Progress in Neuro-Psychopharmacology & Biological Psychiatry 33 (2009) 782–790

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Roles for the subiculum in spatial information processing, memory, motivation and the temporal control of behaviour

Shane M. O'Mara [a,*], Maria V. Sanchez-Vives [b], Jorge R. Brotons-Mas [a,b], Eugene O'Hare [c]

[a] Trinity College Institute of Neuroscience and School of Psychology, Trinity College-University of Dublin, Dublin 2, Ireland
[b] Instituto de Neurociencias de Alicante, Universidad Miguel Hernandez, Consejo Superior de Investigaciones Cientıficas, San Juan de Alicante, Spain
[c] School of Psychology, Queen's University, Belfast, Belfast BT7 1NN UK

ARTICLE INFO

Article history:
Received 8 March 2009
Accepted 30 March 2009
Available online 22 April 2009

Keywords:
Memory
Motivation and reward
Space
Subicular functions
Stressors
Temporal control of behaviour

ABSTRACT

The subiculum is in a pivotal position governing the output of the hippocampal formation. Despite this, it is a rather under-explored and sometimes ignored structure. Here, we discuss recent data indicating that the subiculum participates in a wide range of neurocognitive functions and processes. Some of the functions of subiculum are relatively well-known—these include providing a relatively coarse representation of space and participating in, and supporting certain aspects of, memory (particularly in the dynamic bridging of temporal intervals). The subiculum also participates in a wide variety of other neurocognitive functions too, however. Much less well-known are roles for the subiculum, and particularly the ventral subiculum, in the response to fear, stress and anxiety, and in the generation of motivated behaviour (particularly the behaviour that underlies drug addiction and the response to reward). There is an emerging suggestion that the subiculum participates in the temporal control of behaviour. It is notable that these latter findings have emerged from a consideration of instrumental behaviour using operant techniques; it may well be the case that the use of the watermaze or similar spatial tasks to assess subicular function (on the presumption that its functions are very similar to the hippocampus proper) has obscured rather than revealed neurocognitive functions of subiculum. The anatomy of subiculum suggests it participates in a rather subtle fashion in a very broad range of functions, rather than in a relatively more isolated fashion in a narrower range of functions, as might be the case for "earlier" components of hippocampal circuitry, such as the CA1 and CA3 subfields. Overall, there appears to a strong dorso-ventral segregation of function within subiculum, with the dorsal subiculum relatively more concerned with space and memory, and the ventral hippocampus concerned with stress, anxiety and reward. Finally, it may be the case that the whole subiculum participates in the temporal control of reinforced behaviour, although further experimentation is required to clarify this hypothesis.

1. Introduction

Many theories attribute a central role to the hippocampal formation in the processing of information about space and memory, and great experimental effort is devoted to testing the theories. As is well known, the hippocampal formation is composed of several subfields (dentate gyrus, areas CA3 and CA1, entorhinal cortex and subiculum; Amaral and Witter, 1995; O'Mara et al., 2001; O'Mara, 2005). There are many thousands of papers in the literature investigating the neurobiology of the "early" hippocampal subfields, and there is now a great body of data available across multiple levels of analysis describing the neurobiology of the "early" hippocampal formation. A large body of data implicates the hippocampal formation in the processing of information about space; a similarly-large body of data implicates the hippocampal formation in memory (particularly episodic memory). Neuronal recordings in the freely-moving animal (e.g., O'Keefe, 1979; O'Mara, 1995; Brotons et al., 2006) demonstrate that neurons throughout the hippocampal formation show a remarkable spatial locational correlate—that is, they fire in response to the location of the animal during exploration, rather than preceding or anteceding the ongoing behaviour of the animal. Similarly, data from humans shows that the hippocampal formation is activated during specific memory tasks (Zeineh et al., 2003) as well during spatial tasks in virtual reality environments; damage to the hippocampal formation causes grave and enduring deficits in specific types of memory as well as in spatial information processing.

The subiculum, in contrast to the rest of the hippocampal formation, has received comparatively little empirical or theoretical investigation, although this situation has started to change in recent years (Menendez de la Prida et al., 2006). In this paper we will consider the role the subiculum plays in the processing of information about space and memory, and we will also consider recent data showing that the subiculum may also have a role in some of the neurobiological processes underlying motivation. At the outset we

* Corresponding author. Tel.: +353 1 896 8447; fax: +353 1 896 3183.
URL: http://www.neuroscience.tcd.ie (S.M. O'Mara).

0278-5846/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2009.03.040

should straightforwardly acknowledge that it has been difficult to attach clear functions to the subiculum: its neurons do not have the precise and clear locational response correlate that hippocampal area CA1 "place" neurons possess. Similarly, lesions of subiculum (either total or subtotal) do not, for example, cause obvious and easy to interpret behavioural deficits. But behavioural deficits there are–tasks must be designed to tap into these functions, and the task design should, be based on inferences about likely function, based on the neuroanatomical connections of subiculum. We will take the view that the subiculum is the pivotal structure governing hippocampal output: that it gates hippocampal output, and that it has a multiplicity of functions, rather any simple, single identifiable function. These include roles in spatial information processing, modulating the response to stress, controlling the hypothalamic–pituitary–adrenal (HPA) axis, amplifying and propagating epileptiform activity, contributing to certain motivational responses and the response to reward, among many others. Placing subiculum within the hippocampal formation circuitry obviates the major problem with the trisynaptic circuit hypothesis of hippocampal information processing (see below): that it concentrates on hippocampal inputs to the exclusion of the understanding information through the extended hippocampal formation information processing circuit and beyond.

