Emerging principles of intrinsic hippocampal organization

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The hippocampal formation has a unique and highly distributed network of intrinsic connections. What are the principles of organization that govern information flow through this system? The notion that information processing in the hippocampal formation is segregated in autonomous chips or lamellae appears to be inconsistent with the extremely divergent nature of many of the intrinsic connections. Recent neuroanatomical data suggest, however, that information may be segregated in other ways as it negotiates the links from one hippocampal region to the next.

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Introduction

The hippocampal formation is a heterogeneous region that plays a prominent role in memory [1]. An understanding of the mechanisms by which the hippocampal formation influences memory function will depend on detailed information regarding the flow of sensory information into, through, and out of the various fields that comprise this brain region. While much is known concerning the organization of its intrinsic connections, only recently have certain facets of the orderliness and topography of these projections been appreciated. These recent data indicate that some of the hippocampal fields, such as the CA1 field of the hippocampus, the subiculum and the entorhinal cortex, can be further subdivided based on their patterns of inputs and outputs. As distinct populations of output neurons in the subiculum project to different brain regions, it is possible that different channels of information flow are segregated through the hippocampal circuitry and are ultimately directed to different brain regions.

The hippocampal formation has historically been considered to comprise a series of adjacent cortical regions including the dentate gyrus, the hippocampus, which is itself divided into three subdivisions (CA3, CA2 and CA1), the subiculum, presubiculum and parasubiculum, and the entorhinal cortex, which is divided into two or more subdivisions [2,3].

The purpose of this review is to summarize recent neuroanatomical findings that indicate that the classical view of intrinsic hippocampal circuitry must be amended to provide a more accurate representation of information processing in the hippocampal formation.

The classical hippocampal circuit

Figure 1 illustrates the classical image of the 'trisynaptic circuit' of the hippocampal formation [4]. Illustrations of this type have been extremely influential in shaping researcher's views of hippocampal information processing. In this representation, the first link of the circuit arises in the entorhinal cortex and terminates in the dentate gyrus. The second link originates with the granule cells of the dentate gyrus and terminates on the CA3 pyramidal cells

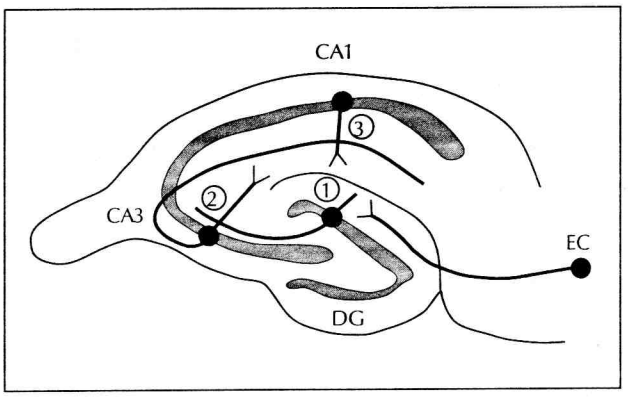

Fig.1. Line drawing of a cross-section through the hippocampal formation illustrating the classical view of the 'trisynaptic circuit'. DG, dentate gyrus. EC, entorhinal cortex.

of the hippocampus. The third link is between axons of the CA3 pyramidal cells and the CA1 pyramidal cells. While this simplified circuit diagram is still commonly seen in research and review papers, it must be modified substantially if it is to adequately reflect our current understanding of hippocampal anatomy (Fig.2–4). First, there are actually two distinct projections from the entorhinal cortex which contribute fibers to all hippocampal fields and to the subiculum (Fig.2) [5,6•]. Second, the CA3 projection to CA1 is portrayed as a single axon that terminates uniformly throughout the CA1 field. But the CA3 projection to CA1 arises from highly collateralized pyramidal cell axons that contribute many branches to CA1 [7,8]. Moreover, subsets of CA1 cells are preferentially innervated by subsets of CA3 cells (Fig.4). Third, the important projection from CA1 to the subiculum was not included in this classical picture (Fig.4) [9,10•].

