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The subiculum: a review of form, physiology and function

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Abstract

We review the neuroanatomical, neurophysiological and functional properties of the mammalian subiculum in this paper. The subiculum is a pivotal structure positioned between the hippocampus proper and entorhinal and other cortices, as well as a range of subcortical structures. It is an under-investigated region that plays a key role in the mediation of hippocampal–cortical interaction. We argue that on neuroanatomical, physiological and functional grounds, the subiculum is properly part of the hippocampal formation, given its pivotal role in the hippocampal circuit. We suggest that the term 'subicular complex' embraces a heterogenous range of distinct structures and this phrase does not connote a functionally or anatomically meaningful grouping of structures. The subiculum has a range of electrophysiological and functional properties which are quite distinct from its input areas; given the widespread set of cortical and subcortical areas with which it interacts, it is able to influence activity in quite disparate brain regions. The rules which govern the plasticity of synaptic transmission are not well-specified; it shares some properties in common with the hippocampus proper, but behaves quite differently in other respects. Equally, its functional properties are not well-understood, it plays an important but ill-defined role both in spatial navigation and in mnemonic processing. The important challenges for the future revolve around the theoretical specification of its unique contribution to hippocampal formation processing on the one hand, and the experimental investigation of the many open questions (anatomical, physiological, pharmacological, functional) regarding its properties, on the other.

Contents

Abbreviations: ab, angular bundle; ACH(s), autocorrelation histograms; AD, anterodorsal nucleus; AHP, after hyperpolarisation; alv, alveus; AM, anteromedial nucleus; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; AV, Anteroventral nucleus; B, bursting neuron; CA1, cornu ammonis 1 (subfield of the hippocampus); CA3, cornu ammonis 3 (subfield of the hippocampus); CM, caudomedial; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; DG, dentate gyrus; EC, entorhinal cortex; f, fornix; fEPSP, field excitatory postsynaptic potential; fi, fimbria; GABA, gamma-aminobutyric acid; GL, granular layer; HFS, high frequency stimulation; IAM, interanteromedial nucleus; IPSP, inhibitory postsynaptic potential; ISI(s), inter stimulus interval(s); LEC, lateral entorhinal cortex; LFS, Low frequency stimulation; LTD, long term depression; LTP, long term potentiation; MEC, medial entorhinal cortex; ML, molecular layer; ms, mossy fibers; NMDA, *N*-methyl-D-asparate; PaS, parasubiculum; PHA-L, phaseolus vulgaris leucoagglutinin; plc, pyramidal cell layer; PoDG, polymorphic layer of the dentate gyrus; pp, perforant pathway; PPD, paired pulse depression; PPF, paired pulse facilitation; PrS, presubiculum; R, regular firing neuron; Rdg, retrosplenial dysgranular cortex; Rga, retrosplenial granular a cortex; Rgb, retrosplenial granular b cortex; RL, rostrolateral; rmp, resting membrane potential; S, subiculum; sc, Schaffer collaterals; S.E.M., standard error of the mean; sl, stratum lucidum; sl-m, Stratum lacunosum-moleculare; so, Stratum oriens; sr, stratum radiatum; TBS, theta-burst stimulation; TPS, two pulse stimulus; TTX, tetrodoxin; V, ventral.

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1. General introduction

The hippocampal formation of the mammalian brain has long attracted the attention not only of psychologists but physiologists and neuroanatomists alike (see Fig. 1). The hippocampal formation consists of a number of subdivisions: the dentate gyrus, the hippocampus proper (areas CA1 and CA3), the entorhinal cortex (EC), which particularly in the rodent, is generally divided into medial and lateral subdivisions and the subiculum (Amaral and Witter, 1989, 1995). The physiology and functions of the dentate gyrus and the hippocampus proper have been the subject of many reviews (for example O'Keefe, 1979, 1999; O'Mara, 1995; Eichenbaum, 1999). The subiculum, by contrast, has received scant attention (with the single exception of Witter and Groenewegen, 1990) and will be the subject of this review.

2. Definition of the subiculum and subicular complex

The subicular complex consists of several cortical fields located between area CA1 of the hippocampus proper and the EC ventrally, and CA1 and the retrosplenial cortex, dorsally (Amaral and Witter, 1995). The 'subicular complex' is usually divided into three subdivisions, namely, the subiculum proper, the presubiculum and the parasubiculum (Witter et al., 1989, see Fig. 2). There are examples of differing subdivisions, particularly in the works of earlier investigators. Lorente de No (1934), for example, described a region between the CA1 and the subiculum which he called the 'prosubiculum'. However, many contemporary researchers (Amaral and Witter, 1995) suggest that this region is a transitional region and should not be defined separately. Brodmann (1909) recognised in several species a separate region, area 48, (regio post- or retrosubicularis), whereas more recent authors (rat, Blackstad, 1956; Haug, 1976; cat, Robertson and Kaitz, 1981) suggest that this region can be considered as part of the presubiculum. The idea that the post-subiculum (area 48), should be treated as a fourth region of the subicular complex has re-emerged through the work of Van Groen and Wyss (Van Groen and Wyss, 1990a). These authors regard the post-subiculum as ventrally and laterally bordered by the presubiculum with its border characterised by an abrupt change in cyto- and histochemical staining; the layer II cell islands of the post-subiculum are not present in the presubiculum. Van Groen and Wyss (1990b) further suggest that in the post-subiculum, layer III neurons are organised in rows parallel to the pial surface; conversely, the presubiculum displays no such organisation. Here, however, we will treat the post-subiculum as the dorsal part of the presubiculum.

There is some controversy regarding whether or not the presubiculum, parasubiculum and subiculum should be considered as a functional and anatomical grouping (Lopes da Silva et al., 1990). If one considers the EC as the major input structure of the hippocampus proper and the subiculum as the major output structure of the hippocampus proper (it receives the major output of area CA1 and in turn sends its major output to the entorhinal and other cortices; Fig. 5), then where do the presubiculum and parasubiculum fit? Furthermore, the subiculum shares with the other hippocampal subfields (CA1, CA3, etc.) the characteristic cytoarchitectonic of the allocortex, that is, three layers (see Fig. 2b), the EC by contrast is multilaminate (typically, having six layers). Both the presubiculum and parasubiculum are more similar to the EC in this respect, having deeper layers continuous with the EC. Both presubiculum and parasubiculum receive inputs from the subiculum, but these inputs are not robust and neither area seem to receive much input from the main hippocampal fields (CA1, CA3, etc.). This is in contrast to the subiculum itself, which receives a large and robust projection from CA1. However, like the EC, the presubiculum and parasubiculum receives a large, direct neocortical input. The presubiculum and parasubiculum send major projections to the superficial layers of the EC in common with most of the other sensory inputs (for example, the visual cortex) and give rise to a major portion of the perforant pathway. Finally, according to Amaral and Witter (1995) the unique feature of the presubiculum and parasubiculum is their strong association with the anterior thalamic nucleus. Thus, they may constitute a major route through which the thalamus influences the hippocampal formation. Here we will treat the subiculum as properly part of the hippocampal formation; we suggest, given the major anatomical differences in terms of intrinsic and extrinsic properties that the term 'subicular complex' does not denote a useful anatomical and, by extension, functional grouping of structures.

3. Cytoarchitectonic organisation and description of the subiculum

The description of the subiculum proper (Fig. 2a and b) has lacked consistency (Brodmann, 1909; Lorente de No, 1934; Lopes da Silva et al., 1990; Witter and Groenewegen, 1990; Taube, 1993; Amaral and Witter, 1995), but there is general agreement that the subiculum has three principal layers. These are (a) a molecular layer, which is continuous with strata lacunosum-moleculare and radiatum of the CA1 field, (b) an enlarged pyramidal cell layer containing the soma of principal neurons and finally, (c) a polymorphic layer. The cell packing in the pyramidal layer of the subiculum is looser than that seen in area CA1. The principal cell layer of the subiculum is populated with large pyramidal neurons- these are consistent in their shape and size and extend their apical dendrites into the molecular layer and their basal dendrites into deeper portions of the pyramidal cell layer. Among the pyramidal cells are many smaller neurons; these are considered the interneurons of the subiculum (Swanson et al., 1987; Amaral and Witter, 1995).

The presubiculum is distinguished from the subiculum, because it has a tightly packed pyramidal cell layer located just superficial to a cell-free zone (layers II and III), which is continuous with lamina dissecans in the EC (layer IV). These superficial layers contain small pyramidal cells. Cells located deep to layers II and III of the presubiculum are considered to be the deep layers of the presubiculum (deep to the lamina dissecans). However these layers appear to be continuous with the deep layers of the EC and the principal cell layer of the subiculum (Haug, 1976; Amaral and Witter, 1995). These are made up of both pyramidal cells

and a collection of polymorphic cells (Lorente de No, 1934).

The parasubiculum is differentiated from both presubiculum and EC because its layers II and III consist of large, lightly stained but relatively densely-packed pyramidal cells. It also has a distinctive staining for heavy metals observable with Timm's sulphide silver method (Haug, 1976). As with the presubiculum, the deeper layers are continuous with those of the EC. However, unlike the presubiculum there is no clear difference between layers II and III.

4. The anatomy and connections of the subiculum

4.1. Connections between the subiculum and the hippocampus

4.1.1. CA1 to subiculum

The subiculum is the major output structure of the hippocampus, receiving a massive input from hippocampal area CA1 (Witter et al., 1989). Amaral et al. (1991) suggest that the CA1 projection to the subiculum is organised in a simple pattern, with all portions of CA1 projecting to the subiculum, and furthermore, that all regions of the subiculum receive CA1 projections. Here, following Amaral et al. (1991), we will use the term 'proximal portion' of the CA1 region as referring to that area bordering the CA3 field and 'the distal portion' as the region of CA1 bordering the subiculum. The subiculum is similarly defined, with the proximal part bordering CA1 and the distal subiculum borders the presubiculum. The following summarises these projections (Amaral et al., 1991); cells in the proximal portion of CA1 project to the distal part of the subiculum, cells in the mid-portion of CA1 project to the middle part of the subiculum and cells in the distal portion of CA1 project just across the CA1/subiculum border into the proximal part of the subiculum. Fibers which arise in the proximal part of CA1 travel to the subiculum mainly via the alveus and the deepest portion of the stratum oriens, whereas the fibers which originate in the mid-portion of the CA1 do not enter the alveus but project to the subiculum through the deep parts of stratum oriens. The axons of CA1 cells which are located in the distal portion travel directly to the subiculum from all parts of stratum oriens (Amaral et al., 1991).

4.1.2. Subicular and pre- and parasubicular connections

There are weak back-projections from the pre- and parasubiculum to the subiculum, and there is a modest bilateral projection from presubiculum to the subiculum (Kohler, 1985). However, the subiculum gives rise to very dense projections to the pre- and parasubiculum. In the rat, these projections terminate primarily in layer I. The projections from the subiculum to the pre- and parasubiculum as well as their weak reciprocal connections appear to be arranged in a rough topographical fashion, such that the dorsal parts of the subiculum are connected to dorsal and caudal parts of the pre- and parasubiculum, while more ventral parts of the subiculum project to ventral and rostral parts of both regions (Swanson and Cowan, 1977; Witter and Groenewegen, 1990). Fig. 3 provides a summary diagram of the projections within the hippocampal formation.

4.2. Connections between the subiculum and cortex

4.2.1. Subiculum to entorhinal cortex (EC)

Projections from the subiculum to the EC have been described in the rat (Beckstead, 1978; Finch et al., 1986; Kohler, 1985; Tamamaki and Nojyo, 1995), the guinea pig (Sorensen and Shipley, 1979), the cat (Van Groen et al., 1986) and the monkey (Amaral et al., 1984). In the rat, guinea pig and monkey this projection terminates primarily in the deeper layers of the medial entorhinal

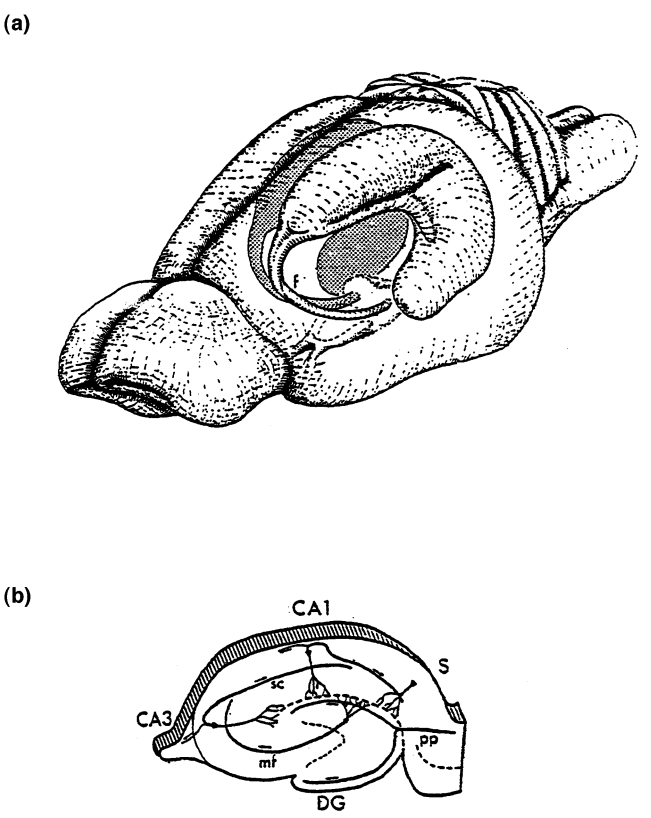

Fig. 1. (a) A three-dimensional representation of the hippocampal formation in the rat brain. (b) Line drawing of a cross-section through the hippocampal formation illustrating the major areas and projections of the hippocampus. S, subiculum; CA1 and CA3, fields of the hippocampus; DG, dentate gyrus; pp, perforant pathway; ms, mossy fibers; sc, Schaffer collaterals; f, fornix (adapted from Amaral and Witter, 1995, reproduced by permission of Academic Press).