2. Anatomy

Confusion persists over the definition of the hippocampal formation, and how it interacts with another set of structures, sometimes referred to as the "subicular complex". The classical theory of hippocampal organisation–the trisynaptic circuit hypothesis–continues to exert a deadweight effect on thinking about the extended nature of hippocampal circuitry. Papers still continue to appear with illustrations of the "wiring diagram" variety of the hippocampal formation, which ignore the central positioning of the subiculum within the hippocampal formation circuit. Instead the trisynaptic circuit will be illustrated—a simple linear projection between the entorhinal cortex, dentate gyrus and the CA subfields, with the subiculum notably absent from the circuit, despite the fact the major output from area CA1 is to subiculum (Amaral et al., 1991), compared with the lesser output CA1 makes to the entorhinal cortex. In line with this outdated reasoning, subiculum has been regarded as part of an obscure set of structures sometimes called the "subicular complex", which, in addition to subiculum, includes the pre-, para- and sometimes pro- and post-subicular cortices. The relationship between these differing structures or regions is more philological or etymological than functional or anatomical, however.

Here, we define the hippocampal formation (HF) as consisting of entorhinal cortex, dentate gyrus, areas CA3 & CA1 and subiculum: a consensus on the anatomical description and definition of subiculum has emerged over the past 2 decades (Amaral and Witter, 1995; O'Mara et al., 2001; Witter and Groenewegen, 1990). There is general agreement that the subiculum has three principal layers: a molecular layer, continuous with strata lacunosum-moleculare and radiatum of the adjacent hippocampal area CA1 field; an enlarged pyramidal cell layer containing the soma of principal neurons and a polymorphic layer. The cell packing in the pyramidal layer of the subiculum is looser than that seen in hippocampal 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).

Hippocampal area CA1 sends its primary projection to all regions of the subiculum, which in turn projects to many cortical and subcortical targets. The subiculum is therefore the major output structure of the hippocampus (O'Mara et al., 2001; 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 all regions of subiculum receiving CA1 projections. Here, following Amaral et al. (1991), we will use the term "proximal CA1" to refer to the area bordering CA3 and "distal CA1" for the area bordering the subiculum. The subiculum is similarly defined, with proximal subiculum bordering CA1 and distal subiculum bordering the presubiculum. To summarise these projections (Amaral et al., 1991); cells in proximal CA1 project to distal subiculum, cells in mid-CA1 project to mid-subiculum and cells in distal CA1 project across the CA1-subiculum border into proximal subiculum. Fibers arising in proximal CA1 travel to the subiculum mainly via the alveus and the deepest portion of the stratum oriens, whereas fibers originating in mid-CA1 do not enter the alveus but project to the subiculum through the deep parts of stratum oriens. The axons of distal CA1 cells travel directly to subiculum from all parts of stratum oriens (Amaral et al., 1991). Neurophysiological depth profiles of the CA1-subiculum projection, examining excitatory postsynaptic potentials 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, confirm this neuroanatomical analysis (O'Mara et al., 2001). Furthermore, combined single unit and morphological studies suggest that the CA1-subicular pathway is a monosynaptic projection (Gigg et al. 2000); the subiculum also returns a minor oligosynaptic projection to CA1 (Commins et al., 2002). Finally, the subiculum receives cortical inputs from the entorhinal, perirhinal and prefrontal cortices, to which it returns important and prominent projections; it also receives inputs from and distributes to some other secondary and tertiary cortices. The particular pattern of convergence of these many cortical inputs onto subicular neurons will, in the model developed below, play a key role in determining the response properties of, in particular, dorsal subicular neurons.

There are extensive reciprocal connections between the subiculum and many subcortical structures (and particularly to various hypothalamic nuclei). Subcortical structures projecting to the subiculum include the ventral premammillary nucleus (to ventral subiculum); the medial septum/nucleus of the diagonal band and all areas of the anteroventral (AV) and anteromedial (AM) nuclei of the thalamus (see Risold et al., 1997; Canteras and Swanson, 1992; Kohler, 1990). There is also some very limited evidence of brainstem projections to the subiculum, possibly deriving from brainstem vestibular nuclei (Witter, pers. comm.). Ventral subiculum projects to the hypothalamus via the postcommissural fornix, the medial corticohypothalamic tract and via the amygdala; these projections innervate the medial preoptic area, the ventromedial and dorsomedial nuclei, and ventral premammillary and medial mammillary nuclei. Lowry (2002) summarises this extensive projection system as follows: "The ventral subiculum projection system projects to a distributed forebrain limbic system associated with inhibitory input to the hypothalamic–pituitary–adrenal (HPA) axis and the hypothalamic–spinal–adrenal (HSA). Inhibition of the HPA axis is thought to be mediated transynaptically via GABAergic neurones that project directly to the paraventricular nucleus or hypothalamic autonomic control systems. Neurones within the median raphe nucleus project extensively and selectively to the ventral subiculum projection system, including the medial hypothalamic defensive system associated with active emotional coping responses". Thus, the role of the subiculum is to act principally to inhibit the HPA axis, and thus it plays a key role in terminating or limiting the response of the HPA axis to stress.

