

# Organization of the Entorhinal–Hippocampal System: A Review of Current Anatomical Data

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Although the hippocampal formation must be regarded as a critical component of the “medial temporal lobe memory system,” there is now convincing evidence that it does not actually store memories for a long time (Zola-Morgan and Squire, 1990; Squire and Zola-Morgan, 1991). The repository of memory traces most probably is in the domain of the association cortex. It can thus be inferred that the hippocampal formation needs to have reciprocal connections with these cortical domains. However, the striking feature of the connectivity of the medial temporal lobe is that the hippocampal formation has its major cortical connections with the entorhinal cortex only, and that this cortical area, and not the hippocampal formation, forms part of numerous multisynaptic cortico-cortical networks. This is mainly achieved through its reciprocal connections with adjacent parts of the parahippocampal cortex (Witter et al., 1989b).

An important issue is whether the parahippocampal cortex–hippocampal formation is organized as a topological system of anatomically defined and restricted channels by which selective attributes of incoming information are processed and eventually returned to the association cortex for permanent storage. A well-known example is the so-called “lamellar hypothesis of hippocampal organization” that was put forward by Andersen and colleagues in the early 1970s (Andersen et al., 1971). They proposed that the hippocampal formation comprises a number of cytoarchitecturally and connectionally stereotyped transverse slices stacked along the longitudinal axis and operating as independent functional units. Recent anatomical findings, summarized by Amaral and Witter (1989), indicate that the hippocampal formation can more reasonably be viewed as a three-dimensional cortical system in which the processing of information takes place along both longitudinal and transverse axes. This does not exclude that, as a result of physiological mechanisms or intrinsic wiring properties of the network, specific activation of neuronal populations in one lamella might occur. This article summarizes the current knowledge about the anatomy of the entorhinal–hippocampal system. Although the most detailed anatomical information is derived from studies in the rat, available studies in other species, such as the cat and monkey, point to a rather similar organization in all three species. The available evidence indicates that specific channels that can be identified anatomically may indeed be present in the hippocampal region, but in contrast to the transverse slices that figure in the

lamellar concept, we propose that such channels make use of longitudinal slabs of hippocampal tissue, in particular in CA1 and the subiculum.

## ENTORHINAL–CORTICAL CIRCUITRY

Within the entorhinal cortex, a differentiation is made between the superficial layers (I, II, and III) and the deep layers (IV, V, and VI). The superficial layers II and III give rise to the major components of the perforant path projection to the hippocampal formation (Nafstad, 1967; Steward, 1976; Steward and Scoville, 1976; Swanson and Cowan, 1977; Schwartz and Coleman, 1981; Wyss, 1981; Ruth et al., 1982, 1988; Witter and Groenewegen, 1984; Germroth et al., 1989a, 1989b; Witter and Amaral, 1991; Witter et al., 1988, 1989a, 1992). The hippocampal formation reciprocates this input and distributes fibers to the deep layers of the entorhinal cortex, predominantly to the cell layer directly deep to the characteristic cell-free zone or lamina dissecans. In the rodent literature and older primate literature this layer is referred to as layer IV and in more recent primate studies is designated as layer Va (Rosene and Van Hoesen, 1977; Swanson and Cowan, 1977; Beckstead, 1978; Sorensen and Shipley, 1979; Finch et al., 1983, 1986; Köhler 1986; Room and Groenewegen, 1986; Van Groen et al., 1986). The laminar segregation is not complete since (1) the deep layers also contribute fibers to the perforant path and (2) the reciprocal connections from the hippocampal formation also innervate the superficial layers of the entorhinal cortex.

## Cortical connections of the entorhinal cortex

### *Cortical afferents*

The entorhinal cortex of the rat receives inputs from a variety of cortical regions. These cortical inputs form two groups: those that terminate in the superficial layers I–III of the entorhinal cortex and those that preferentially distribute to the deep layers IV–VI (V–VI). The first category can be considered as an input source to the hippocampal formation, whereas the second group can be thought to influence neurons that are also under the influence of hippocampal output. A second differentiation can be made according to the distribution of fibers over the extent of the entorhinal cortex. Projections may target specific, topographically and/or hodologically defined regions of the entorhinal cortex, such as lateral versus medial, or specific cytoarchitecturally defined subdivisions, such as the lateral entorhinal area (LEA) and medial entorhinal area (MEA), or may distribute rather diffusely over the entire entorhinal cortex. In general, the cortical afferents

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that reach the deep layers terminate rather diffusely, whereas the afferents that terminate superficially have a more restricted mediolateral and/or rostrocaudal distribution.

A substantial input to the superficial layers of the entorhinal cortex, at least in rodents and the cat, originates from the olfactory domain of the telencephalon, in particular from the olfactory bulb, the anterior olfactory nucleus, and the piriform cortex (Heimer, 1968; Haberly and Price, 1978; Kosel et al., 1981; Room et al., 1984). Olfactory input terminates throughout most of the rostrocaudal extent of both LEA and MEA, selectively in layer I and the superficial part of layer II. Only the most caudal part of MEA in the rat probably does not receive olfactory inputs. Terminations on layer II and III principal cells as well as on GABAergic neurons in layer I have been demonstrated in the rat (Wouterlood and Nederlof, 1983; Wouterlood et al., 1985). By way of this innervation of entorhinal neurons, olfactory activity may eventually reach the dentate gyrus (Wilson and Steward, 1978; Habets et al., 1980; Carlsen et al., 1982). In the monkey, olfactory inputs to the entorhinal cortex are restricted to its most rostral part (Insausti et al., 1987), but the laminar distribution is similar to that described in the rat (Turner et al., 1978).

The second prominent input comes from the laterally adjacent perirhinal cortex. As yet, this projection has only been analyzed in detail in the cat (Witter et al., 1986) and partly in the monkey (Van Hoesen and Pandya 1975a, 1975b; Insausti et al., 1987). Our own preliminary data in the rat appear to confirm the findings in the cat that this projection distributes to a restricted lateral part of both LEA and MEA; the fibers terminate preferentially in layers I and III. The study in the cat has shown that fibers that originate at any particular rostrocaudal level of the perirhinal cortex preferentially distribute to the neighboring level of the entorhinal cortex. In the monkey, besides the strong input from the adjacent perirhinal and parahippocampal cortices, the entorhinal cortex appears to receive an additional input from several multimodal cortical association areas of the temporal lobe, in particular from the superior temporal gyrus (Amaral et al., 1983; Insausti et al., 1987). The latter projection terminates predominantly in the deep part of layer I and in layer II (Amaral et al., 1983).