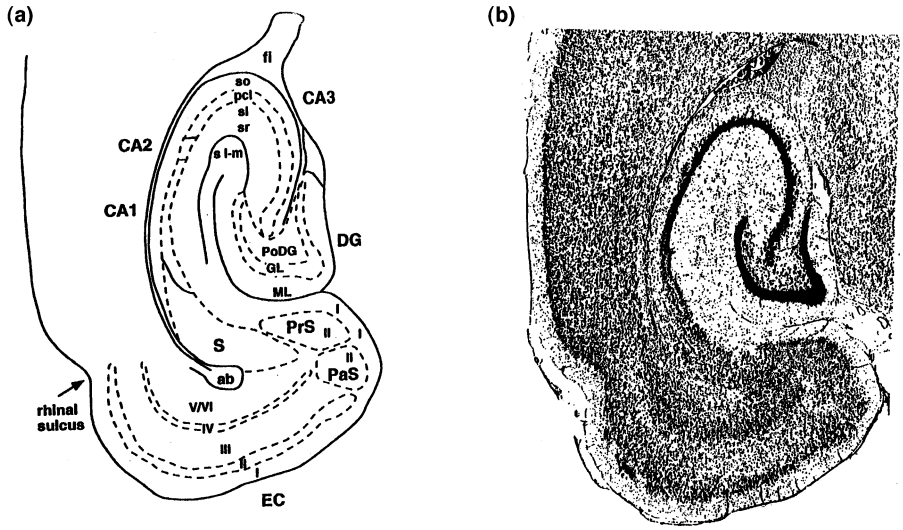

Fig. 2. (a) A line drawing of a horizontal section through the hippocampal formation indicating various regions, layers and fiber pathways. (b) A Nissel-stained horizontal section of the hippocampal formation. ab, angular bundle; PaS, parasubiculum; PrS, presubiculum; ML,Gl, and PoDG, molecular, granular and polymorphic layers of the dentate gyrus; so, stratum oriens; plc, pyramidal cell layer; sl, stratum lucidum; sr, stratum radiatum; alv, alveus; sl-m, stratum lacunosum-moleculare; fi, fimbria; EC, entorhinal cortex (adapted from Amaral and Witter 1995, reproduced by permission of Academic Press).

area, Kohler (1985) suggests that the PHA-L stained fibers radiate from the angular bundle towards layer IV, where they form a relatively dense terminal plexus. The innervation of layer IV is present throughout the dorsal-ventral axis of both the medial and lateral entorhinal area, where this layer seems to be an important route through which the subiculum can interact with entorhinal cells that project to other brain areas including the septum, the nucleus accumbens and frontal cortex. There are weaker projections to the superficial layers of the EC (Kohler, 1985; Witter et al., 1989).

Witter et al. (1990) proposed a division of the subiculum into three regions in the proximodistal dimension because of differences in its subcortical projections. They reported that only the proximal one-third of the subiculum projects to the EC. However, a more recent study by Tamamaki and Nojyo (1995) found that entorhinal projecting neurons exist along the entire proximodistal extent of the subiculum. The authors account for this opposing view by suggesting that the two accounts may be still compatible due to the fact that the subiculum is composed of heterogeneous projection neurons (Swanson et al., 1981). Furthermore Tamamaki and Nojyo (1995) suggest the proximal part of the subiculum and the distal area of CA1 project mainly to LEC, in contrast to the distal part of the subiculum and the proximal region of CA1 project mainly to MEC.

4.2.2. EC to subiculum

Although the perforant pathway fibers traverse the subiculum on their way to the dentate gyrus and the hippocampus proper, the existence of a direct projection from the EC to the subiculum has been a matter of controversy. Many authors suggest, on the basis of data from a variety of species, that the entorhinal fibers are directed towards the molecular layer of the subiculum (rat, Steward, 1976; Wyss, 1981; cat, Witter and Groenewegen, 1984; monkey, Van Hoesen and Pandya, 1975). In the rat, Witter et al. (1989) also showed that the subiculum receives a strong projection from the EC, where the fibers are directed towards restricted portions terminating in the outer two-thirds of the molecular layer. The entorhinal input to the subiculum originates in both layer II and III neurons (Steward and Scoville, 1976; Witter and Amaral, 1991), with layer II neurons terminating in all layers of the subiculum (Tamamaki and Nojyo, 1993), and synapse with primary dendrites to drive postsynaptic subicular neurons. Thus, according to Tamamaki and Nojyo (1995), the entorhinal input through CA1 field to subiculum and the direct input from EC will converge in the subiculum. These combined inputs may then be fed back through projections from the subiculum and also the CA1 field; however, the authors also state that there is no evidence that the EC input to CA1 and subiculum directly contacts cells that project to the EC.

Witter et al. (1989) suggest that injections involving the lateral subdivision of the entorhinal cortex (LEC) project strongly to the molecular layer of the proximal (adjacent to the CA1 field) subiculum, whereas injections in the medial entorhinal cortex (MEC) distribute to more distal portions of the subiculum (adjacent to the presubiculum). In contrast, Kohler (1986) did not observe any marked projections from either lateral areas of lateral and medial entorhinal cortices. The

segregation of inputs from the EC has been highlighted more recently by Witter et al. (2000) and confirms their earlier study suggesting that layer III fibres of the LEC project to the distal part of CA1 and the proximal part of subiculum (at the CA1/subiculum border), whereas MEC projects to the proximal part of CA1 and the distal region of the subiculum. Witter et al. (2000) suggest that the CA1 and subiculum system is designed in such a way so that information arising in the LEC is kept separate from information arising in the MEC.

Fig. 4 summarises the cortical and subcortical inputs to the subiculum.

4.2.3. Perirhinal cortex to subiculum

The perirhinal cortex projects directly to the subiculum in the rat (Kosel et al., 1983), in the cat (Van Groen et al., 1986) and monkey (Van Hoesen et al., 1979). Kosel et al. (1983) found that injections of an anterograde tracer in either the dorsal or ventral parts of the perirhinal cortex resulted in labelled fibers in the inner part of the molecular layer of the subiculum. Dorsally-located injections resulted in heavy labelling in the lateral part of the subiculum near the hippocampus proper, when injections were made ventrally in the perirhinal cortex, the heaviest labelling was restricted to the medial part of the subiculum, near the transition with the presubiculum. Witter et al. (1989) confirmed the topographical nature of this projection, suggesting that the caudal parts of the perirhinal cortex project to proximal parts of the subiculum, whereas more rostral parts project to more distal parts of the subiculum. Kosel et al. (1983) also found that the fibers from the perirhinal cortex which terminate in the subicular region follow the same route as the perforant pathway fibers from the EC (Steward, 1976). There has been some debate recently about the nature of the perirhinal projection to the subiculum. Based on the tracer studies above, there seem to be connections between the two structures; the existence of this projection has not been supported by physiological studies until recently. Naber et al. (1999) have shown that injections of an anterograde tracer in the perirhinal cortex have shown labelled fibres in the border area of CA1 and subiculum and present evidence that the two areas are also physiologically connected. Expanding on this, Witter et al. (2000) suggest that perirhinal cortex projects to the distal part of CA1 and the proximal region of the subiculum, that is, the CA1/subiculum border, however, the postrhinal cortex targets the proximal portion of CA1 and the distal region of the subiculum. The projections from the postrhinal cortex are much stronger to the subiculum than to area CA1, whereas the perirhinal projections are much more evenly distributed (Witter et al., 2000). Furthermore, neurons in layers II and III of both perirhinal and postrhinal cortices project to the molecular layers of area CA1 and subiculum, confirming the earlier findings of Kosel et al. (1983). Naber et al. (1999, 2000) suggest that the projections from the postrhinal and perirhinal cortices are more restricted than the entorhinal projections with regard to the origin and termination of the projections in the subiculum, these authors suggest that the EC may give rise to a projection along 20–25% of the longitudinal axis of the subiculum. Perirhinal and postrhinal projections reach about 10% of the longitudinal axis of the subiculum.

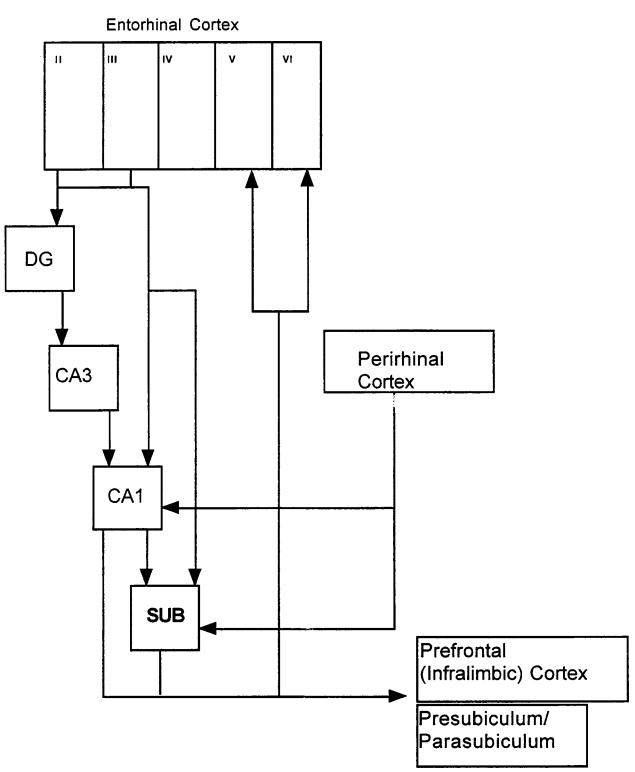

Fig. 3. This figure summarises the intrinsic connections of the hippocampal formation, and includes the recently discovered projection from the perirhinal cortex to both areas CA1 and subiculum. It can be seen that the subiculum takes inputs from entorhinal cortex and area CA1.

4.2.4. Subiculum to perirhinal cortex

The subiculum also projects to the perirhinal cortex in the rat, cat, guinea pig and monkey (Swanson et al., 1978; Sorensen and Shipley, 1979; Kohler, 1985; Van Groen et al., 1986). In the rat, Witter et al. (1990) injected an anterograde tracer (PHA-L) into cells which were located in the proximal part of the dorsal subiculum, directly adjacent to the border with CA1, and found that the labelling was located in the deep layers of the perirhinal cortex. In contrast, injections in the distal part of the dorsal subiculum do not seem to project to the perirhinal cortex, but rather to the retrosplenial and postrhinal cortices.

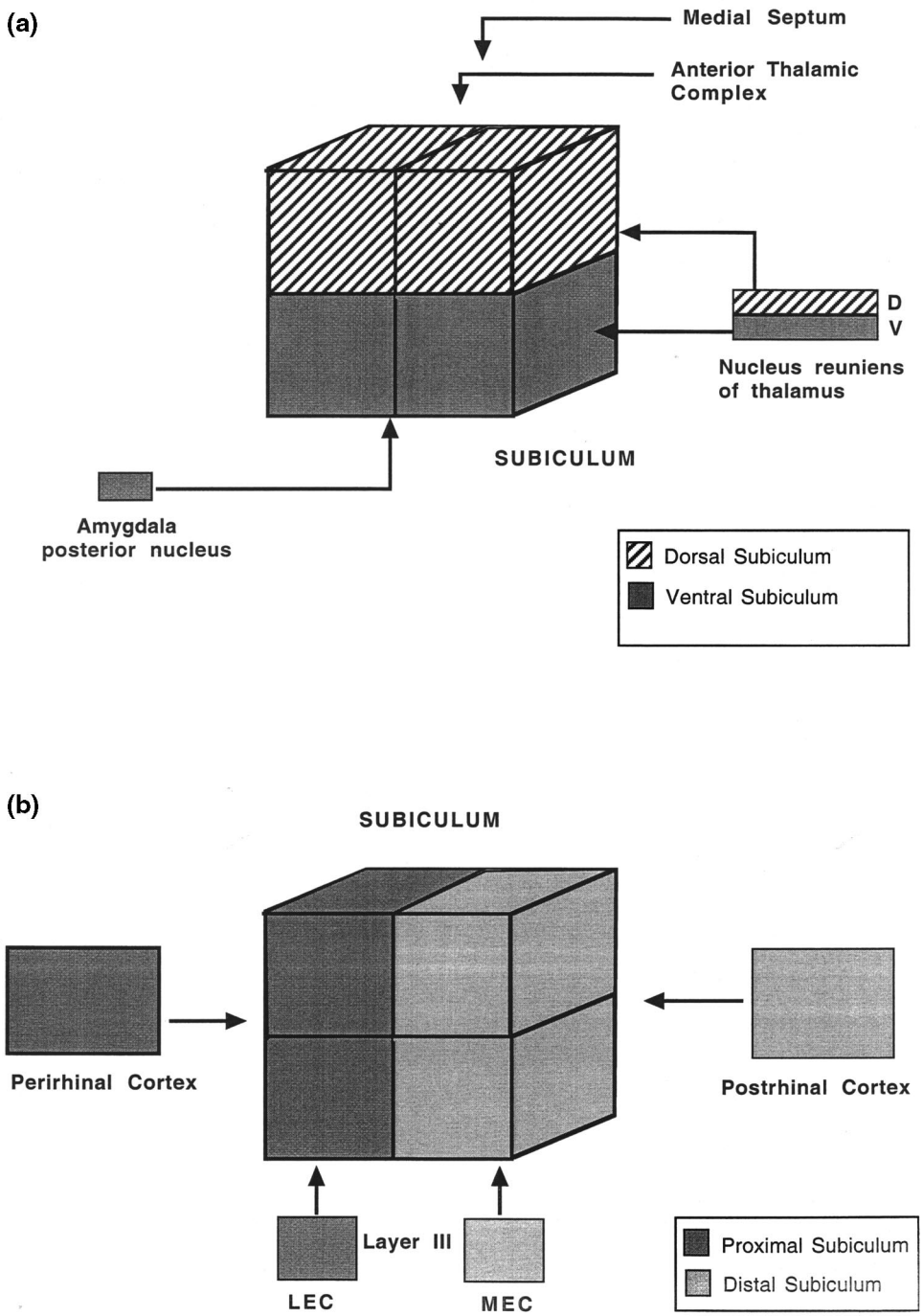

Fig. 4. Organisation of the cortical and subcortical inputs to the subiculum: (a) shows the subcortical inputs to the subiculum divided along the dorsal-ventral axis of the subiculum; (b) shows cortical inputs to the subiculum divided along the proximo-distal axis of the subiculum (LEC, lateral entorhinal cortex; MEC, medial entorhinal cortex).