In the following sections, recent information on each of these topics will be summarized. To speak efficiently about hippocampal anatomy a few terms of orientation need to be defined. The hippocampal formation is an elongated structure that, depending on the species, is more or less C-shaped. The long dimension of the hippocampal formation is referred to as the longitudi-

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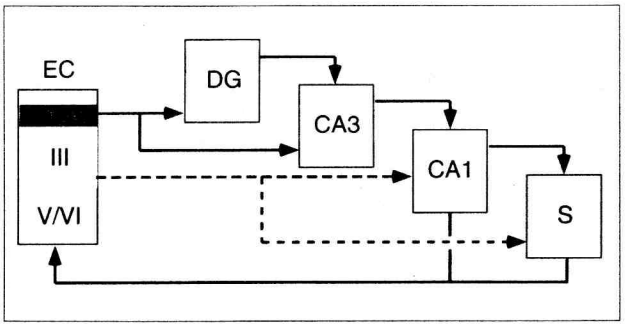

Fig.2. A schematic diagram illustrating the organization of the two perforant pathway projections to the other fields of the hippocampal formation. Cells in layer II of the entorhinal cortex (EC) project to the dentate gyrus (DG) and to the CA3 field of the hippocampus. Cells in layer III of the EC give rise to a distinct pathway that innervates the CA1 field of the hippocampus and the subiculum (S). Monosynaptic links between the various fields of the hippocampal formation (DG –> CA3 –> CA1 –> S) are also indicated. Note that field CA1 of the hippocampus has the distinction of being the first stage in the hippocampal circuitry where information from the layer II and layer III perforant pathways converge. Note also that information carried by the layer II projection will ultimately attain CA1 by both trisynaptic (through the DG) and disynaptic (directly from CA3) pathways. A return projection from CA1 and the subiculum to the deep layers of the entorhinal cortex is included in this illustration but is not discussed in the text.

nal axis and the orthogonal orientation is the transverse axis. In describing positions within the transverse axis of a field, such as CA1, portions located closer to the dentate gyrus are referred to as proximal and those further away from the dentate gyrus are called distal. Thus, the proximal border of CA1 is with CA2 and the distal border is with the subiculum. I will occasionally need to describe positions along the longitudinal axis of the hippocampal formation and for this I will use the terms septal (meaning the portion of the hippocampal formation located nearer the septal nuclei) and temporal (the other end) as commonly used in the rat brain.

There are two distinct and topographically organized projections from the entorhinal cortex

The perforant path projections arise mainly from layers II and III of the entorhinal cortex (Fig.2,4) [5,6•]. Cells in layer II project almost exclusively to the dentate gyrus and the CA3 and CA2 fields of the hippocampus (the layer II projection). Cells in layer III, in contrast, project to the CA1 field of the hippocampus and to the subiculum (the layer III projection). This latter projection has not received much attention in the hippocampal literature, but recent anatomical studies [6•,11] indicate that it is robust and consistently organized in the rat and monkey brains. While few *in vivo* electrophysiological studies have been carried out on the perforant path projections to the hippocampus, Yeckel and Berger [12] have demonstrated in the rabbit that following focal stimulation of fibers of the perforant path, neurons within all fields of the hippocampus discharge simultaneously. They also found that the initial monosynaptic excitation of pyramidal cells by the direct entorhinal projections was followed by weaker excitatory activation of the same cells via the disynaptic or trisynaptic routes through the dentate gyrus and CA3. Interestingly, responses of CA3 pyramidal cells would occasionally precede those of dentate granule cells, and responses in CA3 and CA1 could occur in the absence of granule cell excitation. These observations suggest that the monosynaptic projections from the entorhinal cortex to the hippocampus are sufficiently powerful to produce suprathreshold activation of the pyramidal neu-