The third major input to the superficial layers of the entorhinal cortex originates in the presubiculum and parasubiculum. From tracing studies in rat, guinea pig, and monkey it has become clear that the presubicular fibers terminate specifically in layers I and III, whereas projections from the parasubiculum distribute exclusively to layer II. In all species studied, the presubicular projection is bilateral and distributes exclusively to MEA. By contrast, the parasubicular projection is unilateral and reaches both LEA and MEA (Shiple, 1975; Köhler, 1985; Van Groen and Wyss, 1990a, 1990b; Caballero-Bleda and Witter, 1993; Amaral and Witter, unpublished observations). In the rat, these projections show a marked topography: the point of origin along the dorsoventral axis determines the dorsoventral level of termination in the entorhinal cortex, and the origin along the transverse axis determines the terminal distribution along the lateromedial axis of the entorhinal cortex (Caballero-Bleda and Witter, 1993).

Cortical afferents to the deep layers of the entorhinal cortex arise from a variety of cortical areas that together can be grouped as limbic/paralimbic cortices (Lopes da Silva et al.,

1990). Although detailed anterograde studies are not available in the monkey and the rat, data in the cat that are confirmed by retrograde studies in the other two species indicate the presence of a crude topography. Rostral parts of the limbic cortex project predominantly to the rostral parts of LEA, and the caudally positioned retrosplenial cortex has its main projections to the caudal parts of MEA (see Witter et al., 1989b). The densest inputs come from the prelimbic and infralimbic cortices (areas 25 and 32), the agranular part of the insular cortex, and parts of the orbitofrontal cortex. The retrosplenial cortex (area 29) and, to a lesser extent, the anterior cingulate cortex (area 24) also project to the entorhinal cortex. With respect to the afferents from the retrosplenial cortex, recent anterograde tracing studies in the rat have shown that the projections originate from both the granular and the dysgranular subdivisions and terminate almost exclusively in the most caudal portions of MEA, predominantly in the layers deep to the lamina dissecans (Wyss and Van Groen, 1992).

#### *Cortical efferents*

Efferents of the entorhinal cortex reach widespread parts of the cortex, predominantly the limbic, paralimbic, and olfactory domains (Lopes da Silva et al., 1990). The projections to olfactory areas predominantly originate from layers II, III, and IV (De Olmos et al., 1978; Witter and Groenewegen, 1986). The same layers emit rather strong projections to the infralimbic cortex, the ventral taenia tecta, and the perirhinal cortex. The slightly weaker projections that have been found to reach the prelimbic, orbitofrontal, and agranular insular cortices originate mainly from cells in layer IV. Only weak projections reach the presubiculum, the parasubiculum, and the retrosplenial cortex (Witter and Groenewegen, 1984, 1986; Van Groen and Wyss, 1990a, 1990b; Witter and Amaral, 1991; Wyss and Van Groen, 1992).

An important issue is whether the entorhinal cortex gives rise to prominent and widespread projections to the multimodal association cortex. In the monkey, marked projections from the entorhinal cortex have been reported to reach parts of the temporal cortex (Van Hoesen and Pandya, 1975b; Kosel et al., 1982), but in the cat almost no such projection could be observed (Witter and Groenewegen, 1986). Studies in the rat have indicated that the entorhinal cortex projects to adjacent parts of the temporal cortex (Kosel et al., 1982) or even to a much larger domain of the cortical surface (Swanson and Köhler, 1986). However, in a recent tracing study we confirmed and extended an earlier report (Sarter and Markowitsch, 1985) that only cells in the deep layers of a small, restricted part of the entorhinal cortex, directly adjacent to the perirhinal cortex in the ventral bank of the rhinal sulcus, contribute to these projections (Insausti and Witter, unpublished observations).

### ENTORHINAL-HIPPOCAMPAL CIRCUITRY

#### **Organization of the perforant path**

The organization of the perforant pathway has been analyzed in most detail in the rat, although some facets of its organization have also been addressed in substantial detail in the cat and the monkey. There are two major organizational features. First, the perforant path shows a topographical orga-

nization along the longitudinal axis of the hippocampal formation, such that a lateral-to-medial gradient in the entorhinal cortex corresponds to a septal-to-temporal gradient in the hippocampal formation (Fig. 2A,B; Ruth et al., 1982, 1988; Witter and Groenewegen, 1984; Amaral and Witter, 1989; Witter, 1989; Witter et al., 1989a; Witter and Amaral, 1991). The major point of this organization is that the lateral and caudal parts of both the lateral and medial subdivisions of the entorhinal cortex, which receive the major inputs from the adjacent perirhinal cortex (and in the monkey also from the parahippocampal area TF and TH), project predominantly to the septal or dorsal hippocampal formation (caudal hippocampal formation in the monkey). More medial parts of the entorhinal cortex, which receive prominent inputs from limbic and the periamygdaloid cortices, project more temporally or ventrally in the hippocampal formation. Although this implies a certain kind of specificity, it should be taken into account that small parts of the entorhinal cortex give rise to projections that spread along at least 25% of the longitudinal length of the hippocampal formation (see Amaral and Witter, 1989).

The second aspect of the organization of the perforant path concerns the cells of origin. Although it is well established that the perforant path originates from layers II and III of the entorhinal cortex, it has recently become clear that fibers from each of these layers distribute selectively to different parts of the hippocampal formation and also show marked differences with respect to their terminal organization (Fig. 1A,B; Steward, 1976; Steward and Scoville, 1976; Witter 1989; Witter and Amaral, 1991). Cells in layer II, for example, send their axons almost exclusively to the dentate gyrus and fields CA3/CA2 of the hippocampal formation (Figs. 1A, 2A). However, recent intracellular tracing studies in the rat have provided evidence that layer II cells also send collaterals to the subiculum (Lingenhöhl and Finch, 1991; Tamamaki and Nojyo, 1993). Fibers from any one point in layer II of entorhinal cortex distribute over almost the full transverse extent of the above-mentioned hippocampal fields. There is, however, a marked differentiation within the perforant path with respect to the dendritic domain of termination. Whereas the cells in LEA send their fibers to the outer one third of the molecular layer and stratum lacunosum-moleculare (Fig. 1A), projections from MEA distribute to a narrow field located in the middle one third of these layers (Figs. 1B, 2A). In the rat, there are indications that the so-called "lateral" and "medial" perforant path are functionally different (see Witter et al., 1989b). In the cat, the organization of the perforant path is remarkably similar to that in the rat (Witter and Groenewegen, 1984; Van Groen and Lopes da Silva, 1986; Van Groen et al., 1986). In the monkey there is no clear indication that such a marked anatomical differentiation between lateral and medial components of the layer II originating fiber component of the perforant path is present (Witter et al., 1989a; Witter and Amaral, 1991).

