal cortex activates the dentate gyrus via the perforant pathway, the mossy fiber pathway from the dentate gyrus activates CA3, and the CA3 Schaffer collaterals activate CA1. Some of the earliest and most famous studies of the structure of the nervous system were conducted by Ramón y Cajal, who used a technique developed by Camillo Golgi for darkly staining a small number of neurons.
in the brain. Cajal’s elegant studies and drawings, including the rodent hippocampus (Figure 9), provided the basis for the neuron doctrine.

Because of the complex architecture of the hippocampus, it is helpful to describe its structure in terms of three axes, the longitudinal, transverse, and radial axes. As previously discussed, we use the term septotemporal for the longitudinal axis of the hippocampus. Along the transverse axis, which is orthogonal to the long axis of the hippocampus, the dentate gyrus can be considered the proximal limit and transverse locations designated according to position relative to the dentate gyrus. Thus, the part of the CA3 lying in the V of the dentate gyrus is proximal CA3, and the part closest to CA1 is distal (Figure 10). Similarly, the part of CA1 closest to CA3 is proximal, and so on. Finally, the laminar structure is perpendicular to the radial axis. In this terminology, the molecular layers are superficial and the layers on the opposite side of the principle cell layers are deep.

Based primarily on electrophysiological data and mapping of vasculature, Anderson and colleagues (1971) proposed that the hippocampal formation was organized in parallel lamellae stacked along the longitudinal axis. They further proposed that this lamellar organization would permit strips, or slabs, of the hippocampus to function as independent units. Although the lamellar hypothesis shaped research on the hippocampus for years to come and continues to influence modern concepts of hippocampal function, modern neuroanatomical research has revealed that the hippocampal projections are much more divergent than is suggested by the lamellar hypothesis. Indeed, the major hippocampal and dentate association projections extend along the septotemporal axis as well as the transverse axis.

### 3.03.3.1 The Dentate Gyrus

The dentate gyrus is three-layered cortex whose principle cell layer is V shaped (Figure 10). The molecular layer lies outside the V, and the polymorphic layer lies inside the V. The beginning of the CA3 principle cell layer protrudes into the polymorphic area of the dentate gyrus. This conformation has generated some confusion over the border between CA3 and the dentate gyrus polymorphic layer, as well as the identity of these cells. In earlier nomenclatures, and occasionally in modern reports, the part of CA3 next to the dentate gyrus was sometimes called CA4. With modern techniques for defining connectional characteristics, however, it is now clear that those pyramidal cells belong to CA3.

The dentate granule cell layer contains small, very densely packed, oval cells that have a dark appearance in cell stains (Figure 10(a)). Each granule cell has a small number of primary dendrites (one to four) that are covered with spines. The dendrites

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**Figure 9** Drawing of the circuitry of the hippocampal formation by Ramón y Cajal (1909). Cajal proposed that the nervous system is made up of countless separate units, or nerve cells composed of dendrites, soma, and axons, each of which is a conductive device. He further proposed that information is received on the cell bodies and dendrites and conducted to distant locations through axons. Abbreviations: A, retrosplenial area; B, subiculum; C, Ammon’s horn; D, dentate gyrus; E, fimbria; F, cingulum; G, angular bundle; H, corpus callosum; K, recurrent collaterals; a, axon entering the cingulum; b, cingulum fibers; c-e, perforant path fibers; g, subicular cell; h, CA1 pyramidal cells; i, Schaffer collaterals; collaterals of alvear fibers.
extend into the molecular layer all the way to the hippocampal fissure. In the subgranular region, between the granule cell layer and the polymorphic layer, there are several cell types, most of which are immunoreactive for gamma-aminobutyric acid (GABA). A subset of these cells is also immunoreactive for the calcium-binding protein, parvalbumin (Figure 10(c)). The most prominent types are the basket cell and the axo-axonic, or chandelier, cell. The basket cell interneurons are quite large with a single, aspiny apical dendrite extending into the molecular layer and several basal dendrites extending into the polymorphic layer. Axo-axonic cells have a dendritic tree of radial branches extending through the molecular layer. The axon arborizes extensively in the granule cell layer.

