

COMMENTARY

The Subiculum Comes of Age

Liset Menendez de la Prida,¹ Susan Totterdell,² John Gigg,³ and Richard Miles^{4*}

ABSTRACT: The subiculum has long been considered as a simple bidirectional relay region interposed between the hippocampus and the temporal cortex. Recent evidence, however, suggests that this region has specific roles in the cognitive functions and pathological deficits of the hippocampal formation. A group of 20 researchers participated in an ESF-sponsored meeting in Oxford in September, 2005 focusing on the neurobiology of the subiculum. Each brought a distinct expertise and approach to the anatomy, physiology, psychology, and pathologies of the subiculum. Here, we review the recent findings that were presented at the meeting. © 2006 Wiley-Liss, Inc.

KEY WORDS: anatomy; physiology; synapse; plasticity; place field; epilepsy; schizophrenia; Alzheimer's disease

The Subiculum: The End of the Trisynaptic Pathway or the Heart of the Hippocampal Formation?

Menno Witter, Amsterdam; Fabian Kloosterman, Boston; Fernando Lopes da Silva, Amsterdam; Sarah French, Oxford

The title of the presentation from Mark Stewart provides perhaps the most explicit reason to reconsider the roles and functions of the subiculum. Situated between the hippocampus and the entorhinal cortex (EC), the subiculum is central to the transmission of activity in both directions (Van Groen and Lopes da Silva, 1986; Witter, 1993). The subiculum is also a region of anatomical transition; Nissl or NeuN immunostaining shows the somata of subicular pyramidal cells that are grouped in a

loose zone that contrasts markedly with both the densely packed hippocampal principal cell layers of the rodent and the multi-layered EC (Fig. 1A). The molecular and the polymorphic layers of the subiculum are contiguous with the stratum lacunosum-moleculare and the stratum radiatum of CA1, respectively. Pyramidal subicular cells are glutamatergic neurons with a major apical dendrite ascending to the molecular layer before it ramifies (Fig. 1B). GABAergic interneurons of the subiculum are present in the molecular, pyramidal, and polymorphic strata (Witter and Groenewegen, 1990).

Pyramidal cells of the subiculum have distributed somata and apical dendrites with variable lengths and a loose organization in rows and columns is apparent within the subiculum (Witter and Groenewegen, 1990). Afferent fiber systems are not stratified in contrast to the situation in the CA1 and CA3 regions. Projections from CA1 arrive topographically, with CA1 pyramidal cells proximal to CA3 innervating distal subicular neurons (near the presubiculum) and distal CA1 cells projecting to the proximal subiculum (Amaral et al., 1991; Ishizuka, 2001). Pyramidal cells of the proximal subiculum form recurrent connections with the distal CA1 region (Harris and Stewart, 2001a; Commins et al., 2002). Subicular pyramidal cells are connected bi-directionally with the presubiculum and with the EC (Köhler, 1986; Funahashi et al., 1999). Therefore, the subiculum participates in multiple short- and long-range glutamatergic circuits configured as nested loops (Kloosterman et al., 2003, 2004). Moreover, direct and indirect projections from the peri- and the postthral cortices also innervate the subiculum so bypassing the classical trisynaptic pathway (Naber et al., 1999).

The anatomy suggests that the subiculum might participate in multiple reverberating circuits linking the hippocampus and the wider temporal cortex. It could receive at least three versions of the same processed sensory information and so continuously compare novel stimuli with temporarily stored information (Witter et al., 2000). As one function of the hippocampus is to create a cognitive map of the place in space of an animal (O'Keefe and Nadel, 1978), this anatomical arrangement implies that the subiculum might receive multiple mapped versions of the same space possibly facilitating the construction of distinct spatial maps (Gigg, unpublished data).