The projection that originates from cells in layer III of the entorhinal cortex in the rat shows a pattern of terminal distribution in the hippocampal formation that contrasts markedly with that of the layer II projection (Fig. 2B). First, these fibers terminate exclusively in field CA1 and in the subiculum. Second, fibers from any particular area in both LEA and MEA never distribute over the full transverse extent of these hippo-

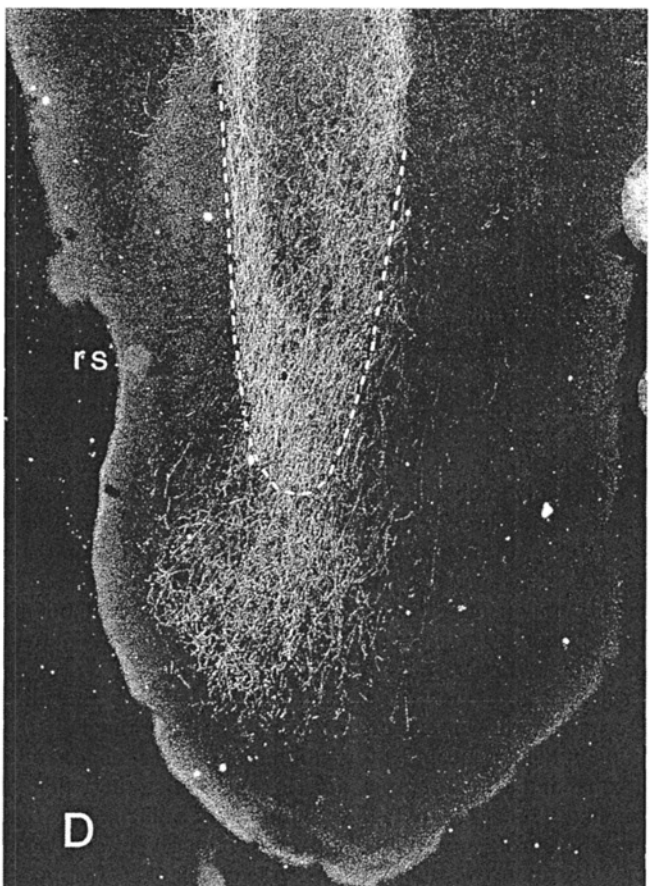
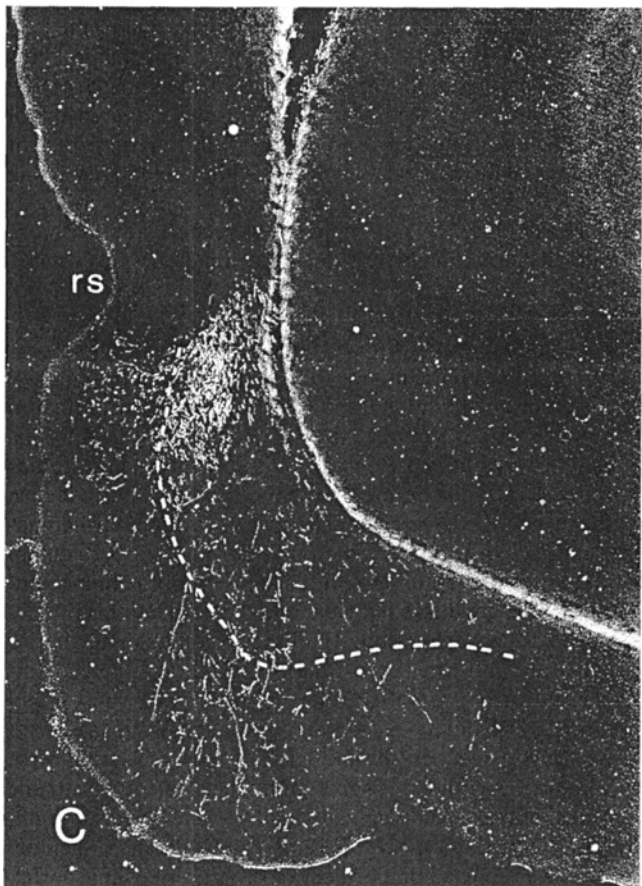
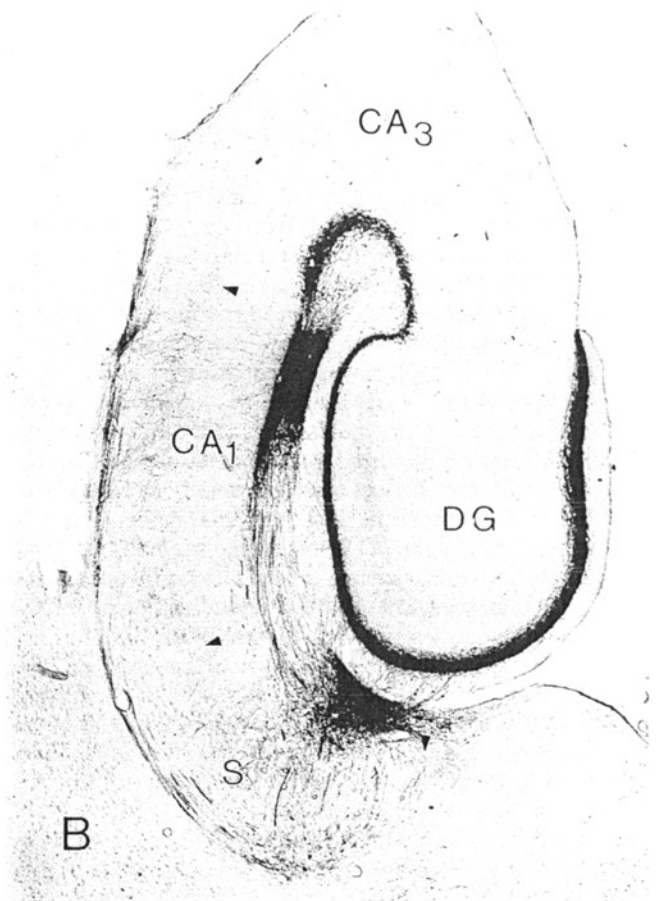
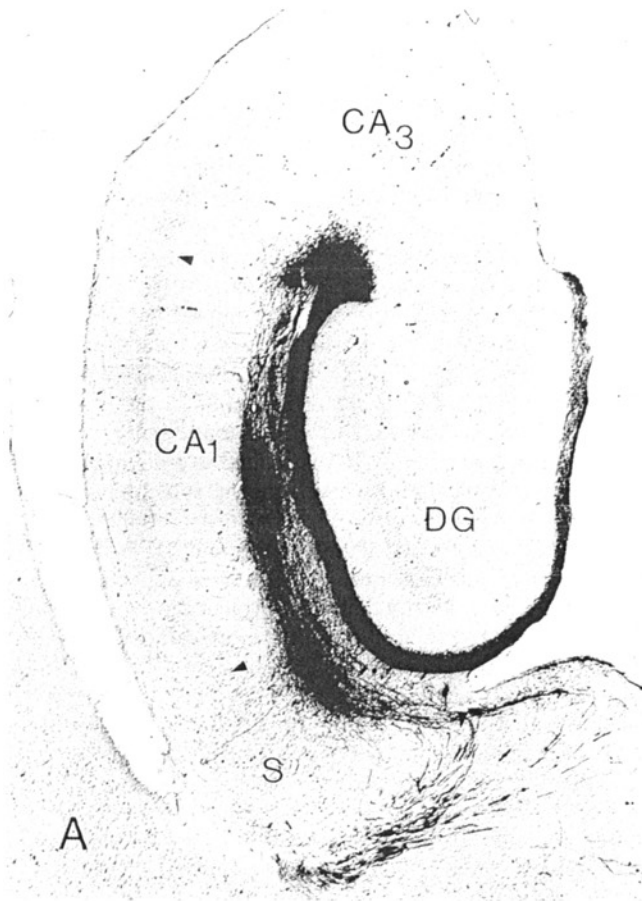
campal fields. Fibers from LEA terminate around the border of CA1 with the subiculum, that is, the distal half of field CA1 and the proximal half of the subiculum (Fig. 1A). In contrast, projections that originate from MEA terminate in the other parts of these fields: in CA1 they terminate close to the border with CA2, that is, in the proximal half of CA1, and in the subiculum they end close to the border with the presubiculum, that is, in the distal half of the subiculum (Figs. 1B, 2B). It can thus be concluded that both CA1 and the subiculum can be roughly subdivided into a lateral and a medial perforant pathway recipient zone. Within each of these lateral and medial recipient zones a further differentiation has been observed, such that the lateral-to-medial axis of origin both in LEA and MEA in case of CA1 is related to a distal-to-proximal terminal distribution, whereas in the subiculum it is related to a proximal-to-distal terminal distribution. In CA1, fibers from lateral parts of both LEA and MEA distribute preferentially to the most distal parts of their respective terminal zone. It is noteworthy that these projections preferentially distribute to more septal levels of the hippocampal fields CA1 and the subiculum. In contrast, medial parts of both entorhinal subdivisions send their axons to the more proximal parts of these zones, and they tend to project toward more ventral levels of the hippocampus. For the subiculum the transverse relation is inverted, whereas the septotemporal relation is similar to that of the entorhinal-CA1 projections (Fig. 2A). A comparable organization for the layer III projection system was reported in the monkey (Witter and Amaral, 1991).