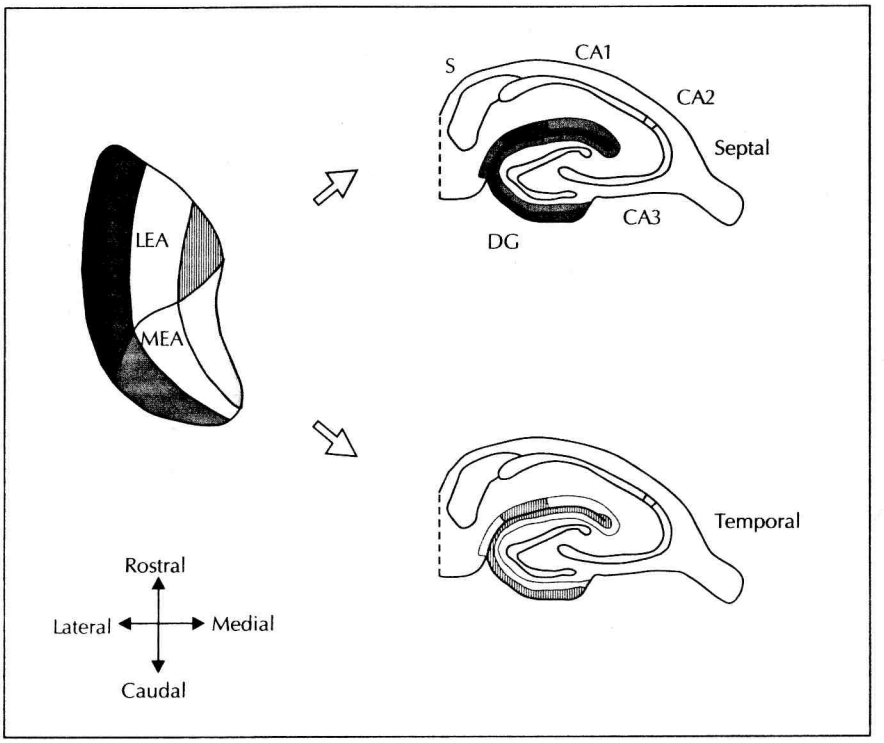

Fig.3. Illustration of septotemporal and mediolateral topography of the perforant path projection to other fields of the hippocampal formation. The illustration on the left represents the surface of the entorhinal cortex. Cells located laterally in the entorhinal cortex project to septal levels of the hippocampal formation, whereas cells located progressively more medially project to more temporal portions of the hippocampal formation. Patterns of termination of the lateral entorhinal area (LEA) and medial entorhinal area (MEA) are described in the text.

rons and must therefore be considered serious sources of sensory information to hippocampus and subiculum.

Jones [13••] has recently highlighted data that indicate that the layer II cells of the entorhinal cortex are under very tight inhibitory control mediated, in part, by local GABAergic neurons. Thus, while activation of afferents terminating in layer II of the entorhinal cortex leads to EPSPs in the resident stellate cells, the dominant responses are IPSPs. Deeper layers in the entorhinal cortex, however, are not as influenced by inhibitory mechanisms. These data raise the prospect that a common input to layers II and III of the entorhinal cortex may not gain access to the granule cells because of the substantial inhibition of layer II, but may be suprathreshold for layer III cells that would subsequently activate CA1 and the subiculum (see [13••] for an elaboration of this argument). One clear implication of the dichotomy of the perforant path projection is that the two components may be functioning independently. One indication that this may be the case comes from the work of McNaughton and colleagues [14] who have demonstrated that neurotoxic lesion of approximately 75% of the granule cells in the dentate gyrus impairs rats performance on various tests of spatial memory. But there is little effect on the spatial selectivity of place fields recorded from pyramidal cells in the CA3 and CA1 fields. These data indicate that spatial information essential for the development of place fields can reach CA3 and CA1 via pathways other than the classical trisynaptic pathway; a likely candidate pathway is the direct perforant path projection (Fig.2).

The layer II and layer III projections of the entorhinal cortex have both similarities and differences in their organizational principles. The two pathways share a similar longitudinal topographic organization (Fig.3). Cells situated laterally in the entorhinal cortex, i.e. close to the rhinal sulcus, project to septal portions of the hippocampal formation (caudal levels of the primate hippocampal formation), whereas cells located medially in the entorhinal cortex project to temporal levels of the rodent hippocampal formation (rostral levels of the primate) [15,16]. The reader should not confuse the use of the words medial and lateral with the terms typically used in the rodent literature to define the two major subdivisions of the entorhinal cortex, i.e. medial entorhinal area and lateral entorhinal area. These terms are quite confusing choices for these regions as the lateral entorhinal area actually lies rostral and lateral to the medial entorhinal area, which occupies the caudomedial portion of the field. The laterally situated cells that project to the septal portion of the hippocampal formation include cells within both the lateral and medial entorhinal areas (Fig.3).

Perhaps the most striking difference between the layer II and layer III perforant paths is how the projections from the lateral and medial entorhinal areas distribute to the dentate gyrus and CA3/CA2 versus CA1 and the subiculum (Fig.3,4). The layer II projection terminates in the outer two-thirds of the molecular layer of the dentate gyrus and in stratum lacunosum moleculare of CA3/CA2. Cells of the lateral entorhinal area contribute projections to the superficial portion of the molecular layer and stratum lacunosum moleculare, whereas projections from the medial entorhinal area terminate in the deeper portion of both terminal fields (Fig.3,4). Thus, all of the granule cells and CA3/CA2 pyramidal cells located at the

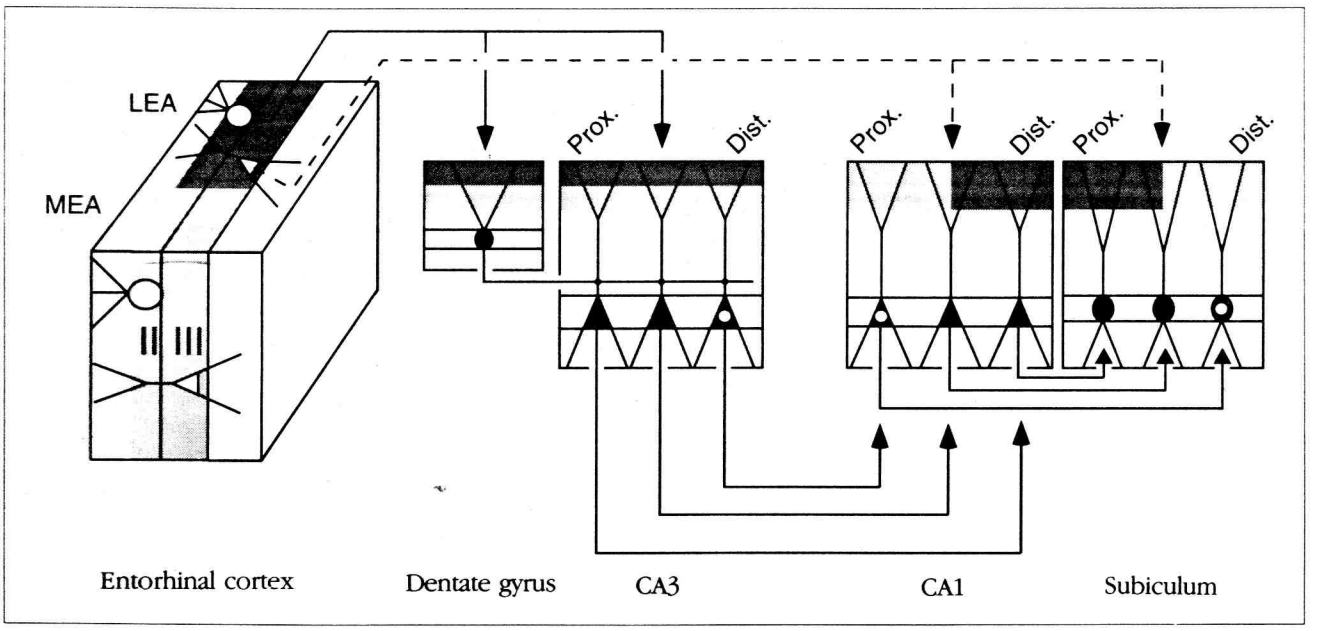

Fig.4. A summary diagram of features of hippocampal intrinsic circuitry described in this review. Entorhinal cortex originates two perforant path projections that terminate in different regions of the hippocampal formation. While axons of the dentate granule cells terminate throughout the full transverse extent of the CA3 field, subsequent projections between adjacent fields show increasingly restricted distributions along the transverse axis. Axons with arrows indicate which portions of each field are connected to the next field. Note that three of the connected cells are indicated with a dot. Prox and Dist refer to proximal and distal portions of each field. LEA, lateral entorhinal area. MEA, medial entorhinal area.

innervated level receive terminals from cells in the medial and lateral entorhinal areas; fibers from these areas terminate on different radial positions of the innervated dendritic trees.

The situation is quite different for the layer III projection (Fig.3,4) which terminates in stratum lacunosum moleculare of CA1 and in the molecular layer of the subiculum. Unlike the layer II projection, the layer III projection does not terminate in a laminated fashion. Rather, it is organized so that projections arising in the lateral entorhinal area terminate throughout stratum lacunosum moleculare, but only in a restricted transverse region located at the border of CA1 and the subiculum [6•]. In other words, cells in distal CA1 and proximal subiculum receive a projection from the lateral entorhinal area, whereas cells located in proximal CA1 and distal subiculum do not. These latter portions of the CA1 and subiculum receive projections from cells located in the medial entorhinal area. Thus, the layer III projection has a more clearly topographic pattern of distribution; different transverse portions of CA1 and the subiculum are in register with different rostrocaudal portions of the entorhinal cortex.

The dentate gyrus to CA3 projection does not demonstrate a transverse topography

The projection from the dentate gyrus to the CA3 field of the hippocampus is formed by the axons of the granule cells, the mossy fibers. While these distinctive axons are relatively selective in their contacts with CA3 pyramidal cells (it has been estimated that each granule cell contacts only 14 CA3 pyramidal cells [17]), the contacts of a single mossy fiber seem to be relatively evenly spaced throughout the transverse extent of the CA3 field (Fig.4). All successive intrinsic connections in the hippocampal circuit, however, demonstrate increasingly strict transverse topographies.

The CA3 projection to CA1 has a transverse topography that is complicated by extensive longitudinal connections

The CA3 pyramidal cells give rise to highly collateralized axons that distribute extensively both within CA3 (the associational connection) and to CA1 (the Schaffer collaterals) [7,8]. Because projections from any particular level of CA3 extend throughout much of the longitudinal axis of the hippocampus, and the terminal fields appear to shift their transverse position at progressively greater distances from the origin of the projection, the transverse organization of this projection is somewhat complex [8,18]. However, a relatively simple statement can be made concerning the organization of projections at about the same longitudinal level as the cells of origin. Cells located proximally in CA3, near the dentate gyrus, tend to project to the most distal CA1 cells where the terminal plexus tends to be heavier in stratum radiatum than in stratum oriens (Fig.4). The projections from the distal portion of CA3, in contrast, terminate mainly in the proximal portion of CA1 and most heavily in stratum oriens and the deep portion of stratum radiatum. The mid portion of CA3 fills in the spaces between these two projections. While the highly collateralized and extensive projections of CA3 to CA1 partially obscure the transverse topography, what is clear is that a proximal CA3 cell will have a relatively high probability of contacting a distal CA1 neuron at the same septotemporal level, while a distal CA3 cell will have very low probability of contacting the same cell. The image gained from the classical illustration showing a single CA3 axon collateral terminating on the apical dendrites of CA1 cells throughout the transverse extent of the field is clearly incorrect.

The CA1 projection to the subiculum demonstrates a striking transverse topography

The CA1 field of the hippocampus differs from the CA3 field in that neurons in CA1 give rise to few, if any, associational connections [9,10•]. The CA1 pyramidal cells do, however, give rise to a very robust projection to adjacent subiculum. This projection terminates throughout the pyramidal cell layer and in the deep portion of the molecular layer in a columnar fashion. The CA1 projection divides the transverse extent of the subiculum into roughly three equal parts. The proximal portion of CA1 projects to the distal third of the subiculum, the distal portion of CA1 projects just across the border into the proximal third of the subiculum, and the middle portion of CA1 projects to the midregion of the subiculum (Fig.4). This columnar organization of CA1 to subiculum projection is all the more impressive in that the axons of single intracellularly labeled CA1 pyramidal cells demonstrate the same type of topographic organization and the same transverse spread of terminal axonal arbors [9].

The output of the subiculum to other brain regions is also organized in a columnar fashion

The subiculum is widely viewed as the major subcortical output field of the hippocampal formation because it contributes prominent projections to the mamillary nuclei, thalamus and nucleus accumbens [19]. It also contributes projections to the deep or output layers of the entorhinal cortex and to other cortical regions. It has recently become clear that the organization of subicular outputs is also organized in a columnar fashion with projections to different brain regions, or different parts of the same brain region, originating from the proximal, middle and distal thirds of the subiculum [19,20]. Neurons in the proximal third of the subiculum project to the infralimbic and prelimbic cortices, the nucleus accumbens and the lateral septal region. Projections from this portion of the ventral part of the subiculum also project to the ventromedial nucleus of the hypothalamus and to the amygdala. The mid transverse portion of the subiculum projects mainly to the midline thalamic nuclei and neurons in the distal portion of the subiculum project to the retrosplenial portion of the cingulate cortex and to the presubiculum. While all portions of the subiculum project to the entorhinal cortex, the pattern of projec-

tions reciprocates the topography of the perforant path projections to the subiculum. Thus, the proximal portion of the subiculum projects to the lateral entorhinal area and more distal portions of the subiculum project to the medial entorhinal area.

Conclusion

Recent detailed studies of the intrinsic and extrinsic circuitry of the hippocampal formation have provided convincing evidence that the organizational principles of this system are substantially different from those described in the 1970s (Fig.4). The serial processing concept implicit in the 'trisynaptic circuit' is no longer valid, and the richness of the two perforant path systems for subserving parallel and serial information transfer to most of the fields of the hippocampal formation provides for monosynaptic, disynaptic and trisynaptic influences of CA1 neurons by the same entorhinal activation (Fig.2). Despite apparent cytoarchitectonic homogeneity in CA1 and subiculum, these fields can be subdivided into at least three zones on the basis of their inputs and output (Fig.4). That the output from the subiculum to various brain regions also honors the transverse organization of this field raises the possibility that information processing from one field to the next in the hippocampal formation follows channels formed by subsets of neurons in different proximodistal portions of each field. If this anatomical organization has functional consequence, one might predict that CA1 cells located in the proximal part of the field would demonstrate physiological response patterns distinctly different from CA1 cells located in the distal portion of the field at the same longitudinal level. Hopefully, future electrophysiological analyses will take into consideration the newly emerging principles of intrinsic hippocampal organization.

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