

# 8

## Hippocampal region

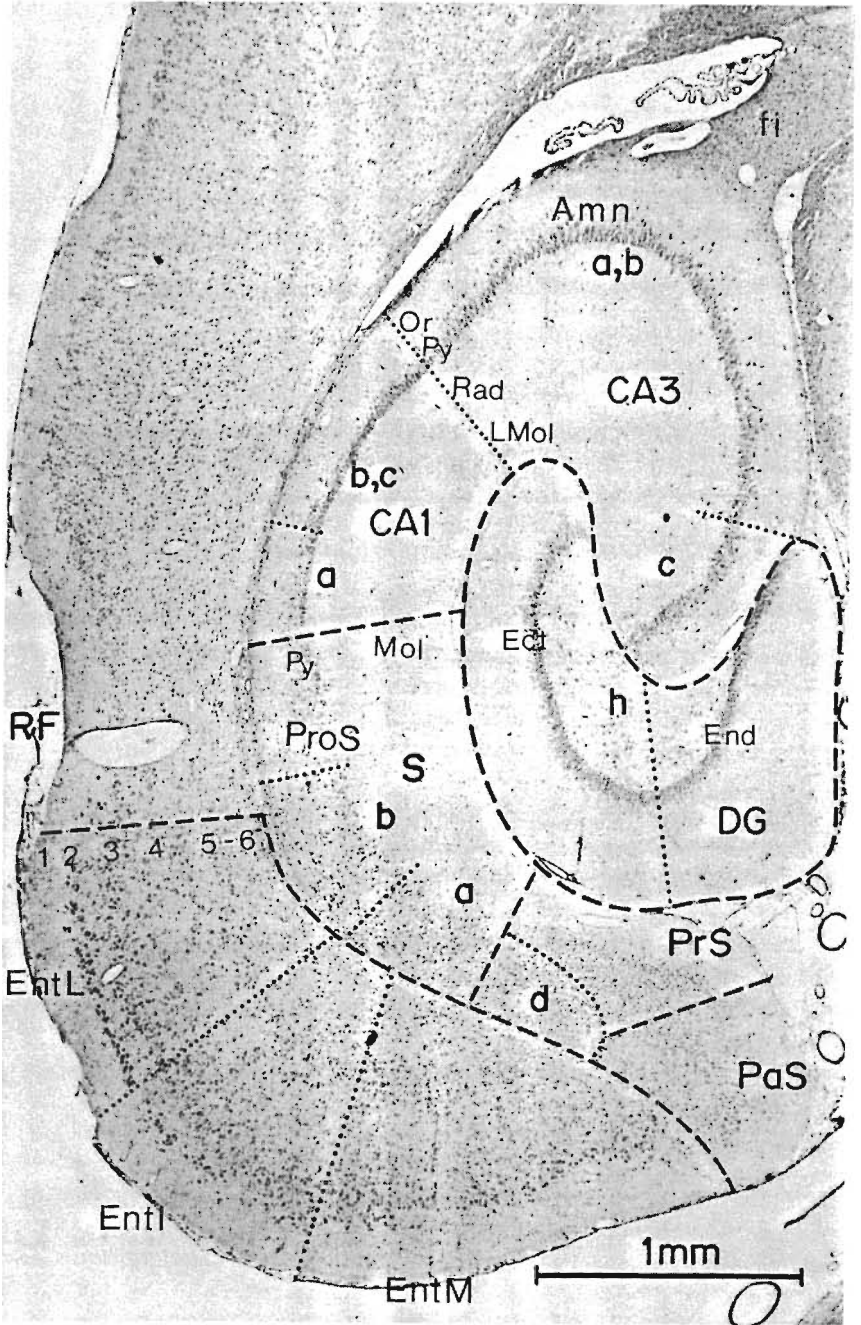
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### I. INTRODUCTION

The anatomy of the hippocampal region has been studied intensely in rodents since Cajal (1911) and his pupil, Lorente de Nó (1934), carried out their classic studies using the Golgi method. In recent years, the cytoarchitecture and connections of the hippocampal region have been further elucidated by the work of Blackstad (1956, 1958), Raisman *et al.* (1965, 1966) and Hjorth-Simonsen (1972, 1973) using lesion methods. Meibach and Siegal (1975, 1977a, b), Swanson and Cowan (1975, 1976, 1977) and Steward (1976) used physiologic transport methods to study hippocampal connections. Finally, Swanson *et al.* (1981) used refinements of axonal tracing techniques and double-labeling methods to add to the literature on hippocampal anatomy. These studies, and many others, have contributed to make the rat hippocampal region one of the best known neural structures.