This organization implies that specific cell populations in the entorhinal cortex may activate restricted populations of cells in CA1 and the subiculum. The organization of the perforant path thus indicates a different type of information processing in different hippocampal fields. The dentate gyrus and CA3/CA2 can be viewed as being diffusely activated by all parts of the entorhinal cortex along the full transverse axis of a particular septotemporal level but with a selectivity along the dendrites of the cells at the innervated level. By contrast, the CA1/subiculum system appears to receive a much more spatially selective input from the entorhinal cortex.

### Organization of the output projections from the hippocampal formation to the entorhinal cortex

Projections from the hippocampal formation to the entorhinal cortex originate in CA1 and the subiculum. In contrast to previous reports in the rat that CA3 also contributes to this pathway (Swanson and Cowan, 1977), recent tracing studies in both the rat and the monkey have provided no evidence for this projection (Amaral and Witter, 1989, unpublished observations). The projections from CA1 and the subiculum originate from the entire longitudinal extent of the hippocampal formation, and in both the cat and the monkey this projection has a topography along the long axis similar to that of the perforant pathway. The situation in the rat appears comparable with that in the cat and the monkey (Swanson and Cowan, 1977; Köhler, 1985; Van Groen and Wyss, 1990c).

Also with respect to the topography along the transverse axis of the CA1 and the subiculum, the projections to the entorhinal cortex are organized similar to the perforant path. In an earlier study on the efferents of the dorsal subiculum in the rat we reported that projections to the entorhinal cortex



originate selectively from the proximal part of the subiculum (Witter et al., 1989c). However, a more detailed analysis of the subiculo-entorhinal and CA1-entorhinal projections along the entire longitudinal axis of the hippocampal formation has revealed that this is not accurate. There is now convincing evidence that the projections to the entorhinal cortex originate from the full transverse extent of the subiculum and CA1 (Figs. 1C,D, 2D; Tamamaki and Nojyo, 1992). The proximal part of the subiculum and the adjacent distal part of CA1 project preferentially to LEA (Figs. 1C, 2D), whereas the distal part of the subiculum and the proximal part of CA1 project preferentially to MEA (Figs. 1D, 2D). In other words, this output system is in register with the organization of perforant path fibers terminating in these two hippocampal subfields (compare Figs. 2B and 2D; Tamamaki and Nojyo, 1992). It should be emphasized that the organization along the transverse axis does not interfere in any way with the described topography of these connections along the septotemporal axis. In summary, at dorsal levels, the distal CA1 and proximal subiculum project to lateral parts of LEA, whereas the proximal CA1 and distal subiculum distribute fibers to latero-caudal parts of MEA. At ventral levels, the distal CA1 and proximal subiculum project to medial parts of LEA, whereas the proximal CA1 and distal subiculum project to rostromedial parts of MEA.

With regard to the laminar termination of hippocampal projections to the entorhinal cortex, it was reported earlier in the rat that the majority of fibers terminate deep to the lamina dissecans, in layer IV of the entorhinal cortex over its full transverse extent (Swanson and Cowan, 1977; Van Groen and Wyss, 1990c). However, as illustrated for the rat in Figure 1C,D, the entorhinal cortex, in particular MEA, receives a rather prominent projection that distributes to the superficial layers I-III. Comparable terminal distributions have been reported in the monkey and the cat (Van Groen et al., 1986; Saunders and Rosene, 1988).

### INTRINSIC HIPPOCAMPAL CIRCUITRY

Restricted portions of the entorhinal cortex are capable of influencing the full transverse extent of the dentate gyrus over approximately 25% of its longitudinal extent. The prominent mossy fiber projection from the dentate gyrus distributes along most of the transverse extent of CA3 where the fibers form en passant synapses on the proximal portions of the dendrites of pyramidal cells (Blackstad et al., 1970; Gjaarskjaer, 1978, 1986; Swanson et al., 1978; Claiborne et al., 1986;

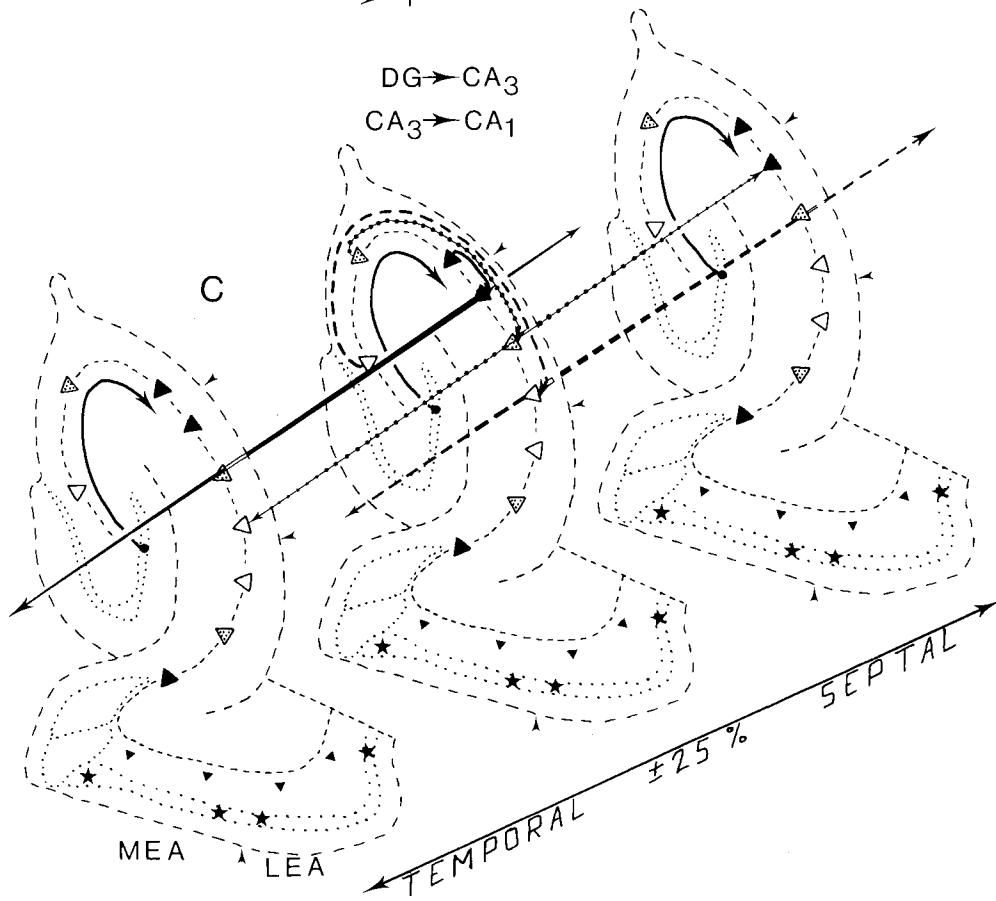
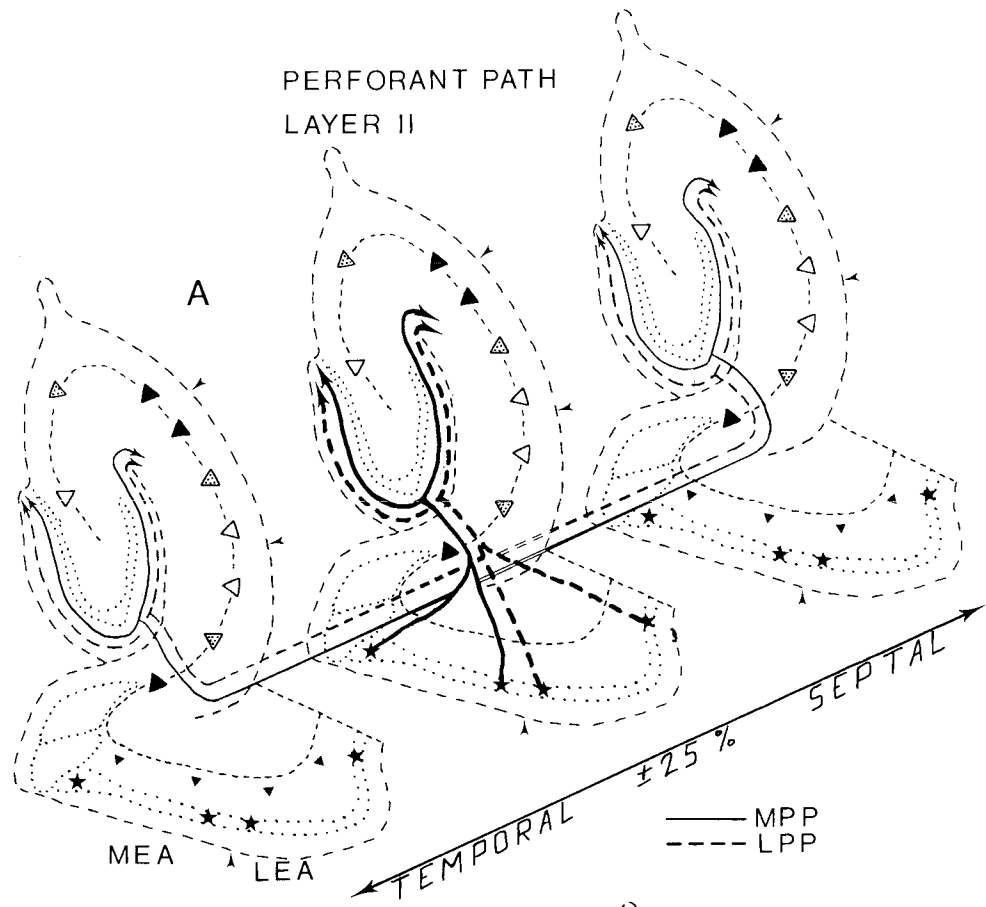
Amaral and Witter, 1989). All available anatomical data show that this system is rather restricted with respect to the spread along the longitudinal axis: any part of the dentate gyrus distributes fibers along the longitudinal axis of CA3 over an area that is maximally three times as large as the area of origin (Fig. 2C).

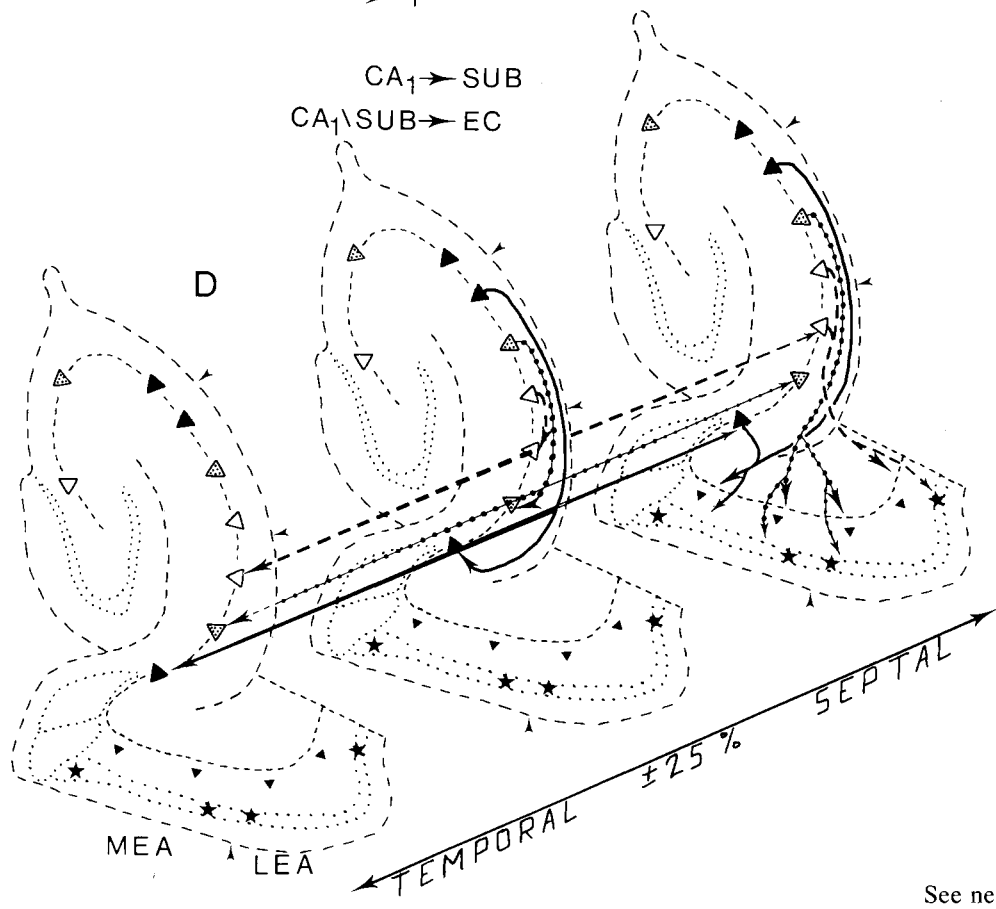
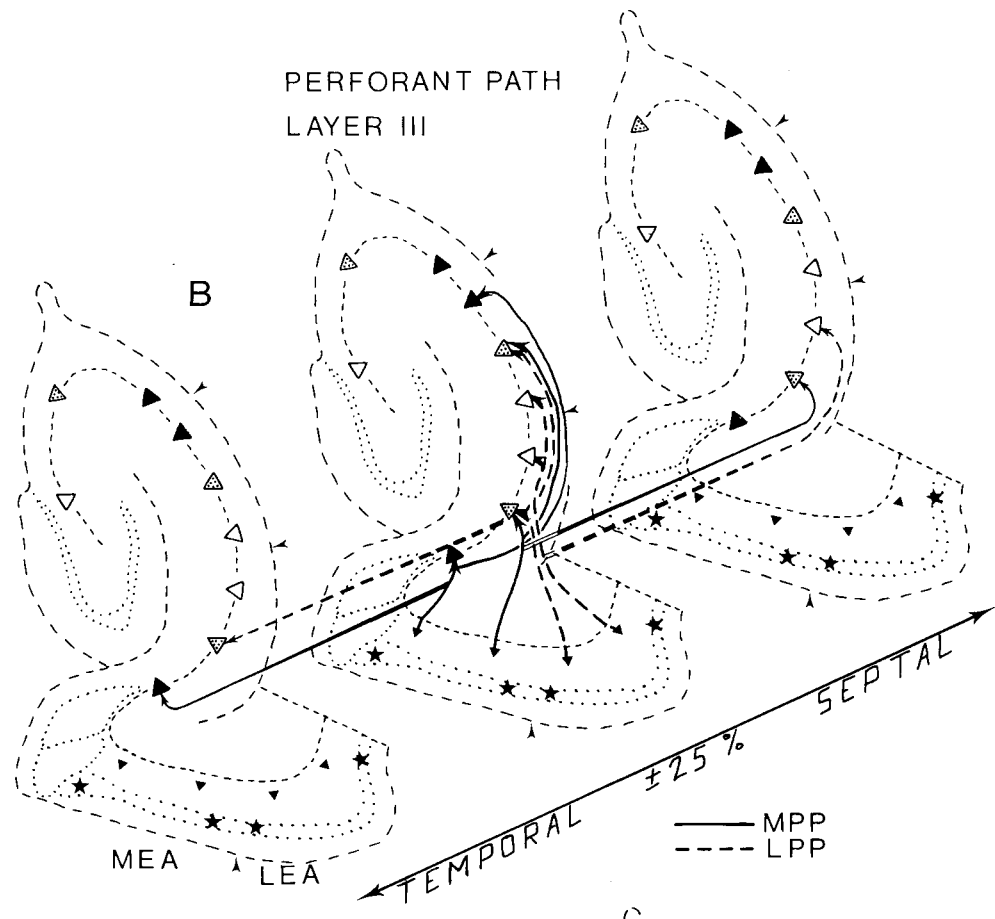
It should be stressed that the dentate gyrus possesses an elaborate and well-developed associational system that originates from neurons in the hilus of the dentate gyrus that are activated by collaterals from the mossy fibers, that is, they receive a copy of the activity that is transferred to CA3 pyramidal cells (Hjorth-Simonsen and Laurberg, 1977; Swanson et al., 1978; Laurberg, 1979; Laurberg and Sorensen, 1981; Ribak et al., 1985; Claiborne et al., 1986). The neurons in the hilus give rise to at least two different intrinsic systems. One system, which originates in somatostatin and GABA-positive neurons and presumably exerts an inhibitory effect, distributes to the outer two thirds of the molecular layer at the level of its origin (Bakst et al., 1986). The other pathway, which arises from excitatory, glutamatergic neurons, distributes preferentially to the inner one third of the molecular layer and specifically avoids the level of origin but terminates densely at all other levels along the longitudinal axis of the dentate gyrus (Zimmer, 1971; Swanson et al., 1978; Amaral and Witter, 1989; Ishizuka et al., 1990).

Pyramidal cells in CA3 give rise to a highly collateralized projection that on the one hand stays confined to CA3 as the so-called "longitudinal association bundle" that distributes along a large extent of the long axis of CA3. On the other hand, the Schaffer collateral system to CA1, which was once thought to be a connection mainly within the transverse plane, is now known to possess a hitherto unappreciated order and widespread distribution (Ishizuka et al., 1990; Tamamaki and Nojyo, 1991; Li et al., 1992). At the level of origin, fibers that arise from CA3 cells located close to the dentate gyrus, that is, in the proximal part of CA3, distribute mainly to the distal part of CA1, that is, close to the border of CA1 with the subiculum. Here, they terminate preferentially in the superficial part of the stratum radiatum. CA3 cells located closer to CA1 project preferentially to parts of CA1 that are closer to CA3 and further to deeper levels of the stratum radiatum and to the stratum oriens. It is difficult to establish whether the transverse organization is a gradient-like phenomenon or it hodologically subdivides CA1 into three subdivisions along the transverse axis. In addition to this marked pattern along the transverse axis, the projections from CA3 to CA1 show

Fig. 1. Organization of the reciprocal connections between the entorhinal cortex and the hippocampal formation. (A) Labeling in the hippocampal formation following an injection of PHA-L in lateral entorhinal area (LEA). Note the terminal field in the outer one third of the molecular layer of the dentate gyrus and stratum lacunosum-moleculare of CA3 and in the stratum lacunosum-moleculare of the distal part of CA1 and the molecular layer of the proximal part of the subiculum. (B) Terminal pattern in the hippocampal formation following an injection of PHA-L in medial entorhinal area (MEA). In the dentate gyrus and CA3 the terminal field is present in the middle one third of the molecular layer/stratum lacunosum-moleculare, whereas in the subiculum and CA1 the labeling is present in the proximal CA1 and distal subiculum. (C) Darkfield photomicrograph of terminal labeling in LEA following an injection in the proximal part of the subiculum. Note the dense terminal labeling in layer IV (V) and the sweeps of fibers into the superficial layers of the entorhinal cortex. (D) Distribution of labeled fibers in the caudolateral part of MEA following an injection in the proximal part of CA1 as illustrated in a darkfield photomicrograph. Labeled fibers are terminating deep to the lamina dissecans, but also in the more superficial layers III and II. White dashed line indicates the position of the lamina dissecans.

PERFORANT PATH  
LAYER II





See next page for legend



a clear organization along the long axis of CA1. In all cases, the highest density of fibers and terminal labeling in CA1 is found about 1 mm or more away from the point of origin along the long axis. It was further noted that cells closer to the dentate gyrus, that is, proximal in CA3, tend to project preferentially into a septal direction. In contrast, cells located closer to CA1 tend to distribute their axons into a temporal direction (Fig. 2C). A second aspect should be emphasized here. Regardless of the transverse origin of the Schaffer collaterals, the terminal distribution of these collaterals tends to be located closer to the subiculum and more superficially in stratum radiatum at progressively more ventral levels. Conversely, at more dorsal levels the fibers and terminal labeling approach the CA3/CA2 border and shift to a deeper position in stratum radiatum and the stratum oriens.

The organization of the projections from CA1 to the subiculum has recently been described in detail in the rat (Tamamaki et al., 1987; Tamamaki and Nojyo, 1990; Amaral et al., 1991). Using an experimental design similar to that used in several recent studies of the perforant path and the intrinsic hippocampal connections in the rat (Gjaarskjaer, 1978; Amaral and Witter, 1989; Amaral et al., 1991), two major organizational features have become apparent: (1) The CA1-to-subiculum projection system shows extensive longitudinal spread, such that fibers from one particular point of origin distribute over

approximately one third of the long extent of the subiculum. This longitudinal spread is thus comparable to that of the perforant path; and (2) When in these cases the patterns along the transverse axis were studied a striking organizational principle was noted (Fig. 2D). Projections from the proximal part of CA1 terminate in the distal part of the subiculum. Conversely, projections from the distal part of CA1 predominantly reach the proximal part of the subiculum; projections from the center of CA1 reach the center of the subiculum. Intracellular fills of CA1 neurons have yielded comparable results and showed that the axon of any one particular neuron distributes along approximately one third of the transverse extent of the subiculum (Tamamaki et al., 1987; Tamamaki and Nojyo, 1990). In contrast to the organization of the CA3-to-CA1 projections, which portrayed a somewhat oblique organization along the long axis, the terminal distribution of the CA1-to-subiculum projection along the longitudinal axis holds a more or less stable position in the transverse dimension (compare Fig. 2C with 2D).

The observation that the CA1-to-subiculum projection divides the subiculum into three slabs of cells along the long axis is of interest in view of the fact that the outputs of the subiculum exhibit a comparable tripartite organization. Along the transverse axis of the subiculum, three populations of cells can be differentiated that show projections to a specific set

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Fig. 2. Summary diagram of the three-dimensional organization of the hodology of the hippocampal formation and the entorhinal cortex based on tracing data in the rat. (A) Layer II of the entorhinal cortex projects to the dentate gyrus and CA3. Projections from LEA (lateral perforant path, LPP) distribute to the outer one third of the dendritic tree of the receiving neurons, and the medial perforant path (MPP), which originates from MEA, distributes to the middle one third. The lateral parts of both LEA and MEA tend to direct their fibers preferentially toward more septal levels of the hippocampal formation, whereas more medial parts of both entorhinal subdivisions tend to project to more temporal levels of the hippocampal formation. (B) Layer III projections distribute differentially along the transverse axis of CA1 and the subiculum; the LPP reaches the adjacent halves of field CA1 and the subiculum, that is, the distal part of CA1 and the proximal part of the subiculum. The MPP distributes preferentially to the proximal half of CA1 and the distal half of the subiculum. More lateral parts of LEA tend to distribute toward the extreme border region of more septal parts of CA1 and the subiculum, whereas more medial parts of LEA project slightly away from the border region to the central parts of CA1 and the subiculum, at more temporal parts of both hippocampal subdivisions. The most medial part of MEA distributes its fibers to the most proximal part of temporal CA1 and the most distal part of the temporal subiculum. More lateral and caudal parts of MEA tend to direct their fibers toward more septal and central parts of CA1 and the subiculum. Note that the distribution of the perforant path to CA1 at levels other than the level of origin is not indicated. (C) Summary diagram of projections from the dentate gyrus to CA3 and from CA3 to CA1. The mossy fiber projections that connect the dentate granule cells with the cells in CA3 distribute along most of the transverse extent of field CA3 and stay more or less confined to a restricted, lamellar component along the long axis of the hippocampal formation. Note that the intrinsic associational projections that originate from cells in the hilus are not indicated in this figure. The projections from CA3 to CA1 are organized in an orderly fashion, such that fibers from CA3 cells located close to the dentate gyrus preferentially innervate more septal levels of CA1. At their origin they distribute to the most distal part of CA1, whereas at progressively more septal levels the terminal field shifts toward a more proximal position. Cells in the most distal part of CA3, close to the border with CA1, preferentially distribute their axons to more temporal levels. At the level of origin they tend to innervate cells in the proximal part of CA1, but at more temporal levels the terminal field changes position toward a more distal location in CA1. Intermediately positioned cells show intermediate fiber distributions, both along the septotemporal and the proximodistal axes. Not indicated are changes along the radial dimension of the dendritic tree (see Ishizuka et al., 1990). (D) Projections from CA1 to the subiculum and from CA1/subiculum back to the entorhinal cortex. Projections from CA1 to the subiculum are mainly organized along the transverse axis. Fibers from the proximal part of CA1 innervate cells in the distal part of the subiculum, both at the level of origin as well as along approximately 25–30% of the total length of the subiculum. Similarly, distal CA1 cells direct their axonal projections to the proximal part of the subiculum, and cells in the central part of CA1 project to the central part of the subiculum. The origin of the output from the subiculum to the entorhinal cortex shows a similar organization and is in register with the terminal organization of the perforant path (compare with B). Cells in the proximal part of CA1 and the distal part of the subiculum give rise to a projection that distributes to the most medial parts of MEA. Cells in the central parts of CA1 and the subiculum project to lateral parts of MEA and medial parts of LEA, whereas cells in the border region between CA1 and the subiculum originate projections to more lateral parts of LEA. These reciprocating projections also exhibit an organization along the septotemporal axis that resembles that of the perforant path (not illustrated).



of brain structures. This transverse organization of the outputs of the subiculum holds along the full extent of the longitudinal axis of the subiculum, although it is more clear at dorsal levels (Witter et al., 1989c; Witter, 1990, unpublished observations). Neurons in the proximal third of the subiculum project to the infralimbic and prelimbic cortices, the nucleus accumbens, and the lateral septum. These projections originate from the full longitudinal extent of the subiculum but also from the adjacent distal one third of field CA1. Projections that originate from the ventral one third of the proximal subiculum are also directed to the core of the ventromedial nucleus of the hypothalamus and to the amygdala. Cells in the central one third of the subiculum project rather selectively to midline thalamic nuclei. From both retrograde and anterograde data it appears that the most dorsal part of this central slab projects predominantly to the interanteromedial nucleus of the thalamus. The intermediate part distributes its densest projection to the nucleus reuniens, whereas the ventral part of the central one third of the subiculum sends its fibers preferentially to the paraventricular nucleus of the thalamus. Cells in the most distal slab of the subiculum have two cortical areas as their major targets. Cells in the dorsal two thirds project to the retrosplenial cortex, whereas the full longitudinal extent of the distal subiculum projects to the presubiculum. Fibers from the dorsal parts of the distal subiculum preferentially terminate in the dorsal presubiculum or postsubiculum, whereas more ventral parts send their fibers to more ventral parts of the presubiculum.

As described, the projections from the subiculum (and CA1) to the entorhinal cortex originate from the full transverse extent of the subiculum. The proximal subiculum projects to LEA, and distal parts of the subiculum project to MEA (Fig. 2D). A similar gradient-like organization along the transverse axis of the subiculum has been noted for the projections to the medial mamillary nucleus (Witter et al., 1989c). The proximal part of the subiculum projects to the rostrolateral part of the medial mamillary nucleus, whereas more distal parts of the subiculum project to more caudomedial parts of the nucleus. This projection also exhibits a dorsoventral topography. The dorsal subiculum preferentially projects dorsally in the medial mamillary nucleus, and progressively more ventral portions of the subiculum project to more ventral levels of the nucleus (Shibata, 1989).

Summarizing the organizational characteristics of the entorhinal–hippocampal network described thus far (Fig. 2), it can be concluded that all cells in the dentate gyrus and field CA3 of the hippocampal formation at a specific transverse level along their longitudinal axis are privy to an entorhinal input representing activity of restricted mediolateral parts of both the lateral and medial entorhinal cortex. The divergent distribution of the perforant path and the organization of the intrinsic connections of both hippocampal subfields, in particular their extensive longitudinal components, favor the notion that information originating focally in the entorhinal cortex is widely dispersed along the septotemporal axis of the dentate gyrus and CA3. Interestingly, the mossy fiber system, which connects the dentate gyrus to CA3, favors a far more restricted transmission of information such that activation of one level of the dentate gyrus is transmitted to a rather restricted level of CA3. The remaining hippocampal network

shows two major organizational features. First, it serves a further dissemination of information along the septotemporal or long axis. Second, it may enable a segregation of the flow of information along the transverse axis. Starting with the projections from CA3 to CA1 there is an increasing tendency for axons not only to influence a restricted part of the dendrites of all neurons within a field in an en passant manner but also to terminate selectively on a particular subset of CA1 neurons. This results in a partition of CA1 along the transverse axis, suggesting that three parts of CA1 can be distinguished. Although there are not sufficient retrograde data to draw firmly based conclusions regarding the relation between these CA3 input-defined thirds of CA1 and the cells that give origin to the projections to the subiculum, it is tempting to suggest that these input-defined slabs of CA1 give rise to projections to the subiculum that at the same time define three slabs in the subiculum. That such is the case can be inferred from intracellular filling of CA1 neurons as reported by Tamamaki and Nojyo (1990), who showed that the axonal arborization in the subiculum of a single CA1 neuron covers approximately one third of the transverse extent of the subiculum. An additional feature of the termination of the CA1–subiculum projections is that they extend throughout the stratum pyramidale and moleculare. The CA1-to-subiculum projections thus not only appear to be able to influence the proximal dendrites of the subicular pyramidal cells but also to influence the cell at the level of the soma and possibly the basal dendritic domain. In other words, the subiculum shows the ultimate hard-wired channel. It is not known whether the slabs in CA1 and the subiculum as defined on the basis of the intrinsic hippocampal circuitry do overlap with the parts that are characterized on the basis of the restricted distribution of the perforant path. Finally, the origin and distribution of the main efferent projections from the subiculum provide evidence that slabs of approximately one third of the transverse extent of the subiculum presumably are wired as to convey information to different hippocampal target structures.

### FUNCTIONAL PERSPECTIVES

The anatomical data summarized clearly point to the hippocampus as a complex three-dimensional structure. Although the basic wiring is constant at all septotemporal levels of the hippocampal formation, the specific topography indicates functional differentiations along both its longitudinal and transverse axes. With respect to the differentiation along the longitudinal axis, the septal–hippocampal formation may be more involved in the elaboration of extrinsic information, whereas the temporal hippocampus may deal with intrinsic information (Witter et al., 1986, 1989). Regarding the differentiation along the transverse axis, it should be stressed that the anatomical evidence described does not give any indication on whether the hippocampal circuitry actually functions in a selective way. There are physiological data that support the idea of a topographical selectivity along the transverse axis. Stimulation of incoming entorhinal fibers results in rather uniform activity of granule cells in the dentate gyrus. By contrast, such an activation results in an active focus in CA1 (Buszaki et al., 1990).

Assuming that functional output channels in the subiculum do exist, there is one intriguing assumption that can be made.

Targets that receive inputs originating from one slab of the subiculum may be receiving the same information, whereas information that targets receive from one of the other subicular slabs may be qualitatively different. It is proposed that the ensemble of targets that receive the same subicular output form part of a functionally related circuit and that this circuit differs from the one made up of hippocampal targets of the other two slabs of the subiculum (Witter and Groenewegen, 1992).

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