3. Space

Spatial information processing is defined conventionally here to mean information required for navigation through extrapersonal space, and our discussion is limited to allocentric spatial information processing by the subiculum only. Spatial navigation is a fundamental

form of interaction with the environment. Animals and humans must move about in their environments in search of food, shelter, or a mate, actions that are basic for the survival of the individual and the species. The brains of different species have evolved in an effort to make individuals capable of navigating their environments in an efficient manner. The understanding of the brain mechanisms underlying the generation of internal maps of the external world, the storage (or memory) of these maps, and the use of them in the form of navigation strategies is a fundamental problem in neuroscience. The hippocampal formation has been the principal structure implicated in representation of extrapersonal or allocentric space in mammals (O'Keefe and Nadel, 1978), particularly hippocampal areas CA3 and CA1; a reasonable assumption in the literature has been that the subiculum would support, in some fashion, spatial processing, perhaps in a related fashion to that of the hippocampus proper. The two principle routes taken to understanding the spatial functions of subiculum have been via lesion analysis or via recording of unit activity in freely-moving animals. There do not appear to have been any transgenic approaches to subicular spatial function to date, and little in the way of targeted and specific pharmacological approaches either. A selective and illustrative review of lesion and unit recording studies of subicular spatial function follows.

Schenk and Morris (1985) conducted the first lesion study of subiculum: one group was given combined lesions of the entorhinal cortex and pre- and para-subiculum; the other experimental group was given lesions of subiculum, pre- and para-subiculum and entorhinal cortex. The two groups were tested on the spatial watermaze, which has been, and continues to be, used to test spatial information processing by the brain; there was 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 other structures, limited the extent of recovery. Although the authors did not specify a particular role for the subiculum, it clearly plays an important part in spatial localisation. In a follow-up study also conducted using the watermaze, Morris et al. (1990) indicated that both hippocampal and subicular lesions cause impairment in the initial post-operative acquisition of place navigation but did not prevent eventual learning to levels of performance almost as effective as those of controls. Different strategies are deployed by hippocampal- and subiculum-lesioned groups: the hippocampal-lesioned group employ a circling strategy staying close to the wall, whereas rats with subicular lesions behave like naïve rats, searching the watermaze in a manner similar to rats with no prior knowledge of the location of the platform. 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. Subicular lesions they suggest, however, may cause an impairment of long-term spatial learning (because subicular lesioned rats were impaired in the postoperative learning of the hidden platform) but little impairment in spatial processing or short-term memory (because subicular lesioned rats displayed a greater and more consistent improvement in escape latency than hippocampal lesioned rats in a delayed matching to place phase).

In a subsequent and comparable study, Oswald and Good (2000) examined the effects of combined lesions of subiculum and entorhinal cortex on performance in the watermaze; they included an intramaze landmark in the watermaze because rats with hippocampal lesions are able to locate the platform when an intramaze landmark is placed in the pool at a fixed distance and direction from the platform (Pearce et al., 1998). Both the lesion and control groups easily acquired this task. In a second experiment in the watermaze, without an intramaze cue, the subicular- and EC-lesioned animals were significantly impaired in finding the hidden platform. 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. Thus damage to subiculum and entorhinal cortex does not affect a general navigational–directional strategy (because rats with this damage could still swim to the platform with the landmark) but impairs the integration of geometric information. Finally, Galani et al. (1997) 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 watermaze 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. Galani et al. (1998) found that rats with subicular lesions were impaired in a working memory task in the water maze (in which the position of the hidden platform was changed before each day's testing) and, interestingly, in an object exploration task (Poucet, 1989) where they failed to react to a non-spatial object change.

3.1. Subicular recordings in freely-moving animals

Understanding the neurocognitive functions of subiculum involves understanding the information represented by subicular neurons. Standardised methods have evolved for studying the discharge correlates of single neurons and neuronal ensembles (O'Keefe, 1979; O'Mara, 1995). Briefly, these require a freely-moving rat to traverse mazes or open fields (often in search of food), neuronal activity is recorded and correlated with the moment-to-moment position of the rat. These correlations are used to generate colour-coded contour maps representing the density of spike firing at all points occupied by the rat. Many hippocampal formation neurons (particular in area CA1) fire in a locally-defined area of the maze (usually a few percent of the total maze area) and remain silent or fire at low rates (<1 Hz) in other areas of the maze. The experimental apparatus may be shielded from the larger laboratory by means of curtains, to control the local cue set; this cue set may be manipulated by means of, for example, cue rotations or selective cue deletions.

What are the discharge correlates of subicular neurons recorded while freely-moving animals traverse mazes or open-field environments or engage in the exploration of objects in these environments? 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 (Muller et al., 1991; O'Keefe, 1979; O'Mara, 1995), it would be surprising if subicular neurons did not demonstrate some such firing correlate also. Our own recordings and those of others indicate that subicular units are not like hippocampal units during this sort of exploratory behaviour: subicular units tend to fire throughout the environment and show multiple peaks of activity; in general, subicular place fields appear to be of lower resolution and comprise much larger areas of comparable environments than those of area CA1 (O'Mara et al., 2000). Barnes et al. (1990) and Muller et al. (1991) provided the first extended descriptions of the spatially-selective firing properties of subicular neurons, recording in the radial arm maze and a cylindrical open field respectively. Barnes et al. (1990) found that, in general, subicular cells showed spatially localised firing on the radial arm maze, though such cells displayed a rather low spatial specificity. Muller et al. (1991) conducted subicular recordings in a cylindrical open-field; they suggest that subicular neurons can be divided into three general classes. The first class of subicular neurons resemble the head-direction cells found in 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.