4.2.5. Retrosplenial cortex

An anterograde injection in the distal part of the dorsal subiculum results in marked labelling in the retrosplenial cortex, mainly in its ventral part directly bordering the presubiculum (Witter and Groenewegen, 1990). Neither injections in the proximal portion of the dorsal subiculum nor the ventral subiculum resulted in notable labelling in the retrosplenial cortex (Witter and Groenewegen, 1990; Witter et al., 1990). No portion of the retrosplenial cortex projects to the subiculum proper (Wyss and Van Groen, 1992).

Wyss and Van Groen (1992) suggest that each subdivision of the retrosplenial cortex projects to a discrete terminal field in the hippocampal formation, with the

retrosplenial dysgranular cortex (Rdg) projecting to the dorsal presubiculum (postsubiculum) and the caudal part of the parasubiculum. The retrosplenial granular b cortex (Rgb) projects only to the dorsal presubiculum, but the retrosplenial granular a cortex (Rga) projects to the dorsal presubiculum (postsubiculum), rostral presubiculum and parasubiculum. Projections that arise from the hippocampal formation and reach the Rdg originate in the dorsal presubiculum, whilst the dorsal subiculum and dorsal presubiculum project to the Rgb, and the Rga is innervated by the ventral subiculum and the dorsal presubiculum. An earlier study by Van Groen and Wyss (1990b) suggests that the projections arising from the subiculum end predominantly in layer II of the Rga, whereas the dorsal presubiculum (postsubiculum) projects to layers I and III–V. The most prominent extra-hippocampal input to the presubiculum is the retrosplenial cortex (the second being layer V of the visual area, Amaral and Witter, 1995).

4.2.6. Prefrontal and anterior cingulate cortex

There has been some controversy over whether rats actually possess a prefrontal cortex or not (see Kolb, 1984; Preuss, 1995 for differing viewpoints). However, both clinical and experimental data indicate that the hippocampal formation and prefrontal cortex contribute to learning and memory (O'Keefe and Nadel, 1978; Fuster, 1991; Squire, 1992; Rolls and O'Mara, 1993; Kolb et al., 1994; Goldman-Rakic, 1995). Since the prefrontal cortex is reciprocally related to the sensory association areas in the parietal and temporal lobes of the hemisphere (Selemon and Goldman-Rakic, 1988), it is possible that the prefrontal cortex functions as an intermediary between limbic and neocortical regions (Jay and Witter, 1991).

Prefrontal cortex has been implicated in cognitive processes such as the temporal ordering of both spatial and non-spatial events in short-term memory and the organisation and planning of responses (Kolb, 1984; Fuster, 1991; Garavan et al., 1999, 2000). In the monkey, the subiculum projects to medial orbital areas (Carmichael and Price, 1996). These projections are also found in the rat, where the fibers distribute only to the prelimbic and the medial orbital cortices, and arise exclusively from restricted portions of CA1 and of the subiculum. The origin of these fibres is restricted to the proximal half of the subiculum. Fibers from both CA1 and subiculum have comparable distribution patterns in the prelimbic and medial orbital cortices with the density and distribution in the prefrontal cortex of the projection from the proximal portion of the subiculum, depending on the location along the dorso-ventral axis; the intermediate portion of the subiculum projecting more densely and diffusely than its dorsal and ventral portion (Jay and Witter, 1991). However, Finch (1993) suggests that it is the temporal (ventral) subiculum portion of the subiculum that projects to prelimbic, infralimbic and anterior cingulate cortices. No inputs have been reported from either prelimbic or infralimbic to the subiculum.

4.3. Connections between the subiculum and subcortical structures

4.3.1. Mammillary bodies and hypothalamus

Injections of the tracer PHA-L in the distal part of the ventral subiculum produces a densely labelled plexus surrounding the ventromedial nucleus in the hypothalamus (Witter and Groenewegen, 1990). Kohler (1990) suggests that these projections increase at successively more ventral levels of the subiculum, with the ventral tip of the region projecting to the hypothalamus via three different routes: the postcommissural fornix, the medial corticohypothalamic tract and a ventral pathway running via the amygdala. A later study by Canteras and Swanson (1992), confirms that the medial corticohypothalamic tract is the main route taken by the fibers from the ventral subiculum to the hypothalamus, where they innervate the medial preoptic area, the surround of the ventromedial nucleus, dorsomedial nucleus, ventral premammillary nucleus and the cell-poor zone around the medial mammillary nucleus. Canteras and Swanson (1992) observed that the ventral premammillary nucleus projects back to the ventral subiculum and adjacent parts of the hippocampal field CA1.

Witter et al. (1990) found that strong labelling is observed bilaterally in the mammillary nuclei, predominantly in the rostral part of the medial nucleus, following injections in the proximal part of the dorsal subiculum. Following injections in the distal part of the dorsal subiculum, both the lateral and medial mammillary nuclei displayed labelling predominantly in the caudal part of the medial nucleus and also, as with the injections in the proximal part, a few fibers were labelled in the supramammillary region and an area lateral to the lateral mammillary nucleus.

4.3.2. Amygdala

Canteras and Swanson (1992) suggests that the projections from the ventral subiculum course either obliquely through the angular bundle to innervate the amygdala, or follow the alveus and fimbria to the precommissural fornix and medial corticohypothalmic tract, where the major amygdalar terminal field is centred in the posterior basomedial nucleus and the posterior basolateral nucleus (see also Witter and Groenewegen, 1990). There is dense labelling in the basolateral nucleus of the amygdaloid complex, following injections involving cells in the proximal part of the ventral subiculum. Other structures that are innervated include the posterior cortical and posterior, central, medial intercalated nuclei and the posterior nucleus of

the amygdala; Canteras et al. (1993) suggest that one of the major efferent projections of the posterior nucleus is a group of fibers which course medially back to innervate the ventral subiculum and adjacent parts of CA1.

4.3.3. Septal complex

According to Namura et al. (1994), both the dorsal and ventral subiculum project to the lateral septum. This confirms the earlier work of Witter et al. (1990), who found projections to the septal region arising from the entire dorso-ventral extent of the subiculum and originating mainly in the proximal part. Nearly all pyramidal cells of Ammon's horn and the subiculum take part in the hippocampo-septal projection, thus implying that the other areas that are innervated by the hippocampal formation must necessarily be reached by collaterals of the hippocampo-septal fibers. The pre- and parasubiculum do not appear to contribute to the septal pathway (Lopes da Silva et al., 1990). The connections of the septal area with the hippocampal formation have been studied in great detail (for example, Chandler and Crutcher, 1983 and Alonso and Kohler, 1984). Projections from the medial septal nucleus reach all areas of the hippocampal formation, whereas those from the nucleus of the diagonal band mainly terminate in the subiculum. In the subiculum both the molecular and the pyramidal cell layer appear to be innervated by septal projections (Lopes da Silva et al., 1990). Fig. 5 and Fig. 6 sumarise the subicular projections to cortical and subcortical structures.

4.3.4. Nucleus accumbens

Witter and Groenewegen (1990) found that following injections in the proximal part of the dorsal subiculum, labelling was visible rostrolaterally in the nucleus accumbens. No labelling was seen after injections in the distal part of the dorsal subiculum. However, injections in the proximal portion of the ventral subiculum, the authors observed labelling in the caudomedial part of the nucleus accumbens. This latter finding was confirmed in a more recent study by Aylward and Totterdell (1993), who also suggest that it is the proximal neurons in the ventral subiculum which project to the nucleus accumbens.

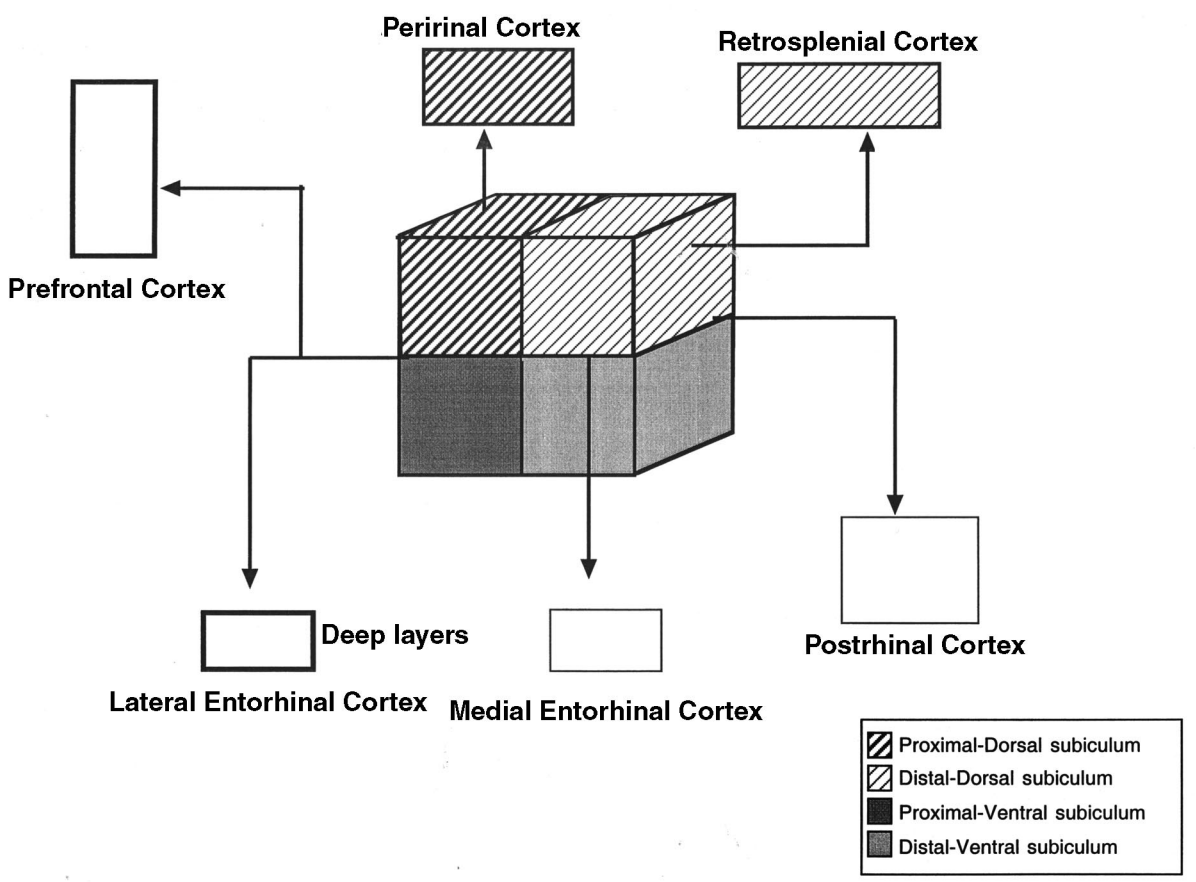

Fig. 5. Subicular projections to cortical structures. The subiculum is divided into four areas (proximal-dorsal, distal-dorsal, proximal-ventral, distal-ventral) with each area projecting to specific cortical targets. Note the perirhinal and lateral entorhinal cortices receive projections from the proximal subiculum and the postrhinal and medial entorhinal cortices receive projections from the distal subiculum, without the dorsal-ventral discrimination.

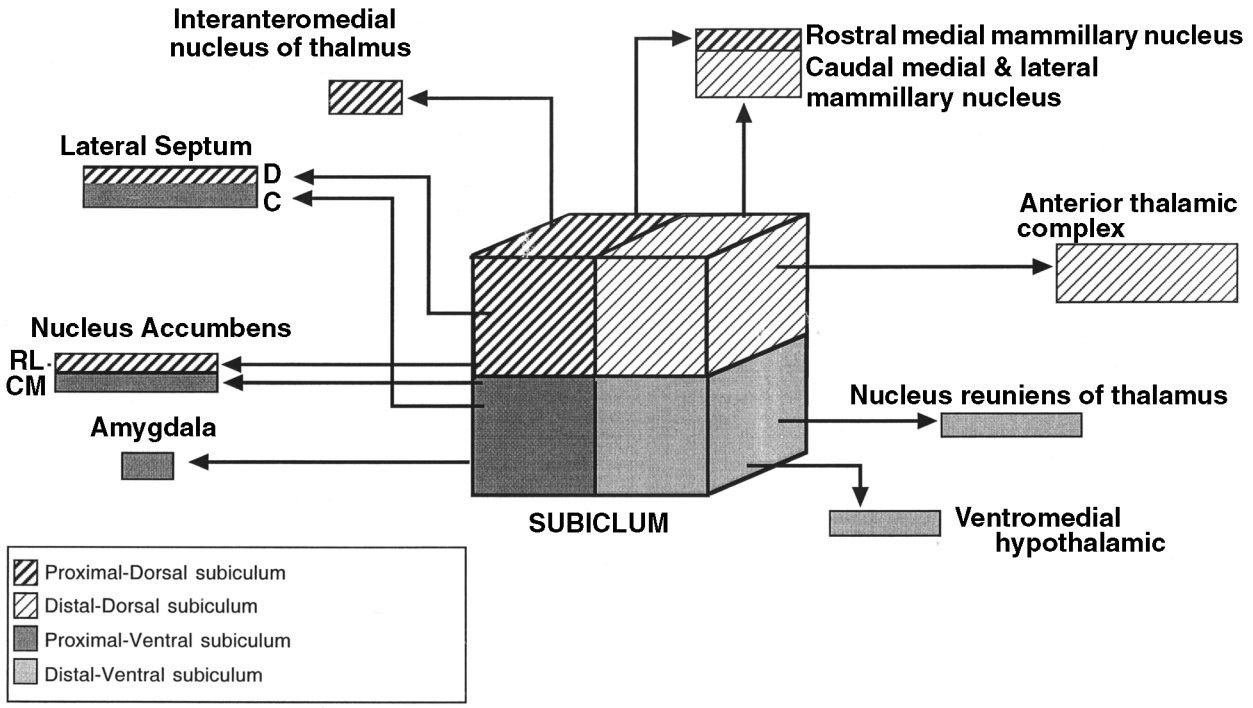

Fig. 6. Subicular projections to subcortical structures. The subiculum is divided into four areas (proximal-dorsal, distal-dorsal, proximal-ventral, distal-ventral). Each subcortical structure receives information from a specific subicular area. D, dorsal; V, ventral; RL, rostrolateral; CM, caudomedial.

4.3.5. Nucleus reuniens of the thalamus

The projections from the subiculum to the nucleus reuniens have not been well documented. In one study, Witter and Groenewegen (1990) found labelled fibers in the nucleus reuniens after injections in the distal part of the ventral subiculum. Wouterlood et al. (1990) found terminal labelling is most dense in the molecular layer of the ventral part of the subiculum, following anterograde injections in the nucleus reuniens, furthermore, the organisation of the fibers seems to be topographic, so that the dorsal nucleus reuniens projects predominantly to the dorsal subiculum, whereas the ventral nucleus reuniens projects predominantly to the ventral subiculum. Zheng (1994) also found that, following PHA-L injections in the nucleus reuniens, fibers terminate mainly in the molecular layer of the subiculum, presubiculum and parasubiculum.

4.3.6. Anterior thalamic complex and interanteromedial nucleus of thalamus

Witter and Groenewegen (1990) found that irrespective of the proximo-distal location of the injections in the ventral subiculum, anterograde labelling in the anterior nuclei of the thalamus or in the interanteromedial nucleus is extremely weak or absent. This compares with the study of Witter et al. (1990) who found that injections of an anterograde tracer in the proximal dorsal subiculum resulted in labelling of the interanteromedial nucleus of thalamus, whereas injections in the distal subiculum gave rise to fibers in the anterior thalamic complex. In a study of the laminar distribution of direct projections from the anterior hypothalamic nuclei to the retrohippocampal region by Shibata (1993), it was found that the anteromedial nucleus (AM) projects to the subiculum whereas the interanteromedial nucleus (IAM) appeared to project to non-subicular regions including the perirhinal and entorhinal cortices. The anteroventral nucleus (AV) projects to the subicular complex with a complex topographic organisation, with the most rostral part of the AV projecting to layers I and III of the ventral presubiculum and the pyramidal cell layer of the subiculum and the deep layers of the parasubiculum. At the mid-rostrocaudal level of AV the lateral parts of the AV projects to layers I and III while the dorsal part projects to layer I and IV–VI of the ventral presubiculum whereas the ventral part of the AV projects to layers I and III and the medial part projects to layers I and IV–VI of the dorsal presubiculum. Furthermore, Shibata (1993) also suggests that all areas of the AV project to the pyramidal cell layer of the subiculum. At the caudal level, the dorsolateral part of the AV projects to layers I and III of the presubiculum and a patchy pattern to the pyramidal cell layer of the subiculum. The anterodorsal nucleus (AD) projects mainly to the deep layers of the pre- and parasubiculum. Van Groen and Wyss (1995) confirmed this finding and suggest that both AD and AV project densely to the

pre- and parasubiculum and lightly to the EC and the subiculum proper. The authors further suggest, that compared to the AD, neurons in the AV have a less extensive projection to the subiculum.

5. The neurophysiology of the subiculum

5.1. In vitro studies

5.1.1. Electrotonic properties of subicular neurons

There have been relatively few detailed studies on the intracellular properties of subicular neurons. Taube (1993) and Stewart and Wong (1993) suggest that pyramidal neurons in vitro can be divided into two groups based on their responses to intracellular current injection and orthodromic stimulation. The first group of neurons ('bursting' neurons) respond with a brief burst of action potentials during the initial 40 ms, with each burst containing 3–5 action potentials embedded in a depolarising envelope, which is followed by 20–30 ms period when neurons do not discharge. This nondischarge period is associated with hyperpolarisation of the membrane and is referred to as 'hyperpolarising afterpotential' and is distinct from after-hyperpolarisation, which occurs at the end of the current pulse. These neurons showed little spontaneous activity at the resting membrane potential. During the last 30–40 ms neurons discharge single action potentials. The second type of neurons ('regular-firing' neurons) respond to depolarising current with firing of single action potentials throughout the current pulse.

There is a general consensus that there are more bursting than non-bursting neurons in the subiculum, although the estimated proportions vary from paper to paper (see Table 1). Taube (1993) suggests that in the rat the ratio is approximately 73–27% in favour of bursting neurons, whereas Behr et al. (1996) put this figure at 54–46% in favour of bursting cells. Mason (1993) estimates that 74% of neurons are bursting cells. In the guinea pig, 66% of subicular neurons are thought to be bursting (Stewart and Wong, 1993). Greene and Mason (1996), suggest that bursting cells are more prominent in the deep cell layers of the subiculum, whereas regular-firing neurons are more numerous in the superficial cell layers. In addition, bursting and regular-firing cells can be localised to definite regions of the ventral subiculum: 52% of neurons in the central column were regular-firing neurons compared with 16% in the proximal portion and 10% in the distal region (Greene and Totterdell, 1997). Bursting cells may be involved in amplification of signals which might facilitate the processing of information. Bursting cells may also be involved in the generation and spread of convulsive activity (Behr et al., 1996).

There are no obvious differences in either the measured membrane characteristics or cable properties of bursting and regular firing subicular neurons (see Table 1). Behr et al. (1996) found that bursting neurons are significantly different to regular firing cells with respect to their resting membrane potentials (the bursting neurons being more negative). Regular firing neurons also display both a fast and slow after-hyperpolarisation (AHP) following an action potential, whereas bursting neurons show only a slow AHP. In a comparison of CA1 and subicular neurons from the same slice, Mason (1993) found that the values for spike duration are significantly smaller in subicular neurons. No other significant difference was found between the various membrane properties assayed.

A single-spiking mode can be induced in bursting cells as a result of a depolarising injection which shifts the from resting potential to approximately -60 mV in the guinea-pig (Stewart and Wong, 1993); in the rat, tonic firing replaces bursting modes at membrane potentials at values less negative than -55 mV (Mattia et

Table 1
This table presents a summary of the published membrane properties of subicular neurons from a number of different authors[a]

Report	Species	Cell-type	RMP (mV)	AHP amplitude (mV)	AHP latency (ms)	Spike threshold (nA)	Spike duration (ms)
Taube (1993)	Rat	B = 53	-67.47 ± 0.77	4.03 ± 0.2	30.1 ± 0.89	0.133 ± 0.015	
		R = 20	-66.47 ± 1.05	3.50 ± 0.44	33.6 ± 2.29	0.165 ± 0.029	
Mason (1993)	Rat	Average = 33	-64 ± 5			15 ± 3mV	1.2 ± 0.1
Stewart and Wong (1993)	Guinea pig	B = 49	-66.9 ± 4.9				
		R = 23	-69.4 ± 6.3	3.0 ± 1.3	2.2 ± 5.0	55.2 ± 8.0	0.73 ± 0.12
Behr et al. (1996)	Rat	B = 46	-67.0 ± 6.8	3.0	24 ± 10.3	$53..3 \pm 8$	0.70 ± 1.12
Mattia et al. (1997a)	Rat	B = 102	-66.1 ± 6.2				
Mattia et al. (1997b)	Rat	B = 85	-65.7 ± 5.8	2.7 ± 0.6			

[a] B, bursting cell; R, regular firing cell; RMP, resting membrane potential; AHP, after-hyperpolarisation.

al., 1997b; Mason, 1993). Conversely, hyperpolarisation of non-bursting cells does not convert them to bursting cells (Stewart and Wong, 1993). The firing pattern during a long depolarising current pulse (i.e., burst followed by single spiking) and voltage dependence of the burst discharge (i.e., the loss of burst firing with depolarisation) is not unique to the subiculum and is similar in layers IV and V of sensorimotor cortex, cingulate cortex (McCormick et al., 1985) and EC (Jones and Heinemann, 1988). In the hippocampus, CA3 pyramidal cells generally exhibit a burst discharge without the subsequent single spiking action (Wong and Prince, 1978). The burst firing mode of CA3 also appears to be resistant to depolarisation requiring the membrane to reach -55 mV before converting to single-firing pattern (Stewart and Wong, 1993).

5.1.2. Responses of subicular neurons to afferent stimulation

Electrical stimulation from several different areas of the hippocampal slice is reported to evoke synaptic responses in the two types of subicular neurons. No differences were observed between the two types of cells with regard to their responses (Taube, 1993). Stimulation of different areas within CA1 (stratum radiatum, stratum pyramidale, stratum oriens and alveus) evokes an field excitatory post-synaptic potential (fEPSP) in subicular neurons and this fEPSP is followed by a longer-lasting IPSP, which has a reversal potential. The IPSPs are quite often biphasic having both early and late components. Iontophoretic application of GABA could evoke hyperpolarisations similar in nature to IPSPs seen following stimulation of CA1. This suggests that these IPSPs are mediated by GABAergic transmission, possibly acting through the activation of both GABAa and GABAb postsynaptic receptors as has been suggested for other hippocampal areas. In some cases, IPSPs are evoked without fEPSPs. At higher levels of stimulation in any of the CA1 areas, one or more action potentials arise from an fEPSP. Multiple action potentials are also triggered at high levels of stimulation in bursting neurons. Other areas of the hippocampal formation produce different subicular responses, a small depolarising response is observed when area CA3 is stimulated, there is no response to dentate gyrus stimulation, stimulation of the presubiculum produces fEPSPs or antidromic spikes at high levels of stimulation. The fEPSPs produced by CA1 or presubiculum are reduced by CNQX, thus suggesting fEPSPs are glutamatergic with distinct AMPA and NMDA components. The depolarising envelope seen in bursting neurons is likely to be a calcium-dependent as this was resistant to application of TTX (Taube, 1993).

Following intracellular and field potential recordings of rat subicular neurons in vitro, Stewart (1997) demonstrated that a number of bursting cells were antidromically activated in response to stimulation of both the superficial and deep layers of the presubiculum, but never when the deep layers of the medial EC were stimulated. In contrast, regular firing subicular neurons were antidromically-driven when the deep layers of the medial EC were stimulated but not when the presubiculum was stimulated. After a single stimulation of either entorhinal, presubiculum or CA1, short-latency (<5 ms) fEPSPs were evoked in both regular and bursting subicular cells. In contrast, long-latency (>10 ms) fEPSPs were only observed in both subicular cell types following stimulation of the presubiculum and not of CA1 or EC. Stewart (1997) suggests that the output of the two cell types may be different with bursting neurons projecting to the presubiculum and regular firing neurons projecting to the EC.

Intracellular recordings from subicular cells following stimulation of layer III of the medial EC produced a combination of short-latency excitatory and inhibitory responses (Behr et al., 1998). Inhibition was blocked using GABA antagonists and the isolated AMPA or NMDA components of subicular neurons were evoked. Following simultaneous activation of alvear fibres and the layer III entorhinal projection subicular fEPSPs were augmented, while delayed stimulation of alvear fibres after activation of the EC produced a weak inhibition of fEPSPs in the subiculum (Behr et al., 1998).

5.1.3. In vitro investigations of the plasticity of subicular synaptic transmission

There are very few studies examining synaptic plasticity in the rat subiculum in vitro: Boeijinga and Boddeke (1996) stimulated the CA1/subiculum border and recorded from the middle portion of the pyramidal layer in the subiculum. Application of theta-patterned stimulation (8 theta-like bursts at 5 Hz, each composing of 4 pulses at 100 Hz) induced robust long-term potentiation in vitro in 14/20 experiments. A clear potentiation ($97 \pm 15\%$) of population spike amplitude was found, which lasted for at least 30 min. Following a second stimulation a further potentiation of $35 \pm 12\%$ was found. This long-term potentiation (LTP) was suggested to be NMDA-receptor mediated (Boeijinga and Boddeke, 1996). Dolen and Kauer (1998) recorded a combination of field EPSP and population spike responses in the external plexiform layer of the subiculum following stimulation of the pyramidal layer of area CA1. Paired-pulse facilitation at the 50 ms interval was found. Following two trains of theta-burst stimulation (a train of 4 pulses at 100 Hz repeated every 200 ms, repeated ten times), LTP was induced that lasted for 20 min (field EPSPs stood at $164 \pm 12\%$ of baseline). This potentiation however, decreased to $115 \pm 7\%$ of baseline 60 min post-stimulation. These authors also suggest that LTP in the subiculum is NMDA receptor-medi-

ated. Methot et al. (1997) demonstrated that tetanic stimulation (frequency = 100 Hz, duration = 1 s) of the stratum radiatum of area CA1 produces long-term potentiation in dorsal subiculum, whereas the same stimulation produces long-term depression in the ventral subiculum. In both cases the changes in amplitude were long-lasting (> 1 h).

5.2. In vivo studies

5.2.1. Anaesthetised preparations: field potential and unit studies of the subiculum

Van Groen and Lopes da Silva (1986) studied the anatomy and physiology of the connections between the EC and subiculum of the cat. Stimulation of the lateral EC elicited the largest fEPSP in the septal part of the subiculum, whereas stimulation of the medial EC produced the largest response in the temporal part of the subiculum. Field potentials were maximally positive in the subicular pyramidal layer and maximally negative in the subicular molecular layer. Van Groen and Lopes da Silva (1986) also studied the 'return' pathway from the subiculum to the EC. Stimulation of the septal subiculum evoked the largest response in the laterocaudal EC; temporal subicular stimulation evoked the largest response in the mediocaudal EC. These physiological data support the conclusion that connections between the EC and subiculum in the cat are reciprocal. Bartesaghi and Gessi (1986) evoked responses in the subiculum of the guinea pig through a polysynaptic mode of excitation; inputs to EC were electrically stimulated, causing activation of the perforant pathway and excitation of its hippocampal targets. These authors suggest that, at least in the guinea pig, maximal activation of the subiculum arises from afferent drive from CA3 with little or no influence from CA1 afferents (as subicular responses could be recorded in the absence of CA1 activation). No consideration was given to the direct subicular input from the EC. This stands in marked contrast to results from the rat where the major influence of subicular activity appears to be from field CA1. Bartesaghi and Gessi (1986) propose that the difference might be explained in terms of interspecies anatomical differences, with the guinea pig CA3 having a much stronger input to the subiculum compared to the rat. The CA3 input to subiculum is also much larger in the rabbit compared with the rat, suggesting that the guinea pig hippocampal formation may be more similar to the rabbit than the rat (Bartesaghi and Gessi, 1986).

Commins (1998) examined fEPSPs evoked in the subiculum following stimulation of different sites by a bipolar stimulating electrode en route to hippocampal area CA1 of the rat in vivo. Stimulating electrodes were aimed at area CA1 and the recording electrodes at the dorsal subiculum. After passing the primary visual cortex and the corpus collosum, the electrode was allowed to settle in the dorsal subiculum (see Fig. 7, open circle). The stimulating electrode was then lowered slowly towards area CA1 of the hippocampus (see Fig. 7, closed circles). Stimulation of the overlying cortex (either sensory or parietal cortex) did not produce a subicular response, as would be expected (see Fig. 7). The first subicular response was produced at the border of the cortex and the cingulum (see Fig. 7c (2)). A large response was observed at the border of the cingulum and the alveus. This was characterised by a positive-going deflection in the subiculum (see Fig. 7c (3)). As the electrode was lowered further, it entered CA1 stratum oriens; the response at this point was characterised by a potential reversal. A large negative-going deflection was observed as the electrode lowered to the deeper parts of the oriens layer and the pyramidal layer of area CA1 of the hippocampus (see Fig. 7c (4,5)). The negative-going response observed in the subiculum after stimulation of the deeper layers of the stratum oriens and the pyramidal cell layer of the hippocampus confirms the anatomical connection between the two structures. Fibers which arise in the proximal part of the CA1 travel to the subiculum mainly via the alveus and the deepest portion of the stratum oriens, whereas the fibers which originate in the mid portion of the CA1 do not enter the alveus but project through the deep parts of the stratum oriens. The axons of CA1 cells which are located in the distal portion travel directly to the subiculum from all parts of the stratum oriens (Amaral et al., 1991).

Gigg et al. (1997, 2000) examined subicular neuronal responses to CA1 and lateral EC activation. Stimulation of CA1 produced excitation-inhibition sequences in bursting and non-bursting principal cells and multipolar cells (presumed inhibitory neurons). The predominant subicular response to EC stimulation was weak inhibition, suggesting that EC bypass the hippocampus, modulating the output of the subiculum and thus hippocampal-cortical interaction. A subset of responsive neurons were injected with biocytin for morphological analysis. These cells were either pyramidal-like or multipolar. The multipolar cell response to CA1 stimulation was excitation followed by long-duration inhibition; the response to EC stimulation was inhibition only. Thus, multipolar cells also receive inhibitory inputs. The lack of excitation to EC stimulation in multipolar neurons suggests EC-evoked inhibition is produced by inhibitory inputs arising outside subiculum. Multipolar neuronal responses varied, suggesting that such cells may be classified by response characteristic.

5.2.2. In vivo investigations of the plasticity of subicular synaptic transmission

Paired-pulse facilitation (PPF) is the phenomenon whereby the fEPSP to a second stimulus is enhanced

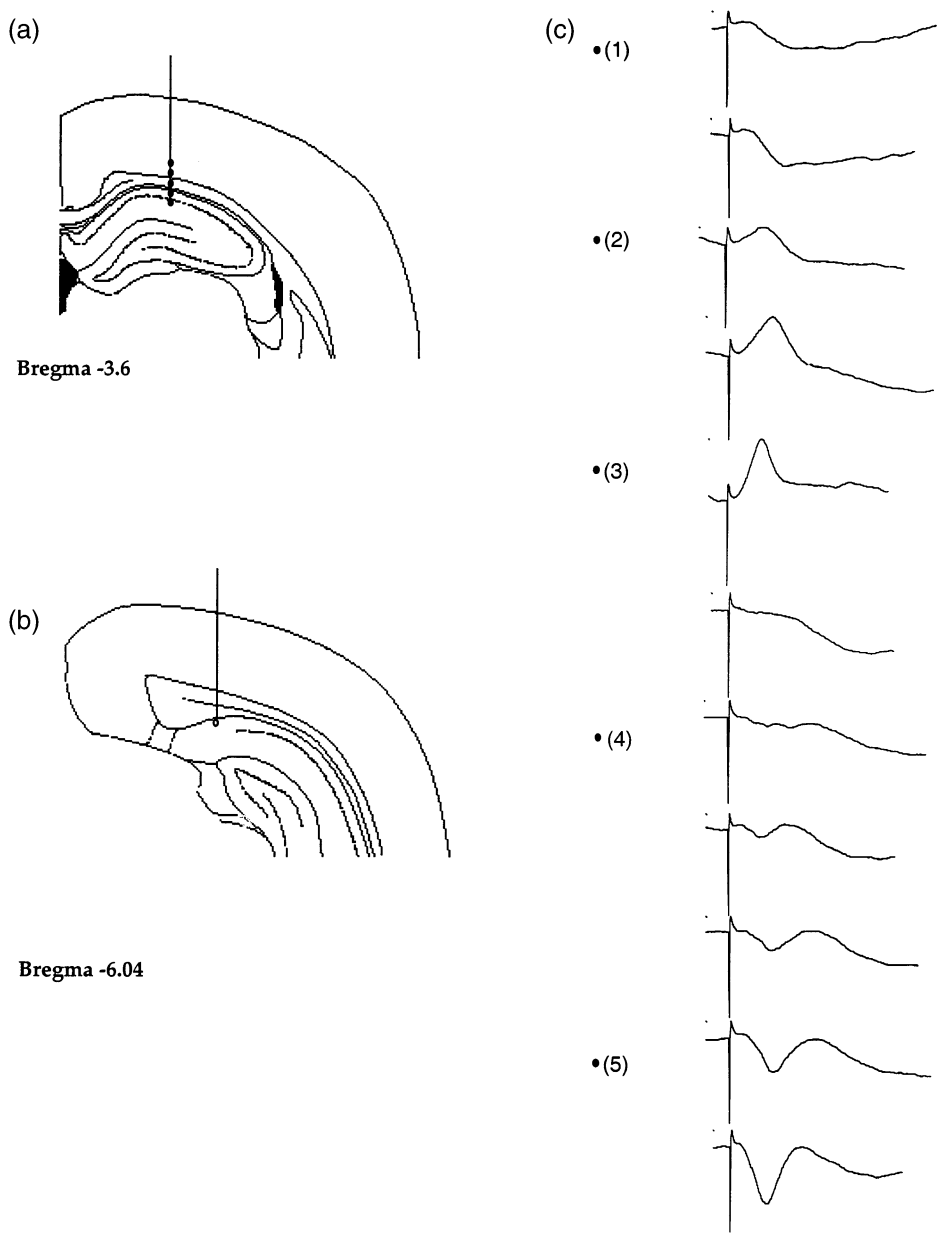

Fig. 7. Depth profile of subicular fEPSPs following stimulation in area CA1. (a) and (b) indicate the positions of stimulating and recording electrodes located in area CA1 and subiculum, respectively. (c) A plot of fEPSPs following stimulation in successive locations as the stimulating electrode is moved towards area CA1 of the hippocampus.

relative to the first, if the second stimulus is delivered relatively quickly after the first (Zucker, 1989). PPF is perhaps the most elementary form of synaptic plasticity; it is thought to be primarily a presynaptic phenomenon, resulting from a transient increase in calcium levels in the presynaptic terminal caused by the first stimulus elevating the response to the second stimulus (Wu and Saggau, 1994). Most synapses display a short-term facilitation (Zucker, 1989). The residual calcium hypothesis of Katz and Miledi (1968) suggests that PPF is due to a non-linear dependence of transmitter release upon intracellular calcium concentration; after a presynaptic action potential, some residual calcium persists at sites of transmitter release (Zucker, 1989). Commins et al. (1998b) found reliable and robust PPF in the CA1-subiculum pathway across a range of interstimulus intervals (ISI) from 10 ms to 500 ms; PPF reached a maximum at 50 ms. No PPF was found at a 1000 ms ISI (see Fig. 8). These results demonstrated for the first time that the CA1-subiculum pathway shows PPF. PPF may act to increase the reliability of synaptic transmission by ensuring that signals which occur in rapid succession are amplified, thus increasing the signal-to-noise ratio of an input, reducing the possibility that a

signal is lost against a noisy background (Commins et al., 1998b). The selectivity of response for particular stimulus intervals may also reduce the probability of random inputs firing their postsynaptic contacts.

5.2.2.1. Long-term potentiation. Long-term potentiation (LTP) is a long-lasting increase in synaptic efficacy resulting from a brief train of high-frequency stimulation (HFS) of afferent fibres. This phenomenon has

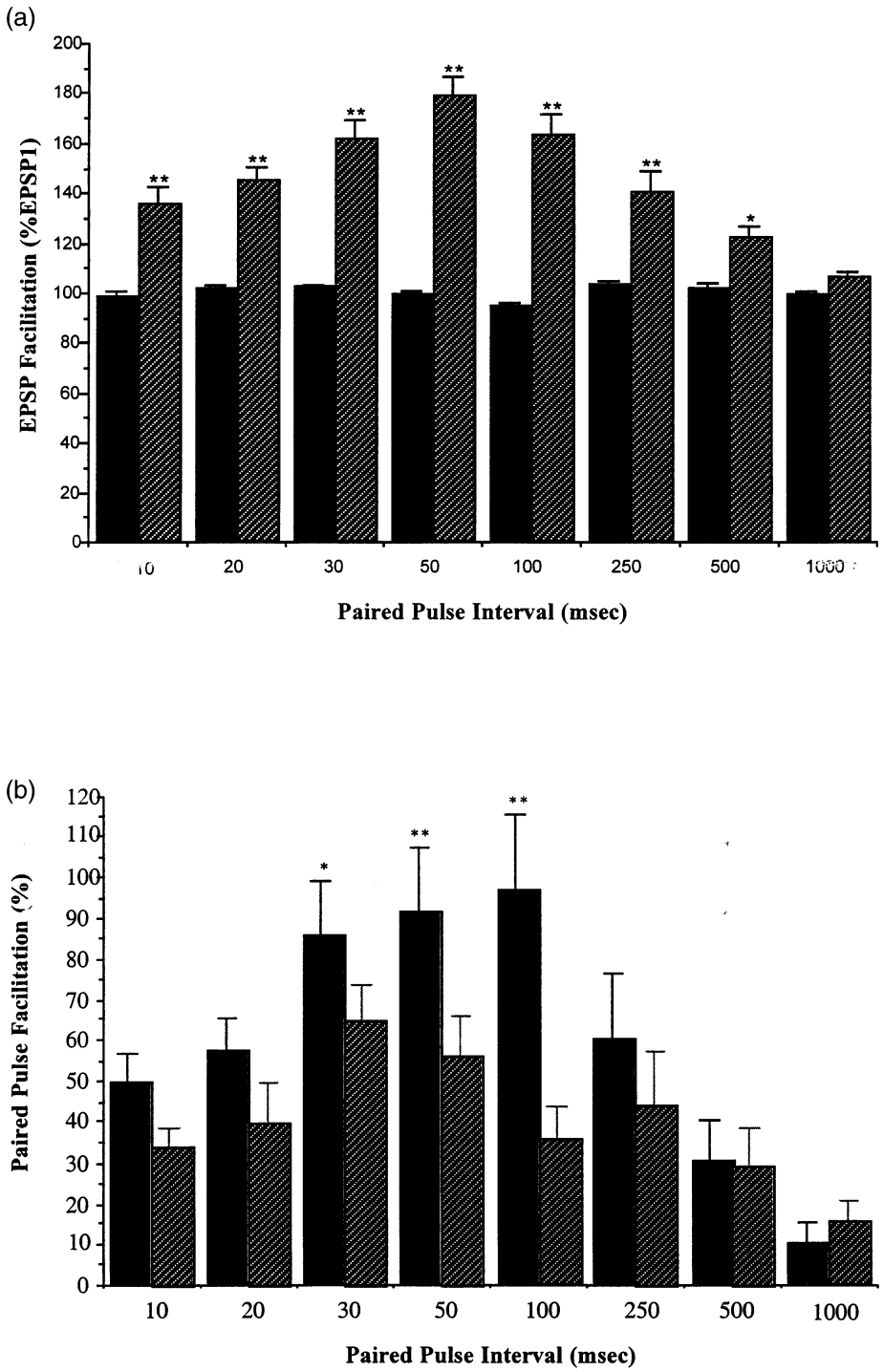

Fig. 8. (a) Paired-pulse facilitation in the CA1-subiculum pathway for the intervals indicated. Bars represent mean peak amplitude for fEPSP1 (black) and fEPSP2 (hatched) (** $P < 0.01$, * $P < 0.05$). Data are normalised to fEPSP1 (100%). (b) Changes in PPF after LTP was induced. Mean PPF before (black) and after (hatched) HFS that induced LTP (** $P < 0.01$, * $P < 0.05$).

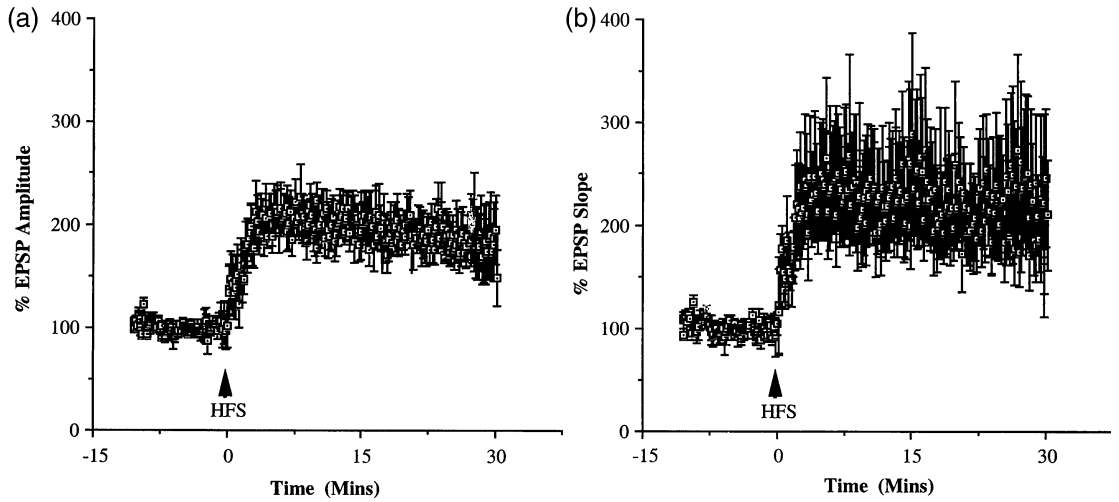

Fig. 9. Long-term potentiation in the CA1-subiculum pathway. Effects of high-frequency stimulation (HFS) on the amplitude (a) and the slope (b) of fEPSPs. In both the cases the post-HFS fEPSP values are expressed as a percentage of the pre-HFS baseline.

been investigated as a possible model for the synaptic changes that occur during learning and memory (Bliss and Lomo, 1973; Bliss and Collingridge, 1993). LTP was first described in the perforant pathway of the hippocampal formation (Bliss and Lomo, 1973), a structure critically involved in learning and memory (Squire, 1992; Rolls and O'Mara, 1993; Nadel and Moscovitch, 1997). Commins et al. (1998a, 1999) examined if LTP occurs in the projection from CA1 to the subiculum in vivo. A rapidly-stabilising potentiation was induced in the CA1-subiculum pathway using high-frequency stimulation (see Fig. 9). Additional experiments showed that potentiation once induced remains unchanged after three hours using the above HFS protocol (Commins et al., 1999). Furthermore, once the CA1 to subiculum pathway is potentiated, it seems resistant to further episodes of HFS (Commins et al., 1999). Commins et al. (1999) also examined the efficacy of theta-burst stimulation (TBS) for LTP induction; this is a more biologically-realistic pattern of stimulation. After TBS, the level of potentiation, measured by fEPSP amplitude, stood at $118.39 \pm 4.5\%$ (relative to baseline), 5 min post-stimulation. Potentiation remained stable over a 30 min period as demonstrated by the fEPSP amplitude at both 15 min and 30 min post-stimulation, which were $116.25 \pm 1.9\%$ and $116.88 \pm 4.2\%$, respectively. PPF decreased significantly in magnitude post-LTP induction across the middle range of ISI values tested (30, 50 and 100 ms; see Fig. 8b; Commins et al., 1998b). There was a positive linear relationship between the initial PPF and the magnitude of LTP obtained in this pathway that varied as a function of ISI. The initial PPF value at a 100 ms ISI correlated more highly with subsequent LTP magnitude compared to the 50 ms ISI; initial PPF and the change in PPF post-LTP was negatively correlated. These data also demonstrate the predictive validity of examining more than one time interval when investigating PPF-LTP interactions; longer intervals predict more precisely the probability of inducing LTP.

5.2.2.2. Long-term depression in the subiculum. Long-term depression (LTD) of synaptic transmission is the persistent decrease in amplitude and slope of evoked field excitatory postsynaptic potentials (fEPSPs) below the level observed in naïve pathways, as a result of repeated low-frequency stimulation (LFS) of the pathway. Like LTP, LTD is regarded as a model of information storage in the mammalian central nervous system (Heynen et al., 1996). Anderson et al. (2000) found no evidence of LTD induction in the CA1-subiculum pathway using two low-frequency stimulation (LFS) protocols (900 stimuli delivered at 1 or 10 Hz) and two two-pulse stimulation (TPS) protocols (450 pairs of stimuli; interpulse intervals (IPIs) of 5 or 40 ms). Indeed, with LFS delivered at 1 Hz and using either TPS protocol, a 'late-developing' potentiation of synaptic transmission was observed instead (at 30 min post-1 Hz LFS, fEPSP amplitude was $115.8 \pm 4.7\%$; at 30 min post-TPS with 5 ms IPI fEPSP amplitude was $114.96 \pm 1.36\%$; at 30 min post-TPS with 5 ms IPI fEPSP amplitude was $118.91 \pm 4.10\%$. This potentiation begins to appear reliably some 10–15 min post-LFS and plateaus at about 25–30 min post-LFS. There was no change in fEPSPs after the administration of the 10 Hz protocol. Fig. 10 presents these data reanalysed from Anderson et al. (2000); it is clear from this figure that the initial depression observed at 5 min post-LFS changes quickly to a modest but significant potentiation 30 min post-LFS in 3 of the 4 protocols tested (except 10 Hz LFS).

5.2.2.3. Interaction between LFS and PPF. The locus of change after LTP induction has been the subject of much debate; it is still a matter of controversy whether LTP is primarily a presynaptic or a postsynaptic phenomenon or some combination of the two (Bliss and Collingridge, 1993). One method of determining the extent to which presynaptic or postsynaptic factors predominate in LTP is to examine the interaction between PPF and LTP (see Section 5.2.2.1). Anderson et al. (2000) found that stimulation of the CA1-subiculum pathway with low-frequency stimulation (LFS: 10 Hz, 900 pulses) does not lead to LTD of synaptic transmission (see above). Commins and O'Mara (2000) found that LFS treatment markedly increased PPF, but that it had no effect on baseline synaptic transmission. It may, therefore, be possible to dissociate the regulation of baseline synaptic transmission from paired-pulse stimulation of the CA1-subiculum pathway. They measured PPF pre-LFS using 50 ms and 100 ms ISI's. For the 50 ms ISI, the increase of the second fEPSP compared to the first was $31.41 \pm 2.8\%$; at the 100 ms ISI, facilitation was slightly less at $23.36 \pm 1.7\%$. The induction of LTD was then attempted by LFS (900 pulses at 10 Hz). Initially there was a depression in synaptic response: fEPSP amplitude stood at $68.56 \pm 10\%$ of baseline 5 min post-LFS. The response recovered back to baseline levels over 15 min (see Fig. 11a). PPF was then measured at the end of the recording period for the two intervals; for the 50 ms ISI the percentage increase of the second fEPSP compared to the first was found to be $44.99 \pm 5.3\%$ and at the 100 ms ISI the percentage facilitation was again less at $38.88 \pm 4.8\%$; there was a significant and unexpected increase in facilitation post-LFS at both the 50 ms and 100 ms ISIs (see Fig. 11b).

5.2.2.4. Interactions between paired-pulse facilitation, low-frequency stimulation and stress in the subiculum. LTD has been typically difficult to induce in vivo (Doyere et al., 1996). One method which does successfully induce LTD effectively in vivo in hippocampal area CA1 is to behaviourally stress the animal for 30 min prior to the commencement of the experiment (Xu et al., 1997). Commins and O'Mara (2000) examined if LTD can be obtained using this protocol in the subiculum. Animals were stressed for 30 min prior to anaesthetisation by placing them in a novel, brightly-lit, elevated environment. For the 50 ms ISI, the percentage increase of the second fEPSP compared with the first was $49.74 \pm 4.03\%$; at the 100 ms ISI, the percentage facilitation was less at $14.16 \pm 2.2\%$. The induction of LTD was then attempted by LFS (900 pulses) at 10 Hz. Initially there was a depression in synaptic response (fEPSP amplitude stood at $43.01 \pm 13.4\%$ of baseline 5 min post-LFS). At the end of the 30 min recording period fEPSP amplitude stood at $89.77 \pm 13.1\%$ of baseline, suggesting that some LTD was present (see Fig. 11c). PPF was measured at the end of the recording period: for the 50 ms ISI, the percentage increase of the second fEPSP compared to the first was found to be $3.89 \pm 5.49\%$. There was evidence of paired-pulse depression (PPD) at the 100 ms ISI; the percentage depression was found to be $-20.32 \pm 6.65\%$ (see Fig. 11d). Thus, there was an interaction between behavioural stress and LFS: the consequence of this treatment was to dramatically reduce the magnitude of PPF or convert PPF to PPD, depending on the ISI examined.

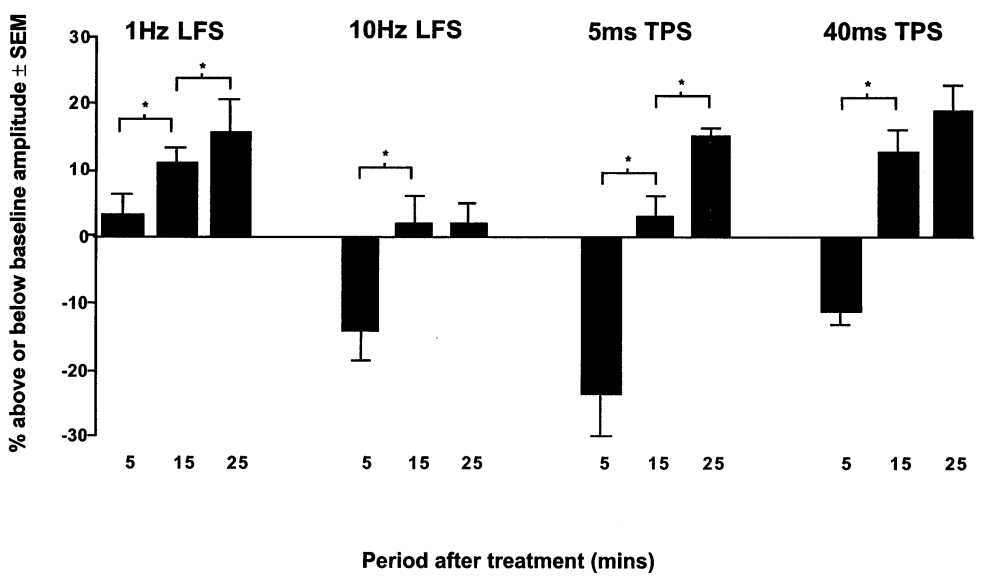

Fig. 10. The effects of two low-frequency stimulation protocols (1 and 10 Hz) and sustained two-pulse stimulation (450 pairs of stimuli with either 5 ms or 40 ms ISI). The data are in 5 min bins for 0–5 min, 15–20 min and 25–30 min. A late-developing potentiation is clearly seen in the displays for 1 Hz LFS, 5 ms TPS and 40 ms TPS (* $P < 0.01$).

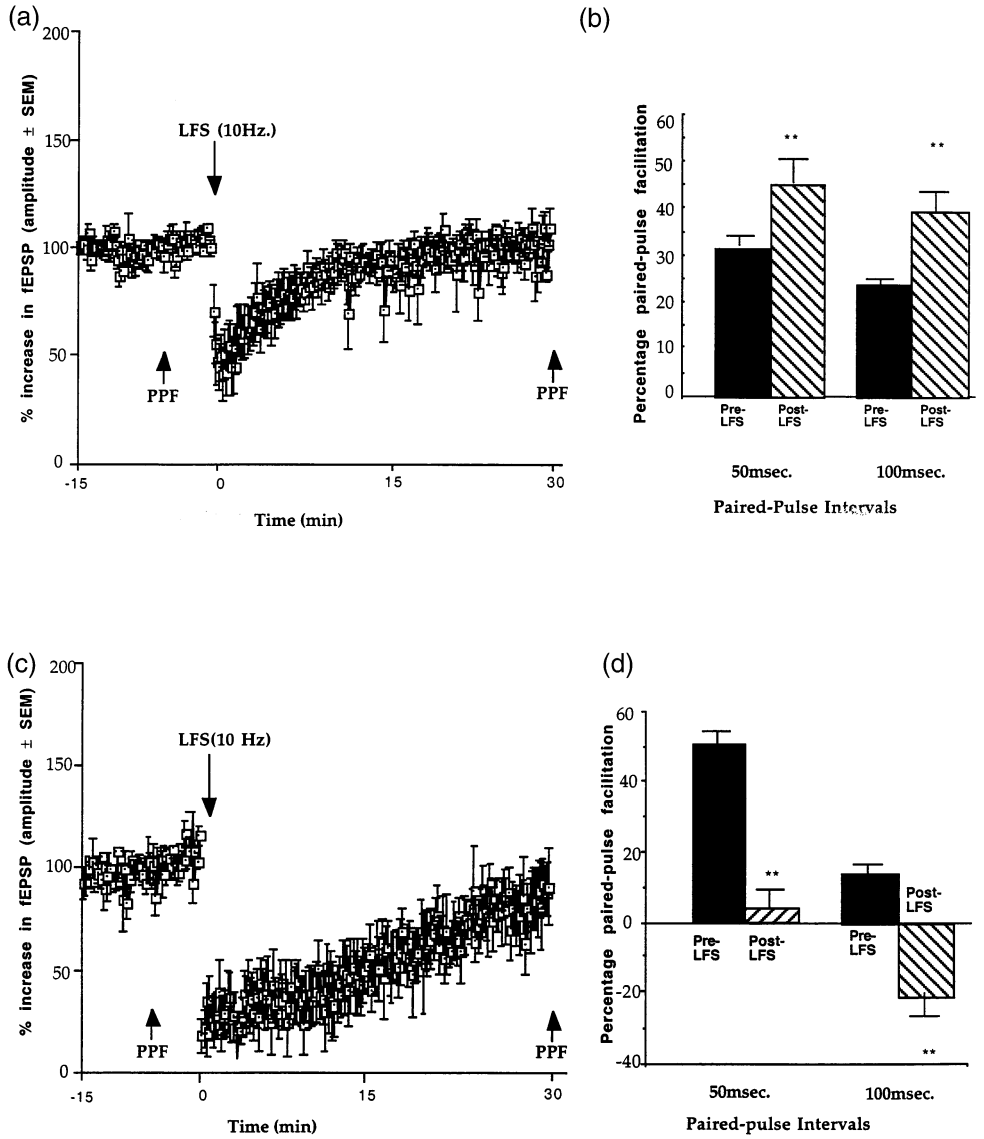

Fig. 11. Interactions between LFS, behavioural stress and PPF. (a) Effects of LFS (10 Hz) on the amplitude of fEPSPs. The post-LFS values are expressed as percentage of the pre-stimulation baseline ± S.E.M. (b) A bar chart showing percentage PPF both pre- and post-LFS for the 50 and 100 ms ISIs. Note the increase in facilitation at both ISIs post-LFS. (c) Effects of stress and LFS (10 Hz) on the amplitude of fEPSPs. The post-LFS values are expressed as percentage of the pre-stimulation baseline ± S.E.M. (d) A bar chart showing percentage PPF both pre- and post-LFS for the 50 and 100 ms ISIs. Note the decrease in facilitation at 50 ms ISI post-LFS and PPD at the 100 ms ISI.

6. Recordings in freely-moving animals

Given the vast body of work which demonstrates that the hippocampus contains cells which, in the freely-moving animal, have a strongly spatially-selective firing correlate (O'Keefe, 1979; Muller et al., 1991; O'Mara, 1995), it would be surprising if subicular neurons did not demonstrate some such firing correlate also. As expected, several studies have reported that subicular neurons do show spatially-selective firing (Barnes et al., 1990; Sharp and Green, 1994; Sharp, 1997, 1999a,b,c; O'Mara et al., 2000). A number of standardised methods have evolved in different laboratories for studying the spatial selectivity of hippocampal neurons. Briefly, these require a freely-moving rat to traverse mazes or open fields (usually in search of food pellets), neuronal activity is recorded and the activity of individual neurons is correlated with the moment-to-moment position that the rat occupies. This correlation can be used to generate colour-coded maps or contour maps which represent the density of spike firing at all points occupied by the rat. Under these conditions, individual hippocampal neurons may show 'location-specific' firing; they fire in a defined area of the apparatus (usually no more than a few percent of the total area of the apparatus) and remain silent or fire

at low rates (< 1 spike/s) in other areas of the test apparatus. The experimental apparatus may be shielded from the larger laboratory by means of curtains, in which case one can control the local cue set; this cue set may be manipulated by means of, for example, cue rotations or selective cue deletions. A proportion of hippocampal neurons under these conditions may be controlled by the local cue set; these hippocampal place cells rotate with rotations in the cue set and continue to fire in the absence of the cues if the cues are removed in the presence of the animal (that is, such cells may continue to respond to idiothetic or other inputs).

Possibly the first study of activity in the subicular complex of the freely-moving rat was conducted by Segal (1972) who found that the responses of many subicular neurons increased when a tone paired with food reward was sounded. Spatial firing correlates of these units were not explicitly manipulated in this study, however. Barnes et al. (1990) and Muller et al. (1991) provide the first extended descriptions of the spatially-selective firing properties of subicular neurons, using recordings in the radial-arm-maze and cylinder, respectively. Barnes et al. (1990) found that, in general, subicular cells were spatially consistent in their firing on the radial-arm-maze, though such cells displayed a rather low spatial specificity. This may be because the authors were unable to separate subicular neurons clearly into complex spike cells (which display very high spatial specificity and consistency in the hippocampus) and theta cells (which have a primary locomotor correlate and a lower spatial specificity), reducing the spatial selectivity of the average of the cell population (Barnes et al., 1990). These authors argue, however, that such a pooling for CA1 or CA3 cells does not greatly reduce their spatial specificity; subicular neurons, therefore, must have a lower spatial specificity than prior hippocampal regions. An alternative explanation is that they simply have a different firing correlate to that of place.

On the basis of their recordings in the cylinder, Muller et al. (1991) suggest that subicular neurons can be divided into three general classes. The first class of subicular neurons resemble the head-direction cells found in the presubiculum; the firing of such neurons is controlled by the angular position of the cue card on the cylinder wall. The second class encode both head-direction and positional information; the firing of these neurons reflects position but is modulated by head direction. Interestingly, such cells may have two preferred orientations, unlike head direction cells of the dorsal presubiculum which have only one preferred direction. The primary correlate of the third class of neurons appears to be place and they are similar to those described by Barnes et al. (1990); these cells have a relatively noisy representation of space compared to the hippocampal representation, but less noisy than the representation in EC.

The most comprehensive analysis of the firing correlates of subicular neurons conducted to date is that of Sharp and Green (1994). In this study, most subicular cells show a robust locational signal. This pattern of firing, however, is distinct from hippocampal firing in that subicular cells tend to fire throughout the environment and show multiple peaks of activity. The authors also identified different types of cells which they classify as bursters, non-bursters, depolarized bursters, and theta units (thought to be interneurons). This classification is similar to subicular cell types identified in vitro (Taube, 1993, see above). Bursting cells did not differ from non-bursting cells with respect to their spatial firing properties, suggesting that differences in membrane properties do not imply a difference in coding of environmental cues. The authors, however, did find that cells located adjacent to the hippocampus have a lower average firing rate, spatial signalling and firing field size when compared to cells located near the presubiculum. This is interesting because of the topographical projections of area CA1 to the subiculum (Amaral et al., 1991 also see above) and also because these two regions have different efferent connections (Amaral and Witter, 1995; Witter et al., 1989). Sharp and Green (1994) also reported that subicular place fields can follow rotations of a salient cue. O'Mara et al. (2000) used a pellet-chasing task to investigate subicular unit activity, similar to that developed by Muller et al. (1987, 1991). Rats were placed in a large, black plastic tub (height 39 cm; width 44 cm) into which food pellets are thrown at 10–15 s intervals. A large white cue card (21×29 cm) was placed on the inside wall of the tub to act as a polarising cue. The task consisted of four conditions, in which the position of the cue card is adjusted in each: (1) the cue card is attached to the side wall in the north position; (2) the cue card is moved to the south position; (3) the cue card is removed; (4) the cue card is returned to the north position. Unit activity is recorded in each condition for 10 min; the animal is returned to its home cage for 5 min between each condition. This study complements that of Sharp and Green (1994) as the effects of cue removal and subsequent cue replacement, as well as cue movement, on the spatial firing correlates of subicular units were examined.

Fig. 12 presents subicular unit data collected under the conditions of this task. Fig. 12(a) shows sample subicular unit waveforms separated using a custom-written template-matching algorithm. Fig. 12(b and c) show firing rate maps of two sample subicular units under the four conditions of the task. Fig. 12(b) (i) shows a unit with a small well-defined place field in the south-west portion of the environment. Following the movement of the card, the place field remains in the south-west, but with slight stretching in the direction of the card (Fig. 12(b) (ii)). Removal of the card has an

interesting effect: two separate fields appear (Fig. 12(b)(iii)). While one of these fields is in the same position as in the first two conditions, the second field appears in a place opposite the first, as if removal of the cue has introduced uncertainty as to the animal's position in the environment. Replacing the cue card returns

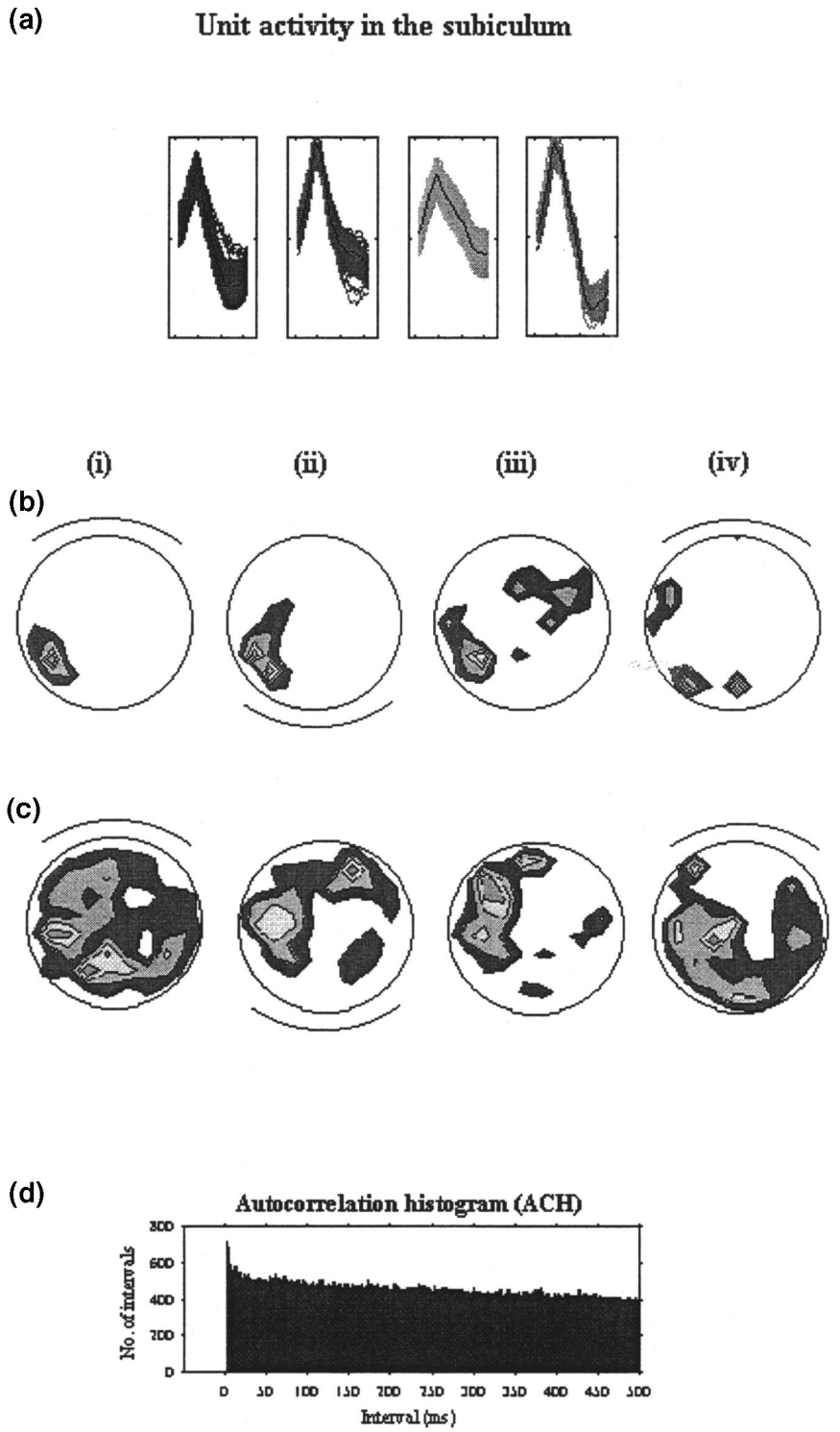

Fig. 12. (a) Sample subicular unit waveforms separated using a template-matching algorithm. (b) and (c) Firing maps for two subicular units in the four conditions of the pellet-chasing task (see text for discussion). Firing rate maps were constructed by dividing the environment into 6×6 cm pixels, and then mapping the resulting matrix as a contour plot. Each contour step represents 20% of the pixel peak firing rate. (d) An autocorrelation histogram (ACH) of the unit in (b). Both units displayed here have similar ACHs.

the place field to its original position, with a slight reduction in its spatial specificity (Fig. 12(b) (iv)). This unit appears to respond predominantly to fixed allothetic cues, or to idiothetic information: movement of the cue card has little effect on its place field. The cue card may modulate its response, however, in light of the impact of cue removal.

A second subicular unit is shown in Fig. 12(c). This unit is more typical of a subicular unit in that its firing field covers a large proportion of the task environment (approximately 70%). In the first condition its peak firing is in the south-west portion of the environment (Fig. 12(c) (i)). Movement of the cue card causes a rotation of the peak firing to the north-east; there is also an apparent reduction in the size of the overall firing field (Fig. 12(c) (ii)). Cue card removal causes the peak of firing to shift slightly, though the area covered by the firing field is largely unchanged (Fig. 12(c)(iii)). When the cue card is returned to its initial position, the firing field returns to the south-west (Fig. 12(c) (iv)). This unit appears to be predominantly under the control of the cue card.

Autocorrelation histograms (ACHs) were constructed for both units. The histogram in Fig. 12(d) shows the ACH for the unit analysed in Fig. 12(b); both units, however, had very similar ACHs. Subicular units with ACHs similar to this have been seen earlier (Barnes et al., 1990). The ACH peaks in the 1–2 ms bin indicating a large number of small intervals between spikes, indicative of burst firing; however, there are large numbers of longer intervals too. There appears to be little rhythmicity in the firing of this type of unit. The average firing rate of these units is in the same range as units recorded in area CA1 — between 5 and 7 Hz, although units with much higher rates have also been encountered (so far up to 35 Hz, similar to Barnes et al., 1990). Subicular unit separation is somewhat difficult to achieve, possibly due to the number of concurrently active units (Barnes et al., 1990) for which stereotrodes and tetrodes do not appear to provide better unit separation (Sharp, 1999a).

Sharp (1997) compared subicular place cell firing with hippocampal place cell firing in two adjacent geometrically and visually distinctive environments (cylindrical and square open fields). Subicular place cells showed very similar patterns of firing in both environments while, in line with earlier work, hippocampal place cells normally showed different patterns of firing in the two environments. This result suggests that the subiculum codes space in a qualitatively different way to the hippocampus. Sharp (1999a) examined subicular place fields in both a large square open field and in a smaller square open field positioned within the large square. Subicular place fields in the large square were expanded versions of those in the small square, suggesting that these place fields expand and contract to fit the size of the environment; again, hippocampal place cells were more likely to re-map after exposure to the small square open field. However, in the presence of a barrier, subicular place fields present in the small square open field did not stretch to fill the large square open field (the barrier was the small square open field with small gaps opened at two corners); rather, the barrier seemed to act as an anchor for the small square place fields.

Sharp (1999b) proposes that the qualitative differences between the hippocampus and the subiculum in the representation of space lend support to a path-integration model of spatial behaviour. Specifically, subicular place cells appear to transfer a single, universal locational firing pattern from one environment to the next, changing the pattern's size and shape to fit into the current environmental boundaries. The model proposes that the subicular/entorhinal spatial representation 'assist[s] the hippocampal layer to rapidly form new environment and context specific 'maps' for each new environment/temporal context ('episode') the animal experiences.' (Sharp, 1999b). Support for this model comes from Sharp (1999c) who demonstrated that subicular place cells appear to anticipate future locations by approximately 50–70 ms, while hippocampal place cells were best correlated with positions about 30–40 ms in the future, showing that the subicular signal is apparently generated earlier than the hippocampal signal and so cannot be the result of simple transmission of spatial information from the hippocampus alone.

7. Lesion analyses of subiculum

There have been few lesion analyses of the subiculum. Schenk and Morris (1985) conducted the first study of the effects of lesions restricted to the subicular complex. There were two experimental groups: one group was given lesions of the EC and pre- and parasubiculum the other experimental group was given lesions encompassing the entire subicular complex and the EC. The two groups were tested on the water maze task — a test of spatial memory. Results indicated that there is a profound impairment in spatial localisation following lesions of both groups. There was a partial and selective recovery of spatial localisation during post-operative training, although larger lesions encompassing most of the subiculum, in addition to the other structures, may limit the extent of the recovery. The authors did not specify a particular role for the subiculum in spatial information processing, it clearly does play an important role in spatial memory.

Morris et al. (1990) found that both the hippocampal and subicular lesions cause impairment to the initial post-operative acquisition place navigation but did not

prevent eventual learning to levels of performance almost as effective as those of controls. Different strategies were deployed by hippocampal and subiculum lesioned groups: the hippocampal lesioned group employ a circling strategy, whereas rats with subicular lesions behave like naive rats in the water maze. Furthermore, both hippocampal- and subicular-lesioned rats were impaired during a subsequent retention/relearning phase. Morris et al. (1990) suggest that hippocampal lesions may cause a dual deficit — a slower rate of learning and a separate navigational impairment, whereas subicular lesions may cause an impairment of long-term spatial learning but little impairment in spatial processing or short-term memory.

Galani et al. (1998) found that rats with subicular lesions were impaired on the 8-arm-radial-maze, although their impairment was less severe than hippocampectomised animals. Interestingly, rats with subicular lesions postoperatively housed in enriched conditions were not significantly different from that of control rats housed in standard conditions. These enriched environments may promote functional recovery of the subiculum. This extends an earlier study by Galani et al. (1997), who examined rats with lesions of various regions of the hippocampal formation on a battery of tasks for examining locomotor activity, reactivity to novelty, spatial, working and reference memory in the Morris water maze and learning in the Hebb-Williams maze. It was found that rats with hippocampal lesions were impaired on most of the tasks, whereas the subicular-lesioned animals were only impaired in the probe trial of the watermaze task.

Are there distinct roles for the dorsal versus ventral portions of the subiculum? Maren (1999) examined the effects of neurotoxic or electrolytic lesions of the ventral subiculum on Pavlovian fear conditioning. Freezing was measured in rats following conditioning by a number of tone-footshock trials in a novel chamber. Ventral subicular lesions made prior to training produced a severe deficit in acquired freezing to the tone but modest context freezing deficits, whereas posttraining lesions produced severe deficits in freezing to both tone and context. Ventral subiculum, therefore, may play an important role in both the acquisition and expression of Pavlovian fear conditioning. Interestingly, lesions of the subiculum had no effect on latent inhibition (prior presentation of conditioned stimulus for a repeated number of trials before pairing of conditioned and unconditioned stimuli), whereas entorhinal lesions seem to disrupt latent inhibition. Latent inhibition is considered to be an animal behaviour that is relevant to schizophrenia; the entorhinal cortex and potentially the subiculum may be considered as possible target sites for antipsychotic drugs (Greene, 1996). Lesions of the ventral subiculum also impair the acquisition of spatial tasks. Laxmi et al. (1999) examined the ability of rats with ibotenic lesions of the ventral subiculum to acquire a rewarded alteration test in a T-maze. Subicular lesioned animals were impaired in this task compared to controls suggesting that the ventral subiculum is required in processing of spatial information.

Oswald and Good (2000) examined the effects of combined lesions of the subiculum and EC on the Morris water maze. Lesioned animals were significantly impaired in finding the hidden platform which was located in a fixed position. The subiculum-entorhinal group was also significantly impaired on the probe task, where the platform was removed entirely from the water maze: the lesioned group spent less time in the platform quadrant than control animals. In a second experiment, where the hidden platform was located at a fixed direction and distance from an intramaze cue, both the lesioned group and control group easily acquired this task; when the visible extramaze cues were hidden by a curtain the control group were unable to locate the platform, whereas the lesioned group did acquire the task. The authors suggest that general navigational abilities are spared in the combined subiculum-entorhinal lesioned animals.

8. The subiculum: open questions

The subiculum is situated at a crucial junction between the hippocampus proper and the EC. We have argued in this paper that it should be thought of as properly a pivotal component of the hippocampal formation and not as part of the cluster of anatomical areas commonly referred to as the 'subicular complex'. We further contend that this phrase is not meaningful either anatomically or functionally. We would argue that the subiculum is positioned in such a fashion that it partially reverses the inhibitory functions of the dentate gyrus; the inhibition present in the dentate gyrus is such that dentate granule cells fire infrequently and at low rates (Jung and McNaughton, 1993), thus acting as a filter or threshold for the hippocampus proper. By contrast, the subiculum appears to be very loosely inhibited, and it may function, at least in part, to amplify the outputs it receives from the hippocampus proper. The subiculum has not received anything like the level of investigation that other prior hippocampal formation areas have received, in consequence, there are many basic pieces of information missing which are needed to generate a comprehensive theory of its unique contribution to hippocampal formation information processing. The list to follow is not intended to be comprehensive.

8.1. Neuroanatomy

Recordings in the subiculum of the freely-moving animal (see above) demonstrate that the place fields of subicular cells are typically larger than hippocampal area CA1 and they have perhaps up to three or so major peaks of activity, again in contrast to area CA1. One reasonable hypothesis is that there is a very high degree of convergence of individual CA1 neurons onto single subicular neurons; the afferent drive from these neurons in turn results in place fields which are larger and multi-peaked. Does this sort of precise anatomical convergence exist? There are also many other questions. What is the exact pattern of laminar termination of subicular neurons in the various cortices to which it projects? What type of synapses are made in these cortices? Are these projections reciprocated in a one-to-one or some other fashion?

8.2. Networks of excitation and inhibition

Little is known of the interactions between local circuit inhibitory interneurons and their influence on pyramidal neurons within the subiculum. What is the ratio of inhibitory interneurons to pyramidal cells? Where do they synapse? What are the activation thresholds of these differing cell types? Are inhibitory conductances in the subiculum similar to those seen in the hippocampus proper? To what extent is feedforward and feedback inhibition present in the subiculum? What are the patterns, if any, of reciprocal projections to the subiculum from these cortices? How closely coupled is the activity of individual subicular neurons to inputs from area CA1 or other input areas? How closely coupled is the activity of individual subicular neurons to its output areas? What is the relationship of single-neuron activity to population activity in the subiculum?

8.3. Epileptiform activity

The ability of subicular bursting cells to fire bursts of action potentials in response to single orthodromic stimulation confers on them an amplifying capacity, in spite of the shortage of local excitatory interconnections (Stewart and Wong, 1993). A simple hypothesis regarding the role of the subiculum in epilepsy is as follows: if seizure activity is initiated in layer II neurons of the EC, which is passed to the dentate gyrus and it is not stopped at this stage, then the whole hippocampal circuit may operate in an unrestrained manner. The signals are maintained and amplified through the combination of recurrent collaterals in area CA3 and amplified in the subiculum before spreading downstream to other cortical areas. However, if seizure activity is initiated in layer III neurons, these signals can also be transmitted directly to area CA1, avoiding the dentate gyrus and be passed on to the subiculum where they are amplified. They may also be transmitted directly to the subiculum which in turn spreads the epileptiform activity to the cortex. Although different areas of the hippocampal formation have different sensitivities to epileptiform activity (Pitkanen et al., 1995), it is clear from the literature that the subiculum plays a pivotal role in seizure propagation in epilepsy (Dreier and Heinemann, 1991).

8.4. Neuropharmacology

Almost nothing is known of the neuropharmacology of the subiculum; there have been no comprehensive investigations of the role and importance of NMDA receptors and metabotropic glutamate receptors in subicular synaptic transmission. There is a need for investigations to compare and contrast the effect of differing neuropharmacological challenges on bursting, non-bursting and inhibitory neurons — the three cell classes found in the subiculum.

8.5. Plasticity of subicular projections

It is currently not known if other stimulation protocols such as primed-burst stimulation, theta-phase or theta-locked stimulation and depotentiation produce long-lasting changes in synaptic transmission more effectively than a standard tetanic stimulus. Equally, little is known regarding the simultaneous use of two or more stimulating loci to enable a detailed investigation into the nature of the interaction between the CA1 and EC projections to subiculum. Such experiments provide access to independent excitatory inputs which can be used to investigate a variety of theoretically important questions regarding interactions between convergent inputs: if heterosynaptic LTP or LTD can be induced (that is, does the response to stimulation of one input increase after LTP of the other input), if there is a relative advantage of in-phase (co-operative LTP) as opposed to out-of-phase stimulation between the two inputs; if potentiation of one input give rise to depression of the other input (simultaneous heterosynaptic LTP and LTD).

8.6. Theoretical analyses

A major challenge for the future is the fine-grained specification of hypotheses regarding the role of the subiculum as a possible mediator of hippocampal-cortical interaction and their subsequent experimental testing. The pattern of data presented here and from other sources clearly demonstrates that the subiculum displays synaptic plasticity at differing levels of analysis. The input to subiculum from hippocampal area CA1 is

capable of showing both short and long-term plastic effects. Furthermore, these effects are sensitive to the behavioural state of the organism — a short period of stress has marked effects on synaptic transmission. Equally, single subicular units in the freely-moving animal also show dramatic changes in their representation of space, depending on the nature of the changes that are made to the environment. Thus, modifications to large polarising cues are rapidly incorporated in the spatial map that appears to be represented in the activity of subicular neurons. The representation of the environment appears to be coarser and to comprise much larger areas than is true of area CA1. Thus, the subiculum has many of the characteristics of a structure that might be important for mnemonic processing: its synapses are readily modifiable and it rapidly incorporates information from the external environment into its representation of that environment. Lesion analyses also demonstrate that the subiculum plays a crucial but ill-defined role in spatial representation and spatial navigation. Thus, the theoretical challenge is to provide an account of the importance of the subiculum in spatial information processing on the one hand, and of its more general role in hippocampal-cortical interaction and mnemonic processing on the other.

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