The hippocampal region occupies most of the ventroposterior and ventrolateral walls of the cerebral cortex. All the major components of the hippocampal region can be viewed simultaneously in sections taken in the horizontal plane. Fig. 1 is a Nissl stained section which corresponds closely to Plate 60 of the stereotaxic atlas of Paxinos and Watson (1982). In proceeding from the rhinal fissure (RF) to the medial cortical edge, one finds six distinct structures (separated by dashed lines): entorhinal cortex (EntL, EntI, EntM, area 28), parasubiculum (PaS, area 49), presubiculum (PrS, area 27), subiculum proper (S), fields CA1-CA3 in Ammon's horn (Amn), and dentate gyrus (DG). The hippocampus (Ammon's horn and the dentate gyrus) extends anteriorly beneath the corpus callosum to the posterior level of the septal nuclei. A rudiment of the hippocampal region extends in a small dorsomedial ridge above the corpus callosum (indusium griseum) into the anteromedial septal region (dorsal tenia tecta). The rudiment continues anteroventrally to mingle with medial parts of the anterior olfactory nucleus (ventral tenia tecta). In this chapter, I will discuss



cytoarchitecture and connections of the six major components of the hippocampal region shown in Fig. 1. There will be an emphasis on classical neuro-anatomical studies. For an excellent review of the chemical neuroanatomy of the hippocampal region, the reader is referred to Walaas (1983).

## II. THE ENTORHINAL CORTEX

### A. Cytoarchitecture

The entorhinal cortex (EntL) has approximately five or six distinct layers. Differences in the appearance and cellular arrangements within these layers allow for a subdivision into lateral (EntL, Fig. 1), intermediate (EntI) and medial parts (EntM). Layer 1 is an outer plexiform zone containing terminal axonal branches and dendrites of the superficial neuronal layers. The large somata of the stellate cells are located in layer 2. These are grouped into "islands" in EntL and EntI, while they form a continuous layer in EntM. Medium sized pyramidal cells are located in layer 3. Layers 2 and 3 are separated by a thin cell-sparse zone in EntL; this separation is less distinct in EntM. Layer 4 is a cell-sparse zone (often called the lamina dissecans) with a few scattered large pyramidal-type cells. Layers 5 and 6 contain medium and small cells in EntL with a predominance of small cells in EntM. Horizontally oriented, medium sized cells are located next to or are embedded within the fibers of the deep white matter.

### B. Afferents to the entorhinal cortex

Projections from the brain stem originate in the caudal part of the dorsal raphe nuclei and the reticular tegmental nucleus of the pons (Beckstead, 1978; Kohler and Steinbusch, 1982; Segal, 1977), the locus coeruleus (Beckstead, 1978; Fallon *et al.*, 1978; Fuxe, 1965) and the posteromedial ventral tegmental area (Carter and Fibiger, 1977; Fallon and Moore, 1978; Simon *et al.*, 1976). Hypothalamic afferents arise in the caudal magnocellular nucleus (Haberly and Price, 1978) and supramammillary nuclei (Carter and Fibiger, 1977). Thalamic afferents arise in the reuniens nucleus (Beckstead, 1978; Haberly and Price, 1978; Herkenham,

◁ Fig. 1: A horizontal section (10  $\mu$ m, paraffin) of the hippocampal region in an adult rat showing all major anatomical subdivisions. The level chosen is similar to Plate 60 in Paxinos and Watson (1982). Abbreviations: Amn, Ammon's horn; CA1, field CA1 pyramidal cells divided into a and b, c subdivisions; CA3, field CA3 pyramidal cells divided into a, b and c subdivisions; DG, dentate gyrus; Ect, ectal limb of the dentate granular layer; End, endal limb of the dentate granular layer; EntI, intermediate subdivision of the entorhinal cortex; EntL, lateral subdivision of the entorhinal cortex; EntM, medial subdivision of the entorhinal cortex; fi, fimbria; h, hilus of the dentate gyrus (also called CA4); LMol, lacunosum moleculare layer; Mol, molecular layer of subiculum; Or, oriens layer; PaS, parasubiculum; ProS, prosubiculum; PrS, presubiculum; Py, pyramidal layer; Rad, radiatum layer; RF, rhinal fissure.

1978; Segal, 1977) and anterior thalamic nuclei (Domesick, 1973). The cholinergic cells of the medial septum project diffusely to the entorhinal cortex (Lewis and Shute, 1967; Meibach and Seigel, 1977a; Swanson and Cowan, 1976). Beckstead (1978) found that the vertical limb of the diagonal band projects to EntM while the horizontal limb projects to EntL. EntL receives projections from the amygdala which arise mainly in the cortical nuclei (Haberly and Price, 1978; Krettek and Price, 1977); Beckstead (1978) reported that EntM also receives input from these nuclei. The basolateral and lateral nuclei project mainly to EntL (Beckstead, 1978; Krettek and Price, 1974).

A large number of telencephalic cortical areas project to the entorhinal cortex. The main olfactory bulb projects to EntL (Heimer, 1968; Price, 1973; Scalia and Winans, 1975). In two recent reports, it is claimed that main bulb afferents extend to ventral EntM (Kosel *et al.*, 1981; Wouterlood and Nederlof, 1983). The piriform cortex projects to EntL (Beckstead, 1978; Cragg, 1961; Haberly and Price, 1978; Krettek and Price, 1977; Powell *et al.*, 1965; Price, 1973). Projections to both EntL and EntM arise from widespread areas of neocortex. These projections have been most often reported in monkeys (Adey and Meyer, 1952; Povlishock *et al.*, 1976; Turner *et al.*, 1980; Van Hoesen and Pandya, 1975). The ventral temporal neocortex of both cats and rabbits projects to the entorhinal cortex (Cragg, 1965); Reep and Winans (1982) recently reported that projections from the temporal neocortex along the dorsal bank of the rhinal fissure terminate in the entorhinal cortex of the hamster. It is most likely that similar projections exist in the rat, but as yet none has been reported.