Sharp and Green (1994) also reported that most subicular cells show a locational signal, but that subicular cells tended to fire throughout the environment, showing multiple peaks of activity. Interestingly, the authors found that place cells in the subiculum also coded for the animal's direction in an open field, which is not typical of hippocampal place cells in a similar apparatus (Mueller et al., 2004). Sharp and Green (1994) and O'Mara et al. (2000) also reported that subicular place fields can follow rotations of a salient cue, indicating that subicular place cells are modulated in at least some respects by allocentric information. 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 previous work, hippocampal place cells normally showed different patterns of firing in the two environments. Sharp (1999) 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 contraction and expansion would be modulated by some gain factor which allows units to adapt their firing to the size of the arena. 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. These results seem to contradict initial suggestion which tried to explain subicular firing as result of multiple hippocampal inputs (Barnes et al, 1990). If subicular unit depended on hippocampal input then remapping of units in the hippocampus should produce some sort of remapping of place cells in the subiculum.

It is possible that the subiculum codes space in a qualitatively different way to the hippocampus, complementing hippocampal-based spatial information processing but not depending solely on hippocampal input. Two possible mechanisms have been proposed to explain the particular spatial processing performed by subiculum. Firstly, arena boundaries could help subicular neurons to set their firing; secondly, subicular place cells could be updating their firing using a path integration system, which would allow them to update the position of the animal continuously. In relation to the first idea, Hartley et al. (2000) proposed the boundary vector cell model, which suggests that hippocampal place cells could be driven by units which fire in relation to a certain distance and angular position to the arena boundaries (boundary vector cells-BVCs). A recent formulation of the model suggests that units in the subiculum could act as BVCs (Barry et al., 2006). Following the second hypothesis, different authors have proposed the subiculum as a key element involved in a path integration system (McNaughton et al, 1996; Sharp, 1999). Sharp (1999) suggested that the subiculum and the entorhinal cortex would represent space as a universal map which could be used across all environments and which would help the hippocampus to generate a fine representation of each environment. This suggestion was based on data suggesting that not only subicular units but also entorhinal units use the same representation across different conditions (Quirk et al 1992). The recent discovery of grid cells (Hafting et al., 2005) would provide some evidence in this direction. "Grid" cells in dorsal medial entorhinal cortex (MEC) present a regular multi-peak structure and their firing pattern was characterised as having a grid-like structure; firing fields were constantly spaced and angular relations between them was always the same. These units seemed to produce more firing fields in larger arenas while preserving distance and angular relationships between firing peaks, therefore keeping the same grid-like structure. Although different firing field structures are displayed by grid cells and subicular units, both seem to share the capability of use the same firing scheme across multiple conditions. Thus, further experiments are necessary to elucidate the interaction between the subiculum and the entorhinal cortex.

In a series of investigations of subicular neuron response properties under differing behavioural/task conditions, we have recorded subicular unit and EEG in rats and correlated neuronal activity with animal's ongoing behaviour (Anderson and O'Mara, 2004). Units were classified into *bursting* and *regular spiking units* (similar to hippocampal CA1 "pyramidal" units); *fast-spiking units* (putative inhibitory interneurons) and *theta-modulated units* (previously undescribed: similar to regular spiking units, but whose firing increases significantly during theta). We conclude that subicular units can be separated into *at least* four classes (bursting, regular spiking, theta-modulated, and fast spiking) on the basis of the electrophysiological characteristics of their firing rate, spike duration, relationship with simultaneously recorded EEG, and spike train time characteristics. We have also found that subicular bursting units show large variation in their propensity to burst (see also Staff et al., 2000). The analysis of unit firing against behavioral state revealed few significant differences between pre- and post-event flag firing rates, and these appeared to be related to arousal levels or movement. The ACHs for bursting, regular spiking, and the fast spiking unit classes are similar to those of Sharp and Green (1994); although the bursting units described here show more variation than Sharp (1997; 1999), it is possible that their "depolarized bursters" are classified here as bursters. Sharp did not report theta-modulated units, but did not record EEG, so these units may have been assigned to the non-bursting class.

What of subicular neuronal responses during object exploration in an open-field environment? The subiculum receives a direct projection from the perirhinal cortex, where neurons are responsive to the novelty or familiarity of objects encountered in the environment. Anderson and O'Mara (2004) conducted recordings of subicular neuronal activity during object exploration tasks that cause changes in the exploratory behaviour of rats and which are dependent upon the integrity of structures within the hippocampal formation. The exploratory behaviour of the rats was also modified in a manner consistent with them perceiving the novelty and familiarity of the objects used as part of the apparatus. Subicular cell firing, however, appeared to correlate best not with object novelty or familiarity, but with the concurrent location and speed of the rats within the task environment.