The molecular layer contains mostly dendrites from cells of the granule and polymorphic layers. In material stained for heavy metals using the Timm’s method, it is possible to visualize the three sublayers of the molecular layer (Figure 10(b)). The inner third of the molecular layer, next to the lightly colored granule cell layer, stains a reddish brown. The middle sublayer stains yellow, and the outer sublayer stains orange. Though the molecular layer mostly contains dendrites, there are a few cell types that stain for VIP, GABA, and parvalbumin. One interesting type of GABA-immunoreactive cell, with its soma in the molecular layer, has an axon restricted to the outer two-thirds of the molecular layer. Thus, its terminal field coincides with the perforant path terminations in the dentate molecular layer.

The polymorphic layer contains a number of cell types, but the best characterized is the mossy cell. These large multipolar cells are so named because of their large dendritic spines, the so-called thorny excrescences. The mossy fiber axons from the granule layer terminate on these spines. There are a number of interneurons with somata in the polymorphic layer that make inhibitory connections on the dentate granule cells. One such cell type is the hilar perforant-path (HIPP) associated cell, which has a dendritic tree in the polymorphic layer that make inhibitory connections on the dentate granule cells. One such cell type is the hilar perforant-path (HIPP) associated cell, which has a dendritic tree in the polymorphic layer that make inhibitory connections on the dentate granule cells. One such cell type is the hilar perforant-path (HIPP) associated cell, which has a dendritic tree in the polymorphic layer that make inhibitory connections on the dentate granule cells. One such cell type is the hilar perforant-path (HIPP) associated cell, which has a dendritic tree in the polymorphic layer that make inhibitory connections on the dentate granule cells. One such cell type is the hilar perforant-path (HIPP) associated cell, which has a dendritic tree in the polymorphic layer that make inhibitory connections on the dentate granule cells. One such cell type is the hilar perforant-path (HIPP) associated cell, which has a dendritic tree in the polymorphic layer that make inhibitory connections on the dentate granule cells. One such cell type is the hilar perforant-path (HIPP) associated cell, which has a dendritic tree in the polymorphic layer that make inhibitory connections on the dentate granule cells.

Figure 10 Photomicrographs of the hippocampal formation. (a) Nissl-stained coronal section showing the dentate gyrus (DG) and hippocampus proper, comprising fields CA3, CA2, and CA1. (b) Adjacent section stained for heavy metals using the Timm’s method. (c) Parvalbumin-stained section showing the same regions. Layers of the DG are the outer molecular layer (ml), the granule cell layer (gcl), and the polymorphous layer (pol). The CA fields contain the outer stratum lacunosum-moleculare (slm), the stratum radiatum (sr), the gcl, and the stratum oriens (so). CA3 also contains the stratum lucidum (sl). The dashed line demarcates the border between the DG and CA3. The solid line shows the location of the hippocampal fissure and demarcates the border between DG and CA1.
The entorhinal cortex provides the only cortical input to the dentate gyrus through the perforant pathway. There is substantial subcortical input from the septal nuclei, the hypothalamus, and the brain stem modulatory systems. The cholinergic input from the septal region originates in the medial septal nucleus and in the nucleus of the diagonal band of Broca. It is topographically organized such that cells in the medial septal areas tend to terminate septally, and cells in lateral septal structures terminate temporally. The projection terminates in the polymorphic layer. The primary hypothalamic input is from the supramamillary area and terminates in a narrow band of the molecular layer just superficial to the granule cell layer. This projection is probably excitatory and appears to target both granule cells and interneurons. The dentate gyrus receives input from each of the modulatory neurotransmitter systems in the brainstem. The noradrenergic input is from the pontine nucleus of the locus coeruleus and terminates in the polymorphic layer. The serotonergic input is from several of the raphe nuclei and also terminates in the polymorphic region. Minor dopaminergic inputs arise in the ventral tegmental area and the substantia nigra.