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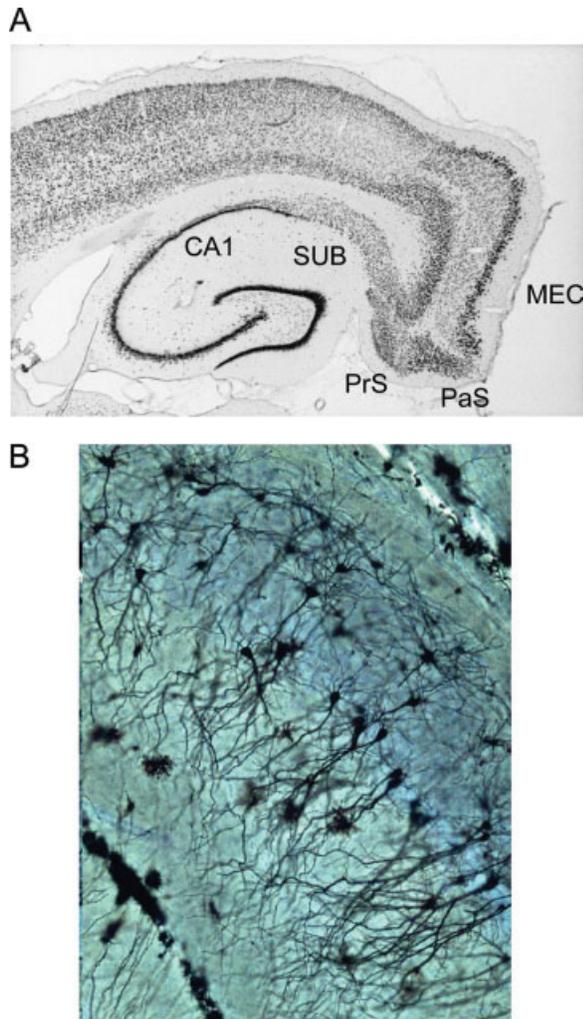


FIGURE 1. Cytoarchitectonic features of the subiculum. **A:** NeuN staining of a horizontal slice showing different fields in the ventral hippocampus. SUB, subiculum; PrS, presubiculum; PaS, para-subiculum; MEC, medial EC. Image from Gunter Sperk. **B:** Rapid Golgi staining shows the different orientation of the main apical dendrite of pyramidal subicular cells. Note the cell with apical dendrite tipping toward CA1. Data and images from Srebro and Stewart. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Cellular Physiology of the Subiculum

John Gigg, Manchester; Liset Menendez de la Prida, Madrid; Mark Stewart, New York

Electrically subicular pyramidal cells are diverse. As shown in Figures 2A,B, some fire spike bursts, rather like CA3 pyramidal cells, while others discharge repetitively similarly to CA1 pyramidal cells (Stewart and Wong, 1993). The relative proportion of bursting and regular-spiking cells tends to vary in the proximo-to-distal and deep-to-superficial axes of the subiculum (Greene and Totterdell, 1997; Harris et al., 2001; Menendez de la Prida et al., 2003). Studies on membrane mechanisms reveal different roles for sodium and calcium currents in subicular and CA3 pyramidal cell bursting (Jung et al., 2001;

Menendez de la Prida et al., 2003). R-type Ca^{2+} channels seem to be particularly important in subicular cells (Spruston, unpublished) and recent data show how a prolonged Na^+ channel inactivation participates in the switch from bursting to regular spiking (Cooper et al., 2005). However, while subicular bursting cells can be made to fire regularly at depolarized membrane potentials (Stewart and Wong, 1993), regular-spiking cells cannot be induced to switch into burst firing mode. Regular and burst firing cells also differ in other electrical properties (Mattia et al., 1993; Greene and Totterdell, 1997; Menendez de la Prida et al., 2003), in responses to somatostatin (Greene and Mason, 1996) and in the expression of NADPH-diaphorase and nNOS (Greene et al., 1997). Burst firing and regular firing cells seem then to be distinct neuronal populations each with a continuum of properties.

Regular-spiking cells appear to project to the EC, whereas bursting cells project to the presubiculum (Stewart, 1997). The spatial distribution (Greene and Totterdell, 1997) and topography of subicular efferents (Ishizuka, 2001) suggests that bursting and regular-spiking cells may target distinct subcortical structures. However, both cell types receive inputs from CA1, the thalamic reuniens nucleus, and the EC (Witter et al., 1989). Distinct inputs seem thus to be distributed topographically across the structure rather than segregated at the single cell level (Witter and Groenewegen, 1990). Even so, different afferent fiber systems may engage different styles of synaptic integration in distinct cell types. *In vivo* studies suggest that burst firing cells in dorsal subiculum are preferentially activated by convergent inputs from CA1 and the EC (Gigg et al., 2000). This raises the question of how the subiculum treats simultaneous synaptic inputs and how plasticity is implemented in distinct pathways.

The Subiculum: Synaptic and Cellular Plasticity

Joachim Behr, Berlin; Yves Gioanni, Paris; Theresa Jay, Paris; Nelson Spruston, Chicago

Its position, long-range connectivity, and reciprocal local connections suggest that the subiculum may play a pivotal role in the hippocampal memory system. Long-term potentiation (LTP) (Commins et al., 1998, 1999) may be induced at the CA1–subicular pyramidal cell synapse but these connections apparently do not exhibit long-term depression (Anderson et al., 2000) except after previous behavioral stress (Commins and O'Mara, 2000). Some, but not all (Roberts and Greene, 2003), forms of subicular LTP are NMDA-independent (Kokaia, 2000) as at the mossy fiber–CA3 synapse. LTP induced by prolonged theta frequency stimulation is also independent of NMDA receptors. It is modulated by β -adrenergic receptors and depends on protein kinase A and protein phosphatase (Huang and Kandel, 2005). Novel data point to cell-specific differences in plasticity. Synapses made by CA1 afferents with bursting subicular cells express a large and presynaptically initiated LTP while potentiation at inputs to regular-firing cells is smaller and initiated postsynaptically (Behr, unpublished data).

Data is emerging on the pre- and postsynaptic expression of the different forms of subicular plasticity. Disruption of the presynaptic cAMP responsive binding protein, CREB, impairs LTP induction in the CA1-subiculum pathway via a BDNF-associated mechanism, as in the CA1 region (Cowley et al., 2004). Plasticity in the CA1-subiculum pathway is strongly modulated by dopamine at D1 presynaptic receptors, whereas this system has little influence on plasticity at the perforant path synapse (Behr et al., 2000). Thus, plasticity in the distinct feedback loops involving the subiculum and the hippocampus can be independently regulated (Kunitake et al., 2004).

The cellular properties of subicular pyramidal neurons are modifiable in the short and long-term. We have noted that burst firing cells can switch to a regular firing pattern when depolarized (Stewart and Wong, 1993; Cooper et al., 2005). Cellular firing mode may also be persistently modified by synaptic stimulus regimes such as those that induce long-term synaptic plasticity. Stimulating CA1 afferents or injecting simulated EPSPs at theta frequencies of 1–10 Hz can transform burst firing cells into regular firing. Thus, hippocampal theta activity may alter the output mode of the subiculum, possibly via the activation of group I mGluRs (Moore and Spruston, 2005).

Building the Cognitive Map: The Role of the Subiculum

Colin Lever, Leeds; Shane O'Mara, Dublin;
Patricia Sharp, Bowling Green

How do these properties of subicular cells and circuits contribute to the distinct attributes of place cells in the subiculum, the CA1 region, and the EC? During spatial navigation, hippocampal place cells are controlled by environmental landmarks and linked to a path integration circuit, which tracks location in space (O'Keefe and Nadel, 1978). Presumably, the hippocampus does not function as the path integrator, since constructing a new map for each environment will destroy information on movement sequences (Sharp, 1999). To track movement between points A and B, ensemble activity should vary according to information about current position, direction, and movement state (McNaughton et al., 1996). The subiculum encodes a universal location-specific map independent of the size and the shape of the environment (Sharp, 1997), while the nearby postsubiculum encodes information on the head direction of the animal (Taube et al., 1990).

Firing fields of subicular cells are larger than those of CA1 pyramidal cells. Subicular cells fire throughout an environment, and many cells show multiple peaks of activity (Sharp and Green, 1994). Pat Sharp (Fig. 2D) has demonstrated a remarkable stability of subicular place field in two adjacent geometrically and visually distinctive environments, such as cylindrical and square open fields (Sharp, 1997). Subicular place cells also anticipate future location faster than CA1 cells by tens of milliseconds (Sharp, 1999). This difference is maintained in the activity of subicular and CA1 place cells during spatial delayed-nonmatch-to-sample tasks (Deadwyler and Hampson, 2004).

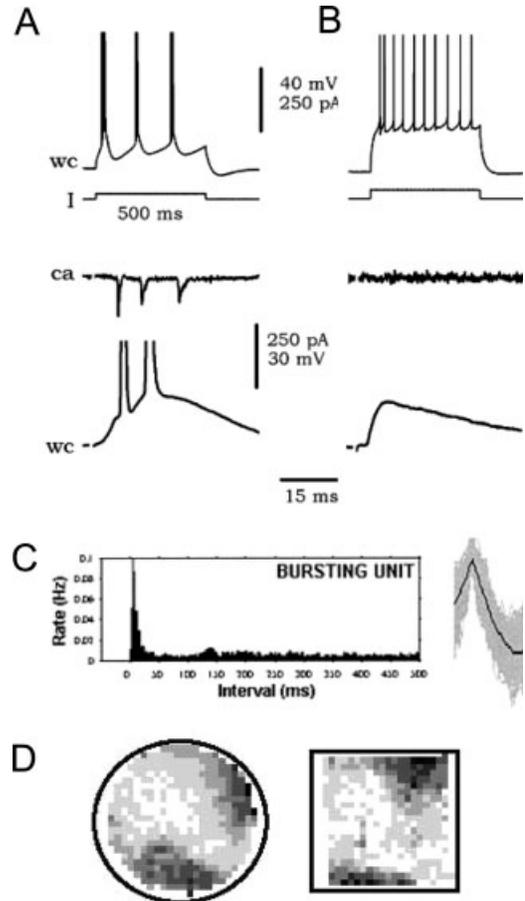


FIGURE 2. A: Bursting cells of the subiculum. Responses to depolarizing current pulses (top two traces) and orthodromic stimulation in cell-attached and whole-cell configurations (lower two traces). B: Regular-spiking cells of the subiculum. Data modified from Menendez de la Prida, *J Physiol*, 2003, 549, 219–230, © Cambridge University Press, reproduced by permission. C: Auto-correlation histogram of a bursting cell recorded in a behaving rat. Spike waveforms (gray) and mean waveform (black) are shown to the right. Data from Anderson and O'Mara, *J Neurophysiol*, 2003, 90, 655–665, © American Physiological Society, reproduced by permission. D: Place firing rate map of a subicular cell in two different open field environments. The place field is multi-peaked and stable in both environments. Data from Sharp and Green, *J Neurosci*, 1994, 14, 2339–2356, © Society for Neuroscience, reproduced by permission.

The subiculum encodes a representation of task relevant information for a relatively short time, whereas CA1 cells become progressively engaged in retrieval processes.

But, how do place fields evolve when an animal enters the environment? Recent reports suggest that the direct pathway to CA1 and subiculum from the EC may suffice to recognize a spatial location (Brun et al., 2002). Moreover, work in progress from Colin Lever suggests that subicular place fields may develop independently of hippocampal place information. On exposure to a new environment, place fields of subicular cells emerge immediately, in contrast to CA1 maps that require two to three trials to develop (Lever et al., 2005).

Can the construction of subicular place fields in the behaving animal be linked to operations in subicular microcircuits? While this question is far from being resolved, discussion at the meeting provided some directions that should be pursued. Certainly, in isolated slice preparations, the subiculum generates several distinct forms of synchronous activity (Behr and Heinemann, 1996). In vitro data also shows that low threshold, burst firing subicular pyramidal cells can recruit other glutamatergic cells and GABAergic interneurons to population burst firing (Harris and Stewart, 2001b; Menendez de la Prida and Gal, 2004). Subicular interneurons may have an especially important role. Inhibitory responses to afferent stimuli generated by local subicular circuits (Finch et al., 1988; Gigg et al., 2000) act to suppress firing after an initial excitation. Data on interneuron and pyramidal cell responses show how GABAergic local circuits exert a strong control over the output of subicular pyramidal cells (Stewart and Wong, 1993; Menendez de la Prida, 2003).

Understanding on the operations of inhibitory subicular circuits in vitro suggests that they will operate to maintain the specificity of information involved in the construction of spatial maps. As an animal explores an environment, afferent information on animal head direction and movement will reach the subiculum nearly simultaneously with context-specific place information from the CA1 region (Sharp et al., 1995). These inputs seem likely to excite specific subsets of subicular cells. In vitro data suggests that excited subicular cells will both transmit activity to pyramidal cell targets and concurrently activate GABAergic inhibitory cells. The rapid operation of local inhibitory circuits will then act to suppress further firing and thus preserve the specificity of afferent induced firing. The combination of an effective recurrent inhibition and low threshold burst firing cells, which exert strong recurrent excitatory actions on their neighbors, may ensure that specific subicular pyramidal cells can participate in different ensembles in response to distinct afferent signals. In vitro data supports this model of subicular function (Menendez de la Prida and Gal, 2004). The temporal persistence of representations, apparent in vivo, implies that spatial information must be transferred from the subiculum to circuits that can sustain tonic firing, such as the EC (Egorov et al., 2002), before it re-enters the subicular loop to maintain spatial coding.

The Diseased Subiculum

*Javier de Felipe, Madrid; Richard Miles, Paris;
John Greene, Oxford; Günther Sperk, Innsbrück;
Thomas Van Groen, Birmingham*

The ventral subiculum, situated between the hippocampus and the EC, has always seemed likely to be involved in epilepsies of the temporal lobe (temporal lobe epilepsy (TLE); Figs. 3A,B). In patients with temporal lobe epilepsies, cell death and reactive gliosis in the subiculum are much less than those in the sclerotic CA1 region (Babb and Brown, 1987; Cavazos et al., 2004). However, the loss of afferents from both CA1 and layer III of the medial EC seem likely to trigger cellular

and synaptic reorganization. Recent data supports such reactive changes, since in temporal lobe slices obtained after surgery on TLE patients, the subiculum but not the hippocampus generates an interictal-like activity (Cohen et al., 2002). A subicular focus should facilitate propagation of epileptiform activity to other temporal regions.

Burst firing cells of the subiculum, hyperexcitable due to deafferentation, and coupled by recurrent excitatory connections as in the CA3 region, might explain this interictal activity. However, in vitro interictal-like activity is suppressed not only by antagonists of glutamatergic but also of GABAergic transmission. Further, a subgroup of pyramidal cells exhibits depolarizing responses to GABAergic activation (Cohen et al., 2002), which apparently contribute to interictal rhythmogenesis. The depolarizing or hyperpolarizing nature of synaptic events mediated by GABA_A receptors (Fig. 3B) depends on the concentration of intracellular Cl⁻, which is controlled in part by the actions of the two opposing cotransporters NKCC and KCC2 (Payne et al., 2003). Modification of Cl⁻ homeostasis in the epileptic subiculum may result from changes in expression or function of these transporters, as during early postnatal development and deafferentation (Coull et al., 2003).

A dramatic sprouting of GABAergic chandelier cell axons observed at the subiculum/CA1 border in sclerotic human hippocampus may also be significant (Arellano et al., 2004). Javier de Felipe has shown anatomically that hypertrophic basket formations may innervate neurons that express normal or increased levels of the Cl⁻ importing cotransporter, NKCC1 (Muñoz et al., 2004). However, a subpopulation of neurons does not express NKCC1. Similarly, hypertrophic basket terminals contact neurons that are either immuno-positive or negative for the Cl⁻ extruding cotransporter KCC2. A lack of KCC2 function is associated in other systems with depolarizing GABAergic signaling. This heterogeneity in expression of NKCC1 and KCC2 in subicular cells of human epileptic tissue points to a need to study mechanisms at the single-cell level.

Chronic animal models of epilepsy provide further information on cellular and network changes in epileptic tissue. They show (Fig. 3A) that the subiculum gates the propagation of epileptic activity (Behr and Heinemann, 1996; Menendez de la Prida and Pozo, 2002; Benini and Avoli, 2005), and suggest that cellular discharge properties may change in different ways in distinct subicular regions. Wellmer et al., 2002 have shown an increase in the proportion of bursting cells in the proximal, near CA1, subiculum while Knopp et al., 2005 report an increase of regular-firing cells in the mid-subiculum. Both studies were done in pilocarpine-injected rats. The ratio of regular-spiking to burst-spiking cells in mid-subiculum described by Knopp et al., 2005 is similar to that in human epileptic subiculum (Wozny et al., 2005). Hence, seizure-induced alterations in membrane properties of subicular pyramidal cells may be differentially regulated in distinct subregions of the subiculum. Animal models also provide evidence that glutamatergic synaptic transmission is enhanced (Cavazos et al., 2004; Knopp et al., 2005), but physiological evidence on changes in GABAergic signaling is less clear. Anatomical (Arellano et al.,

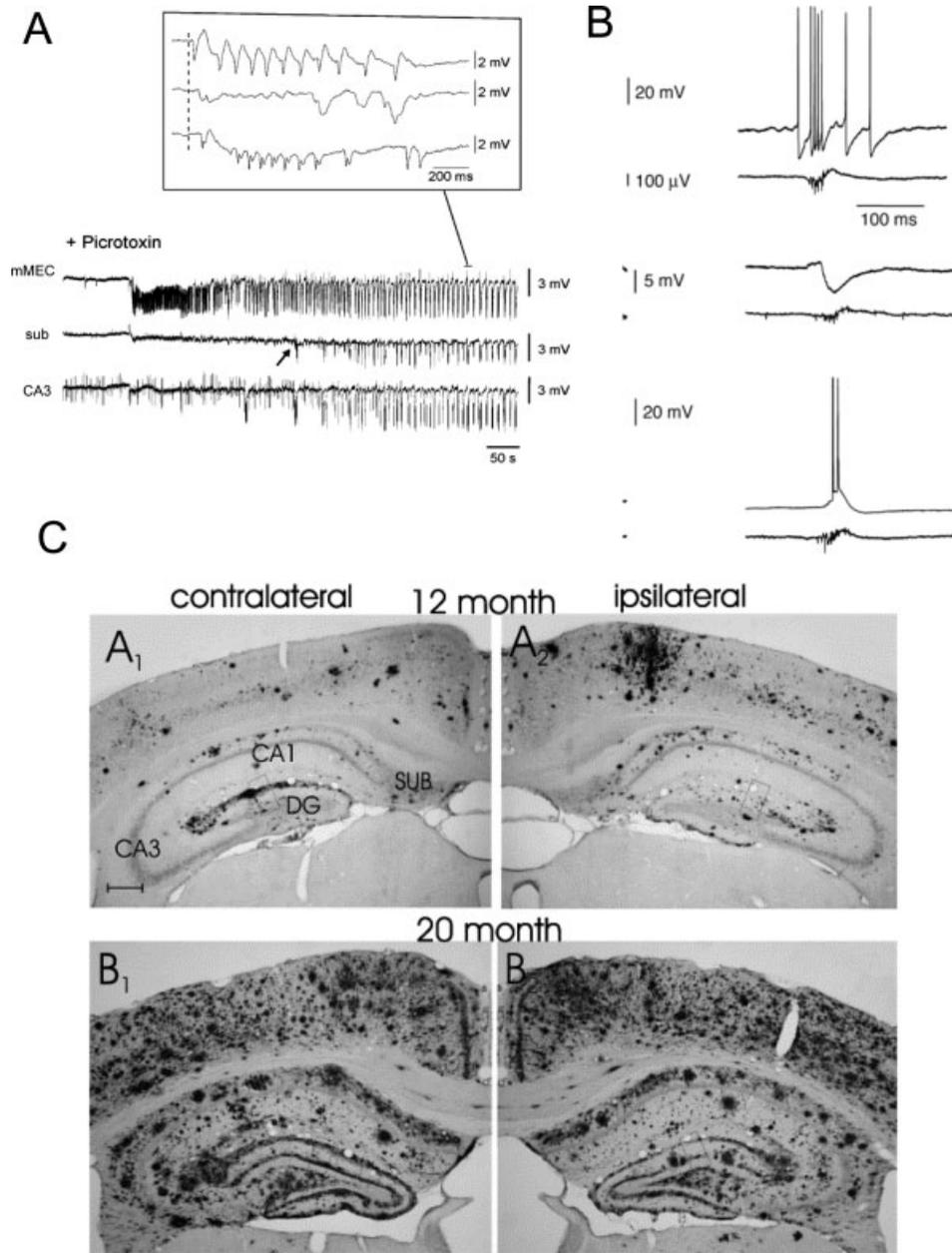


FIGURE 3. A: Simultaneous field potential records from the medial EC (mMEC), subiculum (Sub), and CA3 region of a ventral slice in during bath application of 4AP and Picrotoxin. Data from Benini and Avoli, *J Physiol*, 2005, 566, 885–900, © Cambridge University Press, reproduced by permission. B: Different responses of subicular cells associated with interictal-like synchrony recorded in the human hippocampus *in vitro*. Traces include intracellular records above and extracellular records below. An interneuron was excited during the bursts (upper traces). A pyramidal cell received a small synaptic excitation followed by a larger inhibitory potential (middle). A pyramidal cell was excited

and discharged simultaneously with interictal-like events (top traces). From Cohen et al., *Science*, 2002, 298, 1418–1421, © American Association for the Advancement of Science, reproduced by permission. C: Photomicrographs of coronal sections through the dorsal, septal hippocampus, stained for A β with W0-2 antibody. A and C: 12-month-old mice; B and D: 20-month-old transgenic mice. CA1, CA3, DG, dentate gyrus (DG); SUB, subiculum; scale bars in A and C = 100 μ m. Data from Van Groen et al., *Neuroscience*, 2003, 119, 1185–1197, © Elsevier Science, reproduced by permission.

2004; Muñoz et al., 2004) and molecular studies on human epileptic tissue have shown major changes in the expression of molecules associated with glutamatergic and GABAergic neurotransmission (Loup et al., 2000) as well as modulating transmitters (Furtinger et al., 2001; Csaba et al., 2005).

If the subiculum is now clearly involved in the genesis and transmission of epileptiform activity, it may also be linked to the etiology of schizophrenia. In schizophrenic patients, pathways involving the ventral hippocampus including the septo-hippocampal and subiculo-accumbens projections are impaired. In ani-

mals, acute activation of the subiculum and EC produces a hyperdopaminergic state in the nucleus accumbens, suggesting that hyperexcitability in these regions might underlie schizophrenic symptoms (Mitchell et al., 2000; Floresco et al., 2001). Electron microscopical studies have shown that asymmetrical glutamatergic contacts from fibers originating in the ventral subiculum, in addition to their inputs to the medium-sized, densely spiny projection neurons (French and Totterdell, 2003), specifically innervate nitric oxide immunoreactive interneurons of the nucleus accumbens (French et al., 2005).

One animal model for schizophrenia involves prolonged social isolation after weaning. It induces a hyperexcitability in the subiculum, as measured by a reduction in paired pulse inhibition. At a cellular level, regular firing neurons become more excitable because of changes in the activation of the cationic current I_h (Greene et al., 2001; Roberts and Greene, 2005). The increase in subicular excitability may underlie the increased activity of the nucleus accumbens in schizophrenia. Furthermore, the induction of LTP at the CA1-subiculum synapse is depressed (Roberts and Greene, 2003). Possibly, this loss-of-function is linked to memory impairment in schizophrenia and the reduced hippocampal activation during conscious recall (Geyer et al., 1993; Heckers et al., 1998).

Schizophrenic symptoms have also been associated with the disruption of connections between the ventral hippocampus and the dopaminergic innervation of the prefrontal cortex (Sesack and Carr, 2002). Physiological studies reveal a strong subicular projection to both interneurons and pyramidal cells of the prefrontal cortex (Degenetais et al., 2003; Tierney et al., 2004) that exhibits a reversible form of LTP (Laroche et al., 1990). Theresa Jay has shown that LTP at these synapses is driven by the level of mesocortical dopaminergic activity and that acute stress inhibits plasticity in a remarkable, long-lasting fashion (Gurden et al., 2000; Rocher et al., 2004). Interestingly, both the antidepressant tianeptine and the atypical antipsychotic clozapine reverse the impairment in LTP in these projections (Jay et al., 2004).

Finally, the aging subiculum is implicated in the early progress of Alzheimer's disease (AD). The pathophysiology of AD is characterized by the emergence of neurofibrillary tangles and neuritic plaques, first in the subiculum and temporal cortex and later in the hippocampus (Adachi et al., 2003). Some early onset forms of familial AD are linked with mutations in genes for the amyloid precursor proteins, presenilin 1 and 2 (Price and Sisodia, 1998). Transgenic mice expressing mutated human genes revealed (Fig. 3C) that amyloid plaques develop in the subiculum before diffuse amyloid deposits (Liu et al., 2002; Van Groen et al., 2003). Interfering with amyloid mechanisms in the subiculum may ameliorate the loss of function associated with AD (Van Groen and Kadish, 2005).

CONCLUDING QUESTIONS

The subiculum is more than just a zone of transition and highlighted questions at the interfaces between distinct

approaches. Anatomically, the subiculum participates in multiple nested loops involving the parahippocampal region—when are they functional in physiological or pathological contexts? While slice work has revealed some specificities of subicular cell types, synaptic function, and plasticity, it remains unclear how these properties shape cognitive functions including spatial coding. Furthermore, the psychiatric and neurological diseases that involve the subiculum remain to be clearly related to pathological changes at the circuit, cellular, or molecular level. Answers to these questions will refine our view of the subiculum and its place in hippocampal neurobiology.

Meeting Participants and Acknowledgments

The ESF workshop on “The subiculum in the normal and pathological brain” was sponsored by the European Science Foundation (ESF) and the European Medical Research Council (EMRC) EW04-009. Fernando Lopes da Silva (Amsterdam) gave a keynote lecture. The specific sessions and participants were as follows. *Circuit architecture*: Menno Witter (Amsterdam), Thomas Van Groen (Birmingham, Alabama, USA), Sarah French (Oxford), Fabian Kloosterman (Boston). *Functional organization of subicular circuits*: Joachim Behr (Berlin), Theresa Jay (Paris), Mark Stewart (Brooklyn), John Gigg (Manchester), Yves Gioanni (Paris), Liset Menendez de la Prida (Madrid). *The subiculum and behavior of the normal brain*: Shane O'Mara (Dublin), Nelson Spruston (Chicago), Patricia Sharp (Bowling Green, Ohio, USA), Colin Lever (Leeds). *The subiculum and the pathological brain*: Richard Green (Bristol), Richard Miles (Paris), Günther Sperk (Innsbrück), Javier de Felipe (Madrid). We thank all of them for constructive discussions and comments on the manuscript. More information on the workshop is available at <http://hobbes.fm-c.uam.es/liset/ESF.htm>

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