Afferents from other areas of the hippocampal region also terminate in the entorhinal cortex. These pathways arise in fields CA3 (Hjorth-Simonsen, 1971) and CA1 (Beckstead, 1978; Swanson *et al.*, 1978, 1981) of Ammon's horn and in the subiculum proper (Beckstead, 1978; Finch *et al.*, 1983; Swanson *et al.*, 1981). The presubiculum projects contralaterally via the dorsal psalterium (Beckstead, 1978; Segal, 1977).

### C. Efferents of the entorhinal cortex

The best documented projection is the so called "perforant path" first described by Cajal (1911). These fibers run through the entorhinal cortex to the deep white matter then "perforate" the subiculum to travel superficially in its molecular layer, continue through the lacunosum moleculare layer of the CA fields in Ammon's horn (LMol, Fig. 1), and finally invade the outer two thirds of the dentate molecular layer. Early lesion studies of Blackstad (1958) and Raisman *et al.* (1965) confirmed the pathway traced by Cajal (1911) in Golgi preparations. An ultrastructural analysis of the location of degenerating boutons after EntM lesions showed that terminals existed primarily in field CA3 and in the dentate molecular layer with very few in field CA1 (Nafstad, 1967). Further lesion

studies by Hjorth-Simonsen (1972) showed that the perforant path is topographically organized so that EntL terminates in the superficial third of the lacunosum moleculare layer of CA3 and in the superficial third of the dentate molecular layer throughout both ectal and endal limbs. The EntM terminates in the deep third of the lacunosum moleculare layer of CA3 and in the middle third of the dentate molecular layer; the EntI terminates between the zones occupied by the EntL and EntM (Hjorth-Simonsen and Jeune, 1972). Steward (1976) confirmed these findings with axonal tracing techniques and further reported that the layer 2 stellate cells are the source of the projection (Steward and Scoville, 1976). Steward also reported a sparse topographic projection to field CA1 so that EntL projections terminate in the lacunosum moleculare layer of field CA1a, EntI projections in the lacunosum moleculare layer of CA1b and EntM projections in the lacunosum molecular layer of CA1c. This section of the perforant path arises from layer 3 pyramidal cells (Steward and Scoville, 1976). Both the main perforant pathway to CA3 and the dentate gyrus and the smaller one to CA1 are bilateral with the contralateral projection being more sparse than the ipsilateral projection. The contralateral projections are organized in a similar topographic fashion to the ipsilateral pathways (Steward and Scoville, 1976).

Recent studies of entorhinal efferents have shown that deeper layers of this cortical region (especially from EntL) project to widespread areas of the telencephalon. There are projections to limbic neocortical areas such as the prefrontal cortex medial to the genu of the corpus callosum (Swanson, 1981), and to the cortex just dorsal to the rhinal fissure (areas 20, 35, 36 and 41; Kosel *et al.*, 1982). There are projections to the lateral part of the accumbens nucleus (Krayniak *et al.*, 1981; Wyss, 1981), the anteromedial part of the caudoputamen (Sorensen and Witter, 1983), the medial part of the olfactory tubercle, medial parts of the anterior olfactory nucleus, the tenia tecta and the indusium griseum (Haberly and Price, 1978; Wyss, 1981). There are also entorhinal projections to the piriform cortex and to the underlying endopiriform nucleus (Wyss, 1981). There are projections to several areas of the amygdala, including the anterior amygdaloid area, cortical nuclei (Wyss, 1981) and the posterior parts of the central nucleus (Veening, 1978). In addition, Blackstad (1956) has postulated the existence of a commissural projection to the contralateral entorhinal cortex crossing the midline in the dorsal psalterium.

### III. THE SUBICULAR COMPLEX

#### A. Cytoarchitecture

The subicular complex is a wedge of cortex which curves anteriorly and laterally to wrap around the posterior extension of the dentate gyrus. Posteromedially, it borders the medial entorhinal cortex and, anterolaterally, field of CA1 of

Ammon's horn (Fig. 1). There are three distinct cytoarchitectural areas in the subicular complex. The parasubiculum (PaS) lies next to the medial entorhinal cortex. It is characterized by a superficial layer of moderately packed medium-sized cells. The presubiculum (PrS) lies next to the parasubiculum. It is characterized by a superficial lamina of densely packed small cells. The superficial layers of both the parasubiculum and presubiculum overlie a deep layer (d) of small to medium-sized cells similar to those in the deep layers of the entorhinal cortex. Finally, the subiculum proper (S), instead of a superficial layer of cells, has a loosely packed deep layer of pyramidal cells (Py) and a wide superficial molecular layer (Mol). The width of the pyramidal layer is progressively narrowed between the area near the presubiculum (a) and the area adjacent to Ammon's horn (also called the prosubiculum, ProS).