In recent experiments, we have examined the effects of light–dark–light (LDL) or dark–light (DL) transitions on subicular unit activity. Quirk et al. (1990) found that the firing patterns of most hippocampal CA1 units persisted in the dark. The firing rate of about half of CA1 cells decreased slightly in the dark; the firing rate of the other half increased slightly in the dark. The second condition was dark–light. The largest group of cells was unaffected by darkness when it was immediately preceded by light (L–D–L), but showed a much different firing pattern during the D–L sequence—place cell activity could be totally unrelated to place-related firing in the L–D–L condition. The second group of cells was unaffected by either dark condition. The third group of cells displayed altered firing patterns across both dark conditions. The persistent firing of the majority of cells (c. 85%) can be explained by polymodal inputs to the hippocampus; such cells do not rely on purely visual information to generate their place fields. The remaining cells were sensitive to visual input, and showed altered firing when there was no light present. The effects of darkness and light show that visual cues cannot be the only determinant of spatial firing patterns in the dark; the dependence of firing patterns on conditions that precede the current ones might

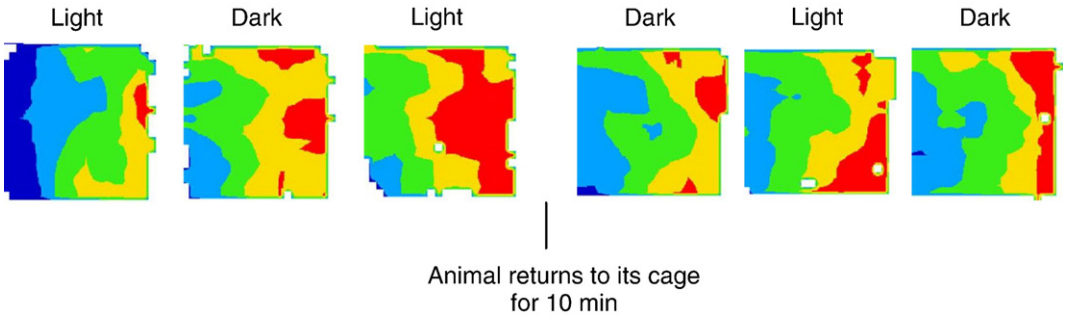

Fig. 1. An example of a subicular place cell, where the effects of transitions from light to dark to light within the one experimental arena were examined on place cell activity. This unit displayed a preferred firing location following the east barrier of the arena and was stable across all conditions independent of the order of the trial. There is a little drift evident in the peak of the firing field during the transition, but also a slight increase in maximal firing rate. The firing field's position remains more or less in the same place after the transition from dark to light.

reflect memory of earlier conditions (as in the L–D–L sequence in the Quirk et al. experiments). We have found that some subicular neurons also respond to light–dark transitions, but in a fashion that is different to hippocampal CA1 neurons. Overall, we have found that place cells in the subiculum seem to be stable across light–dark transitions (Fig. 1), but, contrary to hippocampal place cells (Quirk et al., 1990), the order of conditions (L–D–L vs. D–L) did not seem to affect subicular place cell firing stability. Spatial parameters such as firing field size, spatial coherence, mean frequency and spatial selectivity were not different between light and dark conditions or when protocols were compared. Finally, none of the recorded cells ceased firing during recordings in the dark, proving more robust in the dark than hippocampal place cells (see also: Markus et al., 1994; Save et al., 2000).

4. Memory

As noted above, the hippocampal formation has been implicated in memory for many years, and latterly specific roles for specific hippocampal formation subfields (including subiculum) during mnemonic processing have started to be discerned (e.g. Zeineh et al., 2003). A very important series of studies have been conducted by Deadwyler and Hampson (2004, 2006; also see Hampson and Deadwyler 2003) which have provided important insights into the specific and differential roles played by the subiculum and hippocampal area CA1 in supporting mnemonic processing during a very specific task-delayed non-match to sample (DNMS). These papers will be the particular focus of this section; there are several other papers indicating a specific role for the subiculum during memory (e.g. Ross and Eichenbaum, 2006), but they will not be reviewed here. The DNMS task employed requires a rat in an operant chamber to press a lever, engage in a variable number of nose pokes (to vary the delay) and then to press another lever to obtain liquid reinforcement. Either the left or right lever are presented on a random basis, and the animal is then required to nose poke within a photocell device a variable number of times (up to 30 s); after this delay the house light goes off and the rat is then presented with two levers, and must press the lever opposite to the lever pressed at the start of the trial. Simultaneously, the rats have been implanted with multielectrode bundles in dorsal hippocampal area CA1 and dorsal subiculum. This paradigm has numerous advantages (see Deadwyler and Hampson, 2004; 2006; Hampson and Deadwyler, 2003) for examining mnemonic processing by hippocampus and subiculum. The key advantages for the present discussion are the ability to systematically increase or decrease the sample intervals over a 30-fold time interval (1–30 s) and the demand that the rat remember across this interval the lever that had been pressed previously and to follow the rule to press the previously unpressed lever; finally, neuronal response, stimulus onsets and offsets and behavioural response can be very precisely time-locked, and thus variations in neuronal response can be very precisely correlated to behaviour and mnemonic load. The DNMS paradigm can therefore be used to elucidate the differing cell types underlying performance. Deadwyler and Hampson suggest that the temporal coupling between hippocampal CA1 and subicular neurons underlies retention of trial-specific information during DNMS tasks. Deadwyler and Hampson (2004) showed that hippocampal area CA1 and subiculum operate in a complementary fashion to encode information in a spatial delayed nonmatch-to-sample task. Subicular neuronal responses in the delayed-nonmatch-to-sample task were generally related to shorter delays (15 s or less), and the converse was true for CA1 neurons with activity that was generally related to long-delay (<15 s) trial-specific information. These data have a number of implications. A first major implication is that these data show how specific hippocampal subfields orchestrate their activity to support in a dynamic fashion an important aspect of mnemonic processing. Further, information is represented continuously over time within the differing components of the hippocampal formation. Finally, there is a dynamic responsivity in the representation to error and other aspects of ongoing behaviour: that is, when mistakes are made in performance (e.g. returning to the first pressed lever, rather than the unpressed lever) or when certain key behavioural events occur (e.g. nose-pokes), the neuronal response of subicular and area CA1 neurons changes as function of the behaviour that has occurred or is about to occur. The use of operant methodologies allows the investigation of stimulus- and response-locking of behaviour and neuronal response in a fashion that complements analyses available through unit recording in the freely-moving animal.