The only output of the dentate gyrus is the granule cell mossy fiber projection to CA3. Axon collaterals of each cell project to the full extent of the transverse axis. This is the one component of the hippocampal circuitry that does show a lamellar projection pattern. The fibers travel along or within the CA3 pyramidal layer, eventually reaching the stratum lucidum. In addition to the CA3 projection, the mossy fibers give rise to an associational connection consisting of about seven collaterals that terminate in the dentate gyrus polymorphic layer before entering CA3. The mossy fiber axons can be easily identified in Timm’s preparations in which they stain very darkly (Figure 10(b)).

### 3.03.3.2 The Hippocampus Proper

The hippocampus proper consists of three fields. Proximal to distal from the dentate gyrus, they are the Ammon’s horn fields CA3, CA2, and CA1 (Figure 10). Like the dentate gyrus, these fields are a three-layered cortex consisting of a principle layer located between cell-sparse layers. Deep to the principle cell layer is the stratum oriens. Superficial to the principle cell layer are the stratum radiatum and the stratum lacunosum-moleculare. CA3 has an additional thin layer, the stratum lucidum, which lies just superficial to the principle cell layer and deep to the stratum radiatum.

The principal cell layer consists, primarily, of pyramidal cells. The pyramidal cells in CA3 are larger and the layer thicker compared with CA1. The small and often-overlooked field CA2 contains larger pyramids, similar to CA3, but is similar to CA1 in other ways. For example, it lacks mossy fiber input. Each pyramidal cell has an apical dendritic arbor extending upward through the stratum radiatum and the stratum lacunosum-moleculare and a basal dendritic arbor extending into the stratum oriens. CA3 cells proximal to the dentate gyrus have smaller dendritic trees than the cells distal to the dentate gyrus, but overall, the dendritic arbors of cells in CA3 are larger than those in CA1. The dendritic arbors of pyramidal cells in CA2 are mixed, some with large arbors, similar to CA3, and some with small arbors, similar to CA1.

Interneurons undoubtedly play an important role in the regulation of local circuits in the hippocampus proper. Hippocampal interneurons differ in morphology, immunoreactivity, synaptic properties, laminar location, and connectivity. Hippocampal interneurons are GABAergic, but they may also be immunoreactive for somatostatin, neuropeptide Y, vasopressin, cholecystokinin, parvalbumin, calbindin, and calretinin. Most hippocampal interneurons have short axons, but there are also interneurons with long axons that project outside the hippocampal formation. We mention a few types here, but for a full discussion, see Freund and Buzsaki (1996).

One prominent interneuron type in the pyramidal cell layer is the chandelier or axo-axonic cell. The apical dendrites are radially oriented and span all superficial layers to the hippocampal fissure. The basal dendrites form a thick arbor in the stratum oriens. There is also a heterogeneous group of basket cells whose apical dendrites extend into the stratum moleculare and whose extensive basal dendrites span the entire depth of the stratum oriens. The axo-axonic cells and the basket cells are conveniently positioned to receive excitatory input from all afferents of the hippocampus proper.

Some hippocampal interneuron cell types have cell bodies in stratum oriens and innervate principal cell dendrites, similar to those described for the dentate gyrus. The oriens lacunosum-moleculare (O-LM) cells have a dense axonal arbor restricted to the stratum lacunosum moleculare. The dendritic tree is localized to layers that receive recurrent collaterals. There are many other interneuron
The CA3 pyramidal cell axons are highly collateralized and project to all CA fields both ipsilaterally and contralaterally. There is also a small collateral projection to the polymorphic layer of the dentate gyrus. CA3 does not, however, project to the subiculum, presubiculum, parasubiculum, or entorhinal cortex. The projection to CA1 is called the Schaffer collateral projection, the projections to CA3/CA2 are called the associational projections, and the projections to commissural structures are called the commissural projections. The Schaffer collateral projection exhibits a topography such that proximal CA3 cells (closer to the dentate gyrus) tend to project to levels of CA1 that extend farther in the septal than temporal direction. Distal CA3 cells (farther from the dentate gyrus) tend to project farther in the temporal direction. In addition, projections of proximal CA3 cells tend to terminate more superficially in stratum radiatum, whereas distal CA3 cells tend to terminate more deeply in stratum radiatum and in stratum oriens. The associational projections exhibit complex transverse and radial topographies, but in general the CA3-CA3 associational projections terminate extensively along the septotemporal axis (Witter and Amaral, 2004). The pattern of the terminations of the commissural projections mirrors those of the associational projections.

Extrinsic connections of CA3 are not robust except for the substantial projection to the lateral septal nucleus. The major subcortical input to CA3 is cholinergic and arises in the medial septal nucleus and the nucleus of the diagonal band of Broca. There is a GABAergic component of the projection that terminates primarily on the GABAergic interneurons of the stratum oriens. Temporal CA3 receives a minor input from the amygdala basal nucleus, which terminates in the stratum oriens and the stratum radiatum. Inputs from piriform cortex have also been reported. A noradrenergic projection arises in the locus coeruleus, and a serotonergic input arises in the raphe nucleus.

Field CA2 can be differentiated from CA3 by the lack of mossy fiber input and the associated thorny excrescences (Figure 10(b)). The pyramidal cell layer also stains more intensely for parvalbumin (Figure 10(c)). The intrinsic projections are similar to those of CA3, although the topographies may not be the same. For example, like CA3, CA2 also provides a small collateral projection back to the dentate gyrus. Not much is known specifically about CA2 extrinsic connections, but available evidence suggests that the region is differentiated from CA3 by hypothalamic input from the supramamillary area.

Field CA1 exhibits only a weak associational/commissural connection, a feature that is in striking contrast to the robust associational network present in CA3. This difference has been interpreted as underlying some of the putative functional differences in CA3 and CA1. Other intrahippocampal connections, however, are extensive. CA1 interneurons project to CA3 and to the polymorphic layer of the dentate gyrus. The major projection from CA1, however, is to the subiculum, and that projection exhibits a strict topography. Distal CA1 projects to proximal subiculum, and proximal CA1 projects to distal subiculum. The mid-CA1 projection terminates in midproximodistal subiculum.

Field CA1 receives substantial cortical and subcortical input from extrahippocampal structures. Cortical input arrives from the perirhinal, postrhinal, and entorhinal cortices. Subcortical input to CA1 is grossly similar to the subcortical input to CA3 but differs in the details. The septal input is weaker and terminates in stratum oriens. The input from the amygdala is more substantial, especially to distal CA1. Amygdala input arises in the basal and accessory basal nuclei. There is a prominent input from the nucleus reuniens of the thalamus that terminates in the stratum lacunosum moleculare. Like CA3, CA1 receives weak noradrenergic input from the locus coeruleus and weak serotonergic input from the raphe nucleus. There is also a weak dopaminergic input.

Of the hippocampal CA fields, CA1 has the more robust extrinsic projections. The cortical projections include the perirhinal, postrhinal, entorhinal, retrosplenial cortices, preinfralimbic, and medial prefrontal cortex. In general, the septal half projects more heavily to postrhinal cortex, the medial entorhinal area, and retrosplenial cortex, whereas the temporal half of CA1 projects more heavily to perirhinal cortex, the lateral entorhinal area, and infralimbic cortex. Temporal levels also project to the anterior olfactory nucleus, the hypothalamus, nucleus accumbens, and the basal nucleus of the amygdala.

### 3.03.3.3 The Subiculum

The subiculum is widely considered the output structure of the hippocampal formation. In this way, it differs from its parahippocampal neighbors, the pre- and parasubiculum, which are considered to be
input structures. Like the CA fields of the hippocampus proper and the dentate gyrus, the subiculum is a three-layered cortex with a deep, polymorphic layer, a pyramidal cell layer containing the principle cells, and a molecular layer, which is continuous with the stratum lacunosum moleculare of field CA1. The subiculum can be distinguished from the proximally situated CA1 and the distally situated presubiculum by a principle cell layer that is more loosely packed. The border with CA1 is further demarcated by the widening of the middle layer of the subiculum.

The principle cell layer contains large pyramidal cells. The basal dendrites terminate in the deep part of the principle layer, and the apical dendrites extend into the molecular layer. The pyramidal cells are large and of uniform shape. Electrophysiological findings suggest that there are two populations of pyramids, though they cannot be distinguished morphologically. So-called regular spiking cells tend to be located superficially, and bursting cells tend to be located deep in the layer. Although both types are projection cells, it is possible that only the bursting cells project to the entorhinal cortex. Among the pyramids are numerous smaller cells, probably representing varied types of interneurons. Perforant pathway fibers contact GABAergic cells that stain for parvalbumin. Not much is known about subicular interneurons, but in general, the population of interneurons appears similar to that observed in field CA1 (Witter and Amaral, 2004).

The associational connections of the subiculum extend temporally from the point of origin and terminate in all layers. There is no commissural projection. There are also local associational connections confined to the pyramidal layer and the deepest part of the molecular layer. The available data suggests that the bursting pyramidal cells form a columnar network that is roughly interconnected.

Connections of the subiculum with other hippocampal structures is limited to input from CA1, which is massive. The projection exhibits a topography such that proximal CA1 projects to distal subiculum, midproximodistal CA1 projects to midsubiculum, and distal CA1 projects to proximal subiculum. The projection is not truly lamellar, however, as any part of CA1 projects to about one-third of the septotemporal extent of the subiculum.

The parahippocampal connections of the subiculum are more diverse, but the best-characterized projection is to deep layers of entorhinal cortex. Septal levels of the subiculum provide substantial input to the lateral and medial entorhinal cortices. Septal subicular input to the postrhinal cortex is equally strong, but input to perirhinal cortex, especially area 35, is modest. Temporal subiculum provides massive input to the entorhinal cortex and moderate input to perirhinal and postrhinal cortices. The subiculum also receives a substantial input from the entorhinal cortex. The entorhinal lateral band projects more strongly to septal subiculum, and the entorhinal intermediate and medial bands project more strongly to temporal subiculum. There is also modest input from the perirhinal and postrhinal cortices. Perirhinal cortex projects relatively more strongly to temporal subiculum, and the postrhinal cortex projects relatively more strongly to septal subiculum. The subiculum also projects heavily to the pre- and parasubiculum cortices, though the return projections are modest (O’Mara et al., 2001).

The most prominent neocortical projections are to retrosplenial and prefrontal cortices. The distal and septal part of the subiculum projects to the ventral retrosplenial cortex. The presubiculum projections to frontal areas include the medial orbital, prelimbic, infralimbic, and anterior cingulate cortices. The retrosplenial projection is reciprocated, but available evidence suggests that the frontal projections are not.

The diverse subcortical projections target the septal complex, the amygdala, the nucleus accumbens, the hypothalamus, and the thalamus. All septotemporal levels of the subiculum project to the lateral septum, but the projection arises primarily in the proximal part. Septal input arises mainly in the nucleus of the diagonal band. The amygdala projection arises primarily in the temporal subiculum and targets the posterior and basolateral nuclei. The projection to the nucleus accumbens is topographic such that the proximal part of the septal subiculum projects to rostrolateral nucleus accumbens, and the proximal part of the temporal subiculum projects to the caudomedial nucleus accumbens. The hypothalamic projection also arises primarily in the temporal subiculum. It terminates in the medial preoptic area and the ventromedial, dorsomedial, and ventral premamillary nuclei. Finally, there are documented connections with thalamic nuclei, though the details are not well described. The proximal part of the septal subiculum projects to the anteromedial nucleus of the thalamus, but the distal part projects to the anterior thalamic complex. The latter projection is reciprocated. Temporal subiculum receives input from the nucleus reuniens. Available evidence suggests that the anteroventral nucleus of the thalamus also projects to the subiculum.
3.03.4 Conclusions

3.03.4.1 The Flow of Sensory Information through the Hippocampal System

The entorhinal cortex is widely recognized as the primary way station for sensory information on its way from the neocortex to the hippocampus. Much of the neocortical input arrives by way of the perirhinal and postrhinal cortices, but there are also direct neocortical inputs to the entorhinal cortex. The presubiculum and parasubiculum are also considered input structures for the hippocampal memory system. The distinct patterns of cortical afferentation to parahippocampal structures, the intrinsic connections, and the topography of the parahippocampal–hippocampal connections suggest that parahippocampal structures are involved in the preprocessing of sensory information provided to the hippocampus, and that there is functional diversity within the parahippocampal region. The view that parahippocampal structures have different functions is consistent with emerging evidence that there is also substantial functional diversity among hippocampal formation structures.

In Figure 11, we have attempted to schematize the flow of sensory information through the hippocampal memory system. Beginning with the input structures, perirhinal area 36 receives sensory input from visual, auditory, and somatosensory regions. Longitudinal intrinsic connections integrate across modalities before transmission to perirhinal area 35. This polymodal input to area 35 is joined by olfactory information and then passed on to entorhinal cortex, primarily the lateral band of the LEA. The postrhinal cortex receives visual and visuospatial input from posterior parietal, retrosplenial, and visual association regions, along with a small input from auditory association cortex. That information is integrated and transmitted to entorhinal cortex, primarily to the lateral band of the MEA. Presubiculum is targeted by the subiculum in a topographical manner such that septotemporal levels of the subiculum map onto septotemporal levels of the presubiculum. Subicular input is integrated with direct visuospatial input to the presubiculum, especially the septal component. That information is forwarded to the parasubiculum, the postrhinal cortex, and the MEA.
The most septal component of the presubiculum, the area sometimes termed the postsubiculum, projects massively to the postrhinal cortex. Finally, the parasubiculum, which receives direct, but modest, visual and visuospatial input along with its subicular input, projects to postrhinal cortex and the MEA.

To summarize, information from all modalities reaches the full septotemporal extent of the hippocampus, but the degree of processing of different modalities is weighted differently along the septotemporal axis. Visual and visuospatial input is processed and elaborated along a pathway that includes the postrhinal cortex, lateral MEA, the septal hippocampal formation, septal presubiculum, parasubiculum, and then back to postrhinal cortex and lateral MEA. Olfactory information is less segregated but follows a pathway that includes the perirhinal cortex, medial LEA, and temporal hippocampal formation structures. Thus, there appears to be functional diversity in the processing of sensory information that is organized along the septotemporal axis; visual and visuospatial information is predominant in the septal hippocampus, and olfactory information is predominant in the temporal hippocampus.

### 3.03.4.2 The Comparative Anatomy of the Hippocampal System

As indicated earlier, all components of the parahippocampal region and the hippocampal formation are represented in both the rodent and the primate brain. Many of the connectional principles are also conserved. Taking into account the differences in brain size and sensory processing needs, cortical afferentation of the parahippocampal structures is similar across species. Additionally, the available evidence suggests that the architecture of the perforant pathway is similar in the primate and rodent brains. In the monkey and the rat, the perforant pathway projections to the dentate gyrus, CA3, and CA2 originate in layer II of the entorhinal cortex. Also in both, the projections to CA1 and the subiculum originate in layer III. In addition, the terminations of the projections originating in entorhinal layer III exhibit a transverse topography. The rostral entorhinal cortex in the monkey and the lateral entorhinal area in the rat project to the border of the CA1 and subiculum; the caudal entorhinal cortex in the monkey and the medial entorhinal area in the rat project to proximal CA1 and distal subiculum (Witter, 1986, 1993, Amaral, 1993). The intrinsic connections of the monkey entorhinal cortex also exhibit patterns similar to the lateral to medial bands of intrinsic connectivity observed in the rodent entorhinal cortex. Taken together, the evidence suggests that both the rat and monkey hippocampal memory systems are excellent models for the medial temporal lobe memory system in the human brain.

### References