### B. Afferents of the subicular complex

Afferents from the raphe nuclei (Conrad *et al.*, 1974) and from the locus coeruleus (Jones and Moore, 1977) terminate diffusely throughout the subicular complex. The outer layers of both the parasubiculum and presubiculum receive a dense input from the anterior thalamic nuclei via the cingulum (Domesick, 1973; Raisman *et al.*, 1965; White, 1959). The thalamic reuniens nucleus projects to the ventral parasubiculum and subiculum (Segal, 1977; Herkenham, 1978).

Telencephalic afferents originate in a variety of sources. The vertical limb of the diagonal band and the medial septal nucleus project to the entire subicular complex (Lewis and Shute, 1967; Meibach and Siegel, 1977a; Powell *et al.*, 1965; Segal, 1977). Most septal afferents are diffusely distributed except for a greater concentration of terminals in the inner half of the molecular layer in S (Swanson and Cowan, 1976). The anterior cortical, posterior cortical, basolateral and lateral amygdaloid nuclei project to the ventral parasubiculum and subiculum (Krettek and Price, 1977; 1978). The perirhinal cortex (area 35) projects to the deep half of the superficial molecular layer of the subiculum (Kosel *et al.*, 1983).

Many subicular afferents originate in other structures in the hippocampal region. Projections from the entorhinal cortex have been mentioned above. The CA1 pyramidal cells send a dense projection to the subiculum (Hjorth-Simonsen, 1973; Raisman *et al.*, 1966; Swanson *et al.*, 1978), which may be greater than the CA1 projections to the septum (Finch and Babb, 1981; Finch *et al.*, 1983). According to Swanson *et al.* (1978), the CA3 pyramidal cells of Ammon's horn project to all parts of the subicular complex via extensions of the Shaffer collateral system but, according to Hjorth-Simonsen (1971), all CA3 retrohippocampal projections are destined for the entorhinal cortex.

### C. Efferents of the subicular complex

The subicular complex is one of the most important efferent areas of the entire

hippocampal region for only its axons leave the telencephalon to terminate in the diencephalon. The parasubiculum and presubiculum project heavily to the anterior thalamic nuclei (Chronister *et al.*, 1975; Sikes *et al.*, 1977; Swanson and Cowan, 1977). The subiculum projects sparsely to the anterior thalamic nuclei (Meibach and Siegel, 1977c; Sikes *et al.*, 1977) and to the reuniens nucleus (Herkenham, 1978). The chief diencephalic target of the subiculum is the mammillary body of the hypothalamus which receives a topographically organized projection (Meibach and Siegel, 1975). The dorsal subiculum projects to a dorsal transverse band in the medial mammillary nucleus while progressively more posterior and ventral portions of the subiculum project to correspondingly more ventral transverse bands in the mammillary body. Axons from the most ventral portion of the subiculum do not reach the mammillary body but terminate in more anteromedial hypothalamic areas and possibly in the preoptic area (Hori *et al.*, 1982; Meibach and Siegel, 1977d; Swanson and Cowan, 1975).

Most of the projections to the telencephalon originate in the subiculum. The ventral subiculum projects to the lateral amygdaloid nucleus (Veening, 1978), the bed nucleus of the stria terminalis (Swanson and Cowan, 1976), the tenia tecta, the medial part of the anterior olfactory nucleus (Swanson and Cowan, 1977), and the medial prefrontal cortex (Swanson, 1981). The entire extent of the subiculum terminates in the medial part of the accumbens nucleus (Kelley and Domesick, 1982; Swanson and Cowan, 1977) and in the lateral septal nucleus (Meibach and Siegel, 1977b; Siegel *et al.*, 1974; Swanson and Cowan, 1976; Swanson *et al.*, 1981). The dorsal and intermediate parts of the subiculum and the presubiculum terminate in the caudal cingulate cortex (Finch *et al.*, 1984; Meibach and Siegel, 1977d). In the guinea pig (Sorenson, 1980) and cat (Irle and Markowitsch, 1982) there is a projection to the retrosplenial cortex, a pathway which may also exist in the rat.

Axons from the subicular complex are also distributed in the hippocampal region. Those to the entorhinal cortex have been mentioned above. There are projections from the subiculum to the deep layers of the parasubiculum and presubiculum in the guinea pig (Sorensen and Shipley, 1979) and to the CA1 pyramidal cells in the rabbit (Berger *et al.*, 1980). The presubiculum also has an intrinsic longitudinal association pathway on the ipsilateral side in the guinea pig (Shipley, 1975). Many of these intrinsic projections may also exist in the rat.

#### IV. THE PYRAMIDAL CELLS OF AMMON'S HORN

##### A. Cytoarchitecture

Ammon's horn is a U-shaped fold of cortex containing a narrow layer of pyramidal cells stacked 3-5 deep (Py, Fig. 1). The pyramidal layer extends from the prosubiculum to the hilus of the dentate gyrus, and contains regional cytoarchitectural differences. Adjacent to the prosubiculum is a field of tightly

packed medium-sized cells. Cajal (1911) named this regio superior; Lorente de Nó (1934) called it CA1 and divided it into three zones. Zone a is the region where scattered deep cells extend beneath the superficial cells (see short dotted line in Fig. 1); Zones b and c can only be distinguished in fiber-stained preparations and are considered a single subdivision in this chapter. Following CA1 (long dotted line in Fig. 1), there is a field of large, less densely packed cells. Cajal (1911) called this regio inferior; Lorente de Nó (1934) called it CA2 and CA3. CA2 pyramidal cells occupy a narrow band adjacent to CA1 which can be distinguished from CA3 pyramidal cells in Golgi preparations by the absence of characteristic spiny thorns on the proximal apical dendrites. CA2 and CA3 cannot be accurately separated in Fig. 1 since they appear the same in Nissl-stained preparations. Lorente de Nó (1934) divided CA3 into three Zones (a, b, and c) on the basis of the number of Shaffer collaterals (see below) supplied by the cells. Zones a and b cannot be distinguished in Nissl preparations, but Zone c lies partly within the dentate hilus, and its boundary is marked by the short dotted line in Fig. 1.

Fig. 2 gives some details of pyramidal cell dendritic and axonal structure. In Golgi preparations, Ammon's horn pyramidal cells are characterized by two main groups of dendrites exiting from the cell body. The apical dendrite is a single pole extending from the apex of the perikaryon through the radiatum layer (Rad) and into the lacunosum moleculare layer (LMol). In the Rad, a few fine branches are given off at right angles from the shaft of the main dendrite in the CA1 fields. In the lacunosum moleculare layer many secondary and tertiary branches of the apical dendrite produce a dense tuft. The basal dendrites exit from several places along the base of the perikaryon. These repeatedly branch in the oriens layer (Or) producing another dense tuft. The axon exists either from the perikaryon or from a proximal segment of a basal dendrite. It travels to the alveus (the narrow strip of white matter at the base of the oriens layer) where it may bifurcate. This is especially prevalent in CA1 pyramidal cell axons where one branch travels toward the subicular complex while the other branch heads toward the fimbria (fi). Within the oriens layer, the axons of the CA3 pyramidal cells give off recurrent branches (the Shaffer collaterals) which travel up to the level of the lacunosum moleculare layer. There they take a sharp turn to travel into the lacunosum moleculare layer of field CA1, and further caudally.

## B. Connections of the pyramidal cells

There are two types of afferents to the pyramidal cells: those that terminate diffusely over the entire dendritic surface, and those that terminate in specific layers along restricted segments of either the apical or basal dendrites. The diffuse afferents come from the raphe nuclei (Conrad *et al.*, 1974; Moore and Halaris, 1975; Storm-Mathisen and Guldberg, 1974), the local coeruleus (Blackstad *et al.*, 1967; Fuxe, 1965; Jones and Moore, 1977; Room *et al.*, 1981;



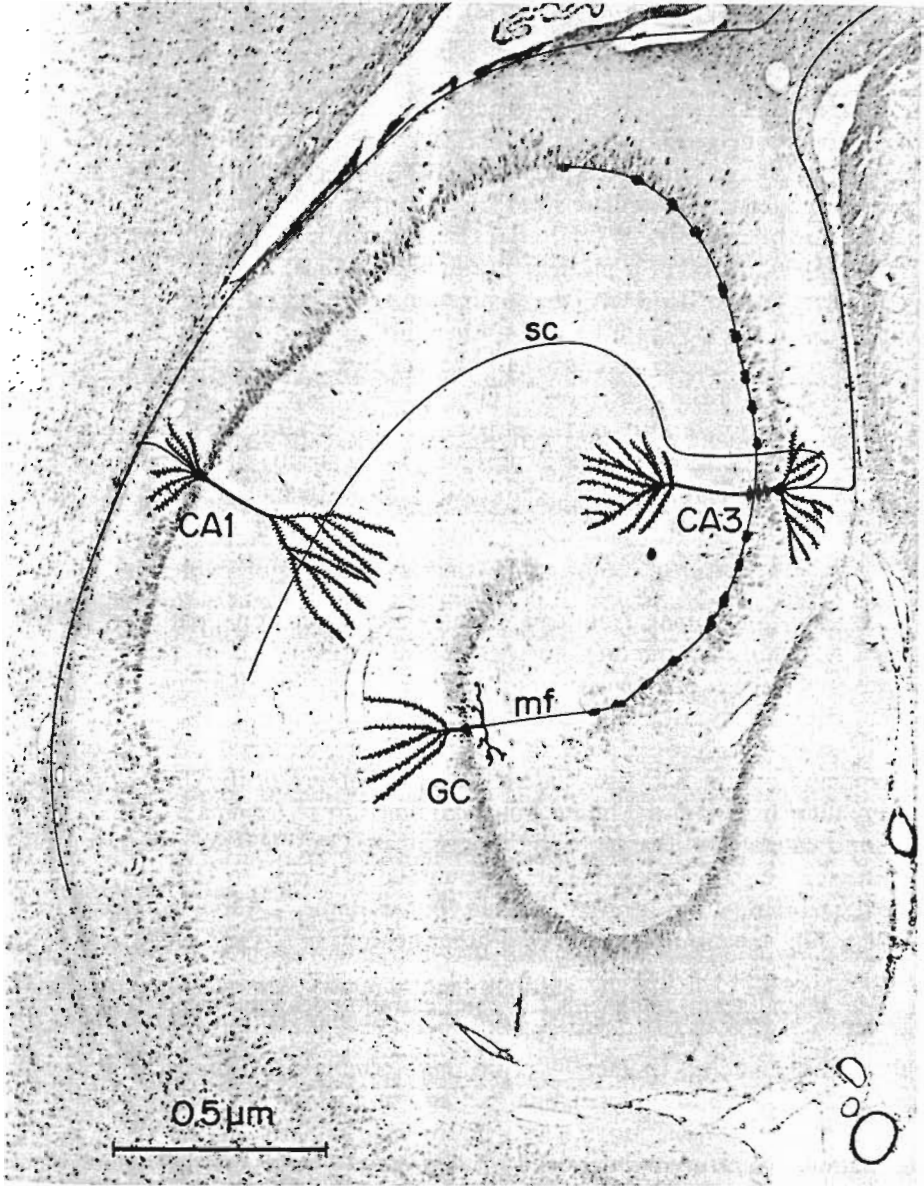


Fig. 2: A semidiagrammatic representation of the typical morphology of CA1 and CA3 pyramidal cells, and of a dentate granule cell (GC). The axon of the CA1 pyramidal cell bifurcates in the white matter (alveus). The axon of the CA3 pyramidal cell gives off a recurrent (Shaffer) collateral (sc) in the stratum oriens which ascends to the stratum lacunosum moleculare. The axon of the granule cell gives off some collaterals in the hilus and a long branch extends into CA3 as a mossy fiber (mf) to contact the heavy thorns on the CA3 pyramidal cells.

Storm-Mathisen and Guldberg, 1974) and the medial septal-diagonal band complex (Lewis and Shute, 1967; Meibach and Siegel, 1977a; Mellgren and Srebro, 1973; Powell *et al.*, 1965; Swanson and Cowan, 1976).

Laminated afferents to the pyramidal cells come from a variety of sources. The lacunosum moleculare layer of CA1 receives massive input from the reuniens thalamic nucleus (Herkenham, 1978). Other laminated afferents come to the lacunosum moleculare layer of CA1 from the piriform cortex (Cragg, 1961; Hjorth-Simonsen, 1972). Besides these extrinsic afferents, there is a sparse topographic projection from the entorhinal cortex (see above). The lacunosum moleculare layer of field CA3 gets laminated afferent input from the entorhinal cortex (see above). Within field CA3 there is a narrow zone just above the cell body layer in the deep parts of the radiatum layer. This region (not labeled in Fig. 1) is called the lucidum layer. In Golgi preparations, the CA3 pyramidal cells contain thick spiny thorns on the proximal apical dendrites in the lucidum layer (Fig. 2). These portions of the dendrite receive a strictly ipsilateral input from the axons of the dentate granule cells (called mossy fibers; Blackstad *et al.*, 1970; Cajal, 1911; Gaarskjaer, 1978; Lorente de N6, 1934). More details about this pathway will be given below.

The remainder of the dendritic surface in both CA1 and CA3 is primarily taken up with terminals from commissural and associational pathways between the CA fields in Ammon's horn (Blackstad, 1956). All of these pathways represent branches of extensively collateralized CA3 axons (Gottlieb and Cowan, 1973; Hjorth-Simonsen and Laurberg, 1977; Swanson *et al.*, 1981). Axons from all fields of CA3 project to both Rad and Or in ipsilateral CA1 via branches extending from the Shaffer collaterals. Another branch of the CA3 axon crosses the midline in the ventral hippocampal commissure to terminate in Rad and Or in contralateral CA1. Various subdivisions of the CA3 field are also intrinsically connected via commissural and associational afferents so that the terminals always remain within a given subfield. For example, CA3c is connected both ipsilaterally and contralaterally with other neurons in CA3c; fields CA3a and b are similarly interconnected.

The lateral septal nucleus is the chief extrahippocampal target for all fields of the Ammon's horn pyramidal cells. Axons from both CA1 (ipsilaterally projecting) and CA3 (bilaterally projecting) terminate in a topographic fashion as follows: the dorsal hippocampal projects to dorsomedial areas of the lateral septal nucleus, while progressively more ventral parts of the hippocampus terminate in correspondingly more lateroventral bands in the lateral septal nucleus (Meibach and Siegel, 1977b; Siegel *et al.*, 1974; Swanson and Cowan, 1976). Branches of the CA1 axons terminate sparsely in other targets outside the hippocampal region. De Olmos *et al.* (1978) reported that some efferents extend to the main olfactory bulb from a few deep pyramidal cells in CA1a of the ventral hippocampus. Swanson (1981) found that some ventral CA1 cells project to the

ventral tenia tecta, to the medial part of the anterior olfactory nucleus and to the prefrontal cortex medial to the genu of the corpus callosum. CA1 projections to the retrohippocampal fields in the hippocampal region have been mentioned above.

## V. THE DENTATE GYRUS

### A. Cytoarchitecture

The dentate gyrus is a sharply folded trilayered cortex that forms a cap over the free edge of Ammon's horn (Fig. 1). Its only cell layer contains densely packed granule cells which are stacked approximately 4–10 deep. The granular layer is thinner toward the end of the ectal, or external, limb (Ect, lying opposite CA1) and toward the end of the endal, or internal, limb (End, lying opposite the thalamus), and is usually thickest in the crest area (transected by a dotted line in Fig. 1). The molecular layer contains the dendrites of the granule cells, which typically show a conically shaped dendritic field (Fig. 2). The apex is a short primary dendrite existing from that part of the soma closest to the superficial part of the granular layer. Long secondary branches with relatively few tertiary branches spread upward to the superficial part of the molecular layer; their terminals form the base of the cone. Granule cell axons are called mossy fibers (Cajal, 1911) and exit from the deep aspect of the cell body. Details of their trajectory will be given below.

The hilus (h) can be distinguished from the layers associated with field CA3c of Ammon's horn by an increase in cell density in CA3c; the dashed line in Fig. 1 marks the boundary between field CA3c and the hilus. The hilus contains polymorph, fusiform, and modified pyramidal cells. Lorente de Nó (1934) considered the hilar area to be part of Ammon's horn and called it field CA4. Today it is usually considered a transition area between the dentate gyrus and Ammon's horn. The scattered cells of the hilus display unique dendritic configurations. The most common neuron is the "mossy cell" (Amaral, 1978) which has long dendrites whose proximal portions are totally covered by thorny spines, typical of a cell receiving input from a mossy fiber. Axons of the mossy cells send collaterals to the dentate molecular layer and a long branch enters the fimbria.

### B. Connections of the dentate gyrus

Similar to Ammon's horn, afferents to the dentate gyrus are either laminated or diffuse. Afferents from the brain stem raphe nuclei (Conrad *et al.*, 1974; Moore and Halaris, 1975; Storm-Mathisen and Guldberg, 1974) the locus coeruleus (Blackstad *et al.*, 1967; Fuxe, 1965; Jones and Moore, 1977; Room *et al.*, 1981;

Storm-Mathisen and Guldberg, 1974) and the medial septal complex (Lewis and Shute, 1967; Meibach and Siegel, 1977a; Melgren and Srebro, 1973; Powell *et al.*, 1965; Raisman, 1966; Swanson and Cowan, 1976) terminate diffusely throughout the molecular layer. The locus coeruleus input tends to be highly concentrated at the base of the granular layer where the axons ramify amongst the polymorph cells (Moore and Halaris, 1975).

Laminated afferents to the dentate molecular layer come almost entirely from other structures of the hippocampal region. Those from the entorhinal cortex terminate in the outer two thirds of the dentate molecular layer (see perforant path above). The entorhinal afferents represent a massive input to the dentate granule cells; the dendritic fields of individual granule cells are shaped so that approximately 60%–70% of their total dendritic length is taken up with perforant path input (Desmond and Levy, 1982). Just below the terminal zone of the medial entorhinal cortex lies a band (the proximal third of the molecular layer) which contains commissural (Blackstad, 1956; Laatsch and Cowan, 1967) and associational (Hjorth-Simonsen, 1973; Raisman *et al.*, 1965) afferents. The source of this projection was presumed to be from CA3 of Ammon's horn. Zimmer (1973) found that small lesions of field CA3c and the hilus gave terminal degeneration of the inner third of the dentate molecular layer. Using horseradish peroxidase, the cells of origin of both the ipsilateral and contralateral projections were further narrowed down to cells in the hilus (Fricke and Cowan, 1978; Laurberg, 1979; Swanson *et al.*, 1978). Finally a laminated afferent input from the hypothalamic supramammillary nucleus comes to the deepest parts of the granular layer (Pasquier and Reinoso-Suarez, 1976; Wyss *et al.*, 1979).

There are two targets for the dentate granule cell axon—the ipsilateral CA3 fields of Ammon's horn, and the mossy cells scattered throughout the hilus. Mossy fibers descend to the hilus and ramify. Some collaterals branch within the hilus, while a long branch goes toward CA3. All branches show varicosities along the way impaled by the thorny spines of both the CA3 pyramidal cells and the mossy cells. After passing out of the hilus, the long branches group into two bundles. The infrapyramidal bundle is short and contacts the thorny spines on proximal basal dendrites in CA3c. The suprapyramidal bundle is long and forms the lucidum layer in CA3. Varicosities in the granule cell axons have been shown by electron microscopy to contain enormous numbers of synaptic vesicles, approximately 20 nm–60 nm in diameter (Blackstad and Kjaerheim, 1961). These swellings represent boutons *en passage*. Dendritic profiles are frequently observed embedded in the bouton and favorable sections show them to be continuous with the thorns on the apical dendrites of the CA3 pyramidal cells.

## VI. CORRELATIONS BETWEEN DEVELOPMENTAL PATTERNS AND ANATOMICAL CONNECTIONS IN THE HIPPOCAMPAL REGION

Precise patterns of topographic anatomical connections in the hippocampal

NEUROGENESIS IN STRUCTURES SUPPLYING AFFERENTS TO THE HIPPOCAMPUS IN RELATION TO DENDRITIC TERMINATION

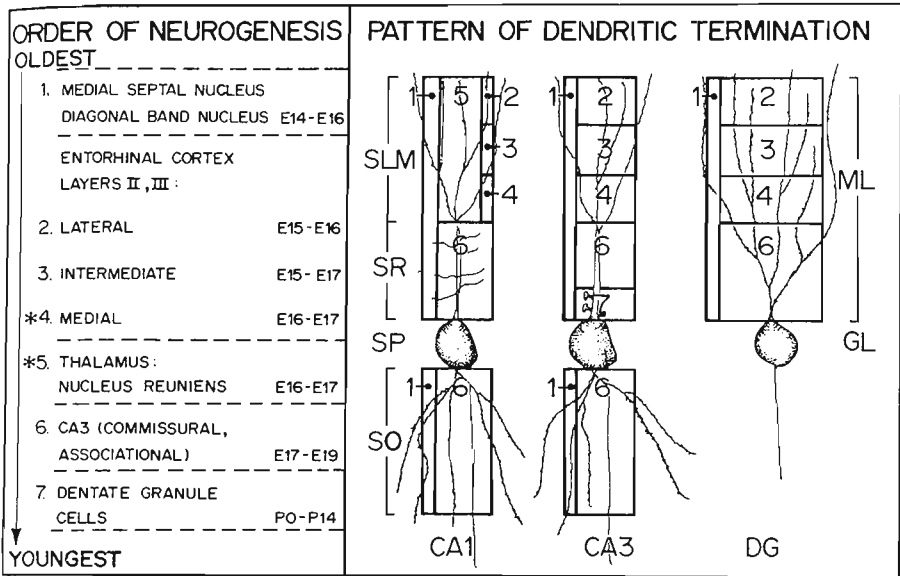


Fig. 3: Order of neurogenesis in cells of origin of afferent fibers related to order of termination on dendrites in CA1, CA3 and the dentate gyrus. Cells supplying septal afferents (1) originate first and terminate diffusely in all dendritic areas; all other afferents represented terminate in specific layers. Earlier originating cells from lateral entorhinal cortex (2) project most distally to the cell body, later originating cells from intermediate (3) and medial (4) entorhinal cortex project progressively more proximally in CA3 lacunosum moleculare layer (SLM) and the superficial part of the dentate molecular layer (ML). Cells projecting from reuniens nucleus (5) terminate throughout SLM of CA1. Younger afferents from CA3 (6) terminate in the more proximal radiatum (SR) and oriens (SO) layers. Hilar cells originate nearly simultaneously with CA3 and are the source of commissural and associational fibers to zone 6 in the dentate gyrus. The dentate granular layer has the youngest cells (7) supplying mossy fibers to zone 7 on the CA3 dendrite (lucidum layer), which is most proximal to the cell body (from Bayer, 1980).

region can be correlated with equally precise timetables of neurogenesis (Bayer, 1980). When one looks at zones of afferent terminals on CA1, CA3 and dentate granule cell dendrites from a developmental aspect, an interesting pattern emerges. Fig. 3 summarizes these relations: the left column lists the order of neurogenesis in afferent sources, while termination zones are mapped in the right half of the figure. In all cases, the most proximal parts of the dendrites receive input from the youngest afferents, while progressively older afferents terminate more distally. For example, on the CA3 apical dendrite mossy fibers (youngest afferents) terminate just above the cell body in zone 7, while lateral entorhinal cortical afferents (oldest) terminate most distally in zone 2.

Other correlations exist between neurogenetic patterns and anatomical connections. Throughout the hippocampal region, there is an interstructural

neurogenetic and morphogenetic gradient such that those structures closest to the rhinal fissure are older, while progressively younger structures are located nearer the dentate gyrus (rhino-dentate gradient). Two structures are "out of line" in this scheme. The presubiculum originates slightly later than the subiculum, and CA1 originates slightly later than CA3. Interestingly, both the presubiculum and CA1 get heavy thalamic input (see above). Since thalamic afferent sources are quite distant from the hippocampal region, neurogenesis in both the presubiculum and CA1 may be slightly delayed to correlate with a later arrival of thalamic fibers. There are also correlations between the order of neurogenesis in the lateral septal nucleus and medial mammillary nucleus and the patterns of anatomical connections with Ammon's horn and the subiculum. For example, in the medial mammillary nucleus older cells receive input from the dorsal subiculum, while younger cells are contacted by the ventral subiculum axons. Since fibers from the dorsal subiculum have a shorter distance to grow, they may arrive at the target first and contact older cells in the medial mammillary nucleus. Fibers from the ventral subiculum may arrive later and contact younger cells.

These relationships (and others throughout the central nervous system) have prompted the formulation of a hypothesis: *Temporal patterns of neurogenesis are important prerequisites for the establishment of precise anatomical interconnections in the developing brain.* To test this hypothesis, developmental anatomical studies are being carried out (Bayer, in preparation) and confirmation should be provided within the next few years.

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