5. Motivation and reward

There are hints that the subiculum may play a role in motivation (see Cooper et al., 2006), specifically in instrumental behaviour assessed using operant conditioning and related techniques, as well as several suggestions that the subiculum may have a role in drug addiction or drug-seeking behaviours. There have been several suggestions of differences between the roles played by dorsal and ventral subiculum in memory and motivation-related processes (e.g. O'Mara, 2005; Herman and Mueller, 2006); the earliest hints of a possible dissociation between dorsal and ventral subicular function seem to derive from this literature. In what is probably the earliest study of its type, Segal (1972) reported a relationship between subicular unit activity and the sounding of a tone paired with food reward, offering a hint that there is reward-related activity in the subiculum. In an early paper, Rawlins et al. (1989) investigated the role of subicular outputs in the development of the partial-reinforcement extinction effect (PREE). Rats ran in an alley for food reward on every trial (Continuous Reinforcement, CR) or 50% of trials (Partial Reinforcement, PR); the running response was then extinguished via

non-reward for running. The PREE was present in sham-operated controls: PR-trained animals were significantly more resistant to extinction than CR-trained animals. The PREE was abolished by a knife cut interrupting the ventral subicular fibres destined for the ventral striatum. A functional anatomical dissociation was also observed (O'Mara & Walsh, 1997): there was a decrease in resistance to extinction in the lesion PR group, but a large lesion also encompassing the dorsal subicular pathway left the PREE intact. Rawlins et al. concluded that previous reports demonstrating reduction or abolition of the PREE following conventional total septal or lateral septal lesions, may have achieved their results through damage to subicular fibres en passage through the septum. Subsequently, Tonkiss and Rawlins (1992) performed either electrolytic mammillary body lesions or restricted electrolytic subicular output lesions and found that subicular output lesions produced subtle long-lasting differential reinforcement of low-rate responding (DRL) impairments in rats. Rats with transection of fibres projecting from subiculum to ventral striatum showed systematic variations in timing behaviour, compared to the other groups.

Using pharmacological methods, Andrzejewski et al. (2006) provided evidence for a possible dissociation of function between dorsal and ventral subiculum during instrumental (operant) learning, motor behavior, and general motivation. Andrzejewski et al. (2006) reasoned that inhibition of the dopamine receptor cascade should impair learning and memory and that inhibition of dopaminergic transmission in ventral subiculum in particular should impair acquisition of instrumental learning, given a previous demonstration of the role of ventral subiculum in cocaine-reinforced instrumental learning (Sun & Rebec, 2003). They infused the selective D1R antagonist SCH-23390, targeted bilaterally into either dorsal *or* ventral subiculum, and found that the effects of selective D1 antagonism differed substantially depending on whether the infusions were dorsally or ventrally directed in subiculum. They conducted three experiments: an investigation of instrumental learning and performance; an investigation of the effects of a progressive ratio (PR) schedule of reinforcement; and finally and importantly, an investigation of spontaneous locomotor feeding behavior. Andrzejewski et al. found that ventral subicular D1R antagonism resulted in deficits in instrumental learning and performance, a reduced break point in PR tests, and an intra-session decline in responses during test sessions. Ventral subicular D1R antagonism was without obvious effect on spontaneous motor or food-directed behavior. By contrast, dorsal subicular D1R antagonism had no effect on instrumental learning, performance, PR break point, or food-directed behavior, but did reduce spontaneous motor behavior (assayed by spontaneous locomotion and feeding behavior). These experiments provide convincing evidence that the functions of dorsal and ventral subiculum are dissociable. Dorsal subiculum does not appear to play any particularly special role in instrumental behavior (either acquisition or performance) compared to ventral subiculum during instrumental learning. Thus, Andrzejewski et al.'s work also hints at an important function for ventral subiculum: that it acts as a physiological interface between memory and motivation systems within the brain (see also Vorel et al., 2001).

5.1. Drug addiction and drug-seeking in relation to subicular function

Several studies are starting to define a role for ventral subiculum, in particular, in the brain circuits involved in addiction; some studies that illustrate this point will be reviewed here. In a study investigating relapse to cocaine-seeking in freely-moving animals, Vorel et al. (2001) found that theta-burst stimulation mimicking endogenous EEG rhythms via electrodes implanted in ventral subiculum reinstated cocaine-seeking behaviour and cocaine self-administration in freely-moving rats. Stimulation at other rates did not cause this relapse—the effect was specific to stimulation rates representative of characteristic EEG signatures found in the hippocampal formation during exploration. Furthermore, pharmacological blockade of a specific ventral subicular target–the ventral tegmentum area (VTA)–using the non-selective glutamergic ionotropic glutamergic receptor antagonist kynurenic acid applied into the VTA, prevented this stimulation-induced relapse. These data imply that there is an important role for ventral subiculum in the control of some aspects of the behaviours associated with addiction. In an interesting *ex vivo* neurophysiological study, Cooper et al. (2003) treated rats with five daily injections of amphetamine or saline, and subsequently harvested ventral subicular brain slices either 1–3 days or 14 days after withdrawing amphetamine treatment. They found that neuronal excitability was decreased for days but not weeks after amphetamine withdrawal. Bursting activity, characteristic of subicular neuronal activity, was suppressed in the short-term withdrawal animals and action potential thresholds increased. These data provide the first evidence that psychostimulants can cause plasticity of hippocampal formation output. Cooper et al. (2006) have subsequently shown that acute cocaine administration in ventral subicular slices changes bursting cells from burst-firing mode to single-spiking mode; thus, it can be concluded that certain psychoactive drugs disrupt the normal pattern of switching between burst-firing and single-spiking. A parallel series of studies (Martin and Ono, 2000; Martin, 2001) in which simultaneous recordings of dorsal subiculum and nucleus accumbens were performed in association with a stimulating electrode in the medial forebrain bundle (MFB) to induce stimulation reward as revealed that both subicular and nucleus accumbens neurons modulate their firing rate during the anticipation of reward. Rats were trained on a spatial task where they received stimulation reward in random spatial locations. When a cue was sounded, stimulation reward was also available in the center of the cylindrical recording arena. The rats quickly learned to move to the centre of the arena to receive stimulation reward. Simultaneously recorded groups of subicular and accumbens neurons showed altered firing rates after MFB stimulation. Interestingly, subicular and nucleus accumbens neurons altered their firing rates before arriving in the arena center when cued: they anticipated predictable rewards.

5.2. Fear, anxiety and stress

A role for subiculum, and particularly, ventral subiculum is increasingly being defined for components of the overall pattern of response during fear, anxiety and stress; this role arises from the pivotal position of the ventral subiculum with respect to the hypothalamic–pituitary–adrenal (HPA) axis. In a comprehensive review of the relevant anatomy Lowry (2002) suggests that ventral subiculum exerts a dynamic and inhibitory influence on the HPA axis, and therefore substantially orchestrates the stress response: Lowry suggests that "[N]o neural system is so exquisitely poised to limit the activity of the HPA axis, as well as the autonomic and behavioural elements of the stress response to unconditioned stimuli' as is ventral subiculum." The subiculum is therefore likely to have a pivotal role in the regulation of the response to stress: a straightforward prediction is that ventral subicular lesions should attenuate the HPA response to systemic and behavioural stressors, and this is what appears to occur (Mueller et al., 2004; Herman and Mueller, 2006). 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 post-training 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. Standard long-term depression induction protocols do not induce depression of synaptic transmission in the CA1-subiculum pathway (Anderson et al., 2000),

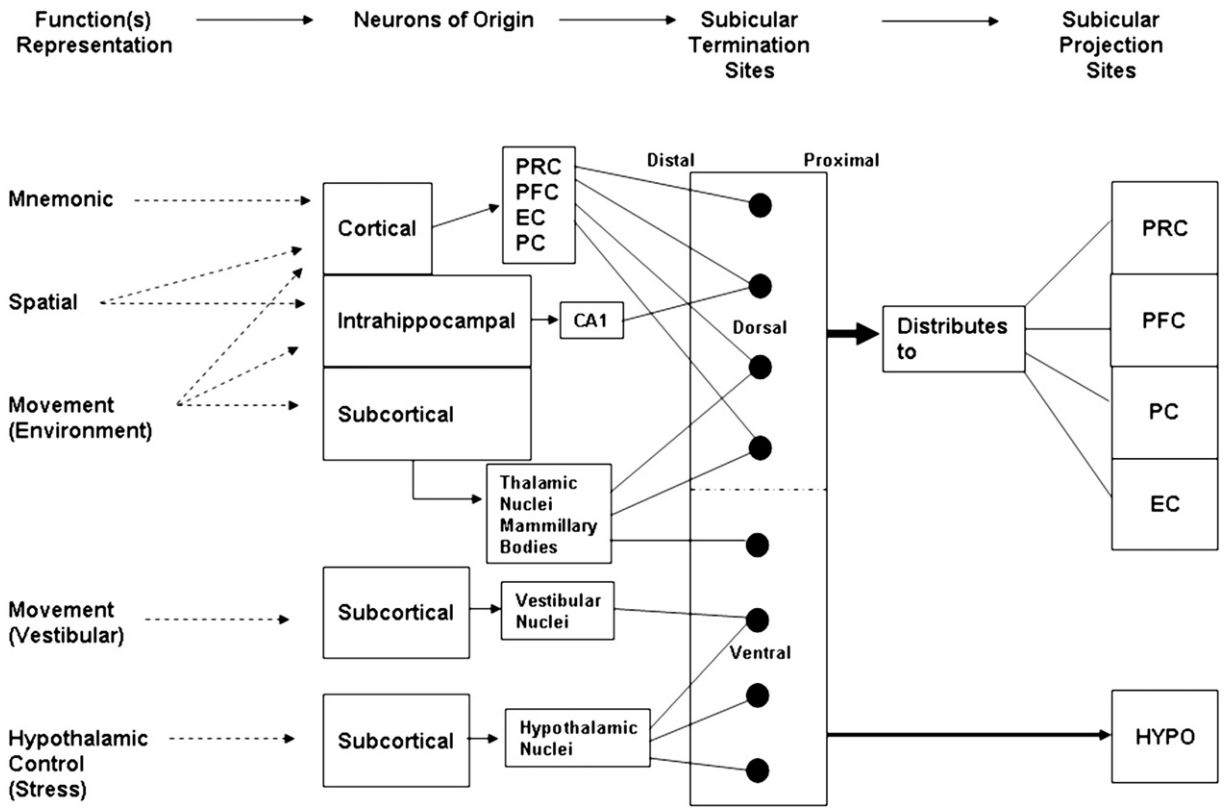

Fig. 2. A model of subicular function(s) (see text for full details). Here, synaptic transmission and anatomical connectivity runs from left to right (a deliberate simplification); information of differing types (mnemonic, etc.) derives from various anteceding cortical and subcortical circuits, and is projected to the subiculum, converging in particular patterns, thereby giving rise to differing neuronal response types. EC: entorhinal cortex; Hypo: hypothalamus; PRC: perirhinal cortex; PFC: prefrontal cortex; PC: parietal cortex. For simplification no details of distal–proximal distribution of fibres is provided (but these do vary); nor are there details of intrasubicular longitudinal associational fibres.

but prior behavioural stress (inescapable photic stimulation) facilitates substantial and sustained LTD induction in this pathway (Commins and O'Mara, 2000). Behavioural stress also abolishes paired-pulse facilitation by increasing the amplitude of the first excitatory postsynaptic potential (EPSP) of EPSP pairs at a short interval pair (50 ms), and causes paired-pulse depression with a long interval pair (100 ms). Thus, behavioural stress can regulate both basal and paired-pulse (presynaptic) synaptic transmission in this key hippocampal output pathway.

6. Some implications: a model of subicular functions in space, memory, motivation and the temporal control of behaviour

What are the functions of the subiculum, given its pivotal position as an interface between the hippocampus proper and key cortical and subcortical structures? A simple framework for understanding subicular function has been provided by O'Mara (2005) and O'Mara et al. (2001) (Fig. 2). O'Mara et al. (2001) suggested that 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 outputs received from hippocampus. 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 (Anderson and O'Mara, 2003; Staff et al., 2000; Stewart and Wong, 1993); it is notable that drug (amphetamine) action can suppress this characteristic form of subicular neuronal activity. Recent data indicating a central role for subiculum in the propagation of epileptiform activity from human hippocampus to cortex supports this view (Cohen et al., 2002). Subsequently, O'Mara (2005) and Brotons et al. (2006) proposed there is a dorso-ventral segregation of function within the subiculum: with dorsal subiculum principally concerned with processing of information about space, movement and memory, and ventral subiculum acting as an interface between the hippocampal formation and the hypothalamic–adrenal–pituitary (HPA) axis (where it plays a major regulatory role in the inhibition of the HPA axis; Lowry 2002). It was also suggested that subicular neurons have convergent inputs from within and without the hippocampal formation, and that the particular pattern of convergence of neuronal inputs determines the response properties of subicular neurons in dorsal and ventral subiculum.

What are the implications of this model? As noted above, subicular neurons show multiple peaks of activity within an environment, and consistently are modulated by movement-related activity. Multiple CA1 place cells (perhaps up to 4 or 5) may converge on single subicular neurons in addition to a convergence of movement information onto single subicular neurons. These separate inputs generate a combined place and movement signal. The multiple peaks of place-related activity reflect separate place cell inputs, whereas the movement signal is assumed to derive primarily from tonic inputs from CA1 inputs, in addition to inputs from other cortical sources that converge on entorhinal cortex. We predict therefore that microlesions of the inputs from entorhinal cortex to subiculum will substantially reduce the movement modulation of subicular neurons (as will carefully placed microlesions in CA1), although these latter lesions will further reduce the spatial selectivity of subicular neuronal

response. Overall, therefore, we suggest that dorsal subiculum is a site of integration between hippocampal spatial information and whole-body movement-related information. Finally, we assume that cortical inputs from other areas (particularly entorhinal prefrontal and perirhinal cortices) are important determinants of subicular neuronal response, giving rise to the possibility of subicular neurons that combine spatial and working memory information and neurons that combine spatial and object information. There is some evidence for the former possibility (Deadwyler and Hampson, 2004), and less for the latter (Anderson and O'Mara, 2004).

We assume here, along with Lowry (2002), that ventral subiculum exerts a dynamic and inhibitory influence on the HPA axis, and therefore substantially orchestrates the stress response. The subiculum is therefore likely to have a pivotal role in the regulation of the response to stress: a straightforward prediction is that ventral subicular lesions should attenuate the HPA response to systemic and behavioural stressors, and this is what appears to occur (Herman and Mueller, 2006). We assume further here that the prefrontal cortical inputs to the hypothalamus are to the same hypothalamic nuclei as are those of subicular neurons, but that these prefrontal inputs are primarily to excitatory neurons (allowing for a rapid activation of the HPA axis in response to evaluations of extero- or interoceptive stimuli). A straightforward prediction is that the prefrontal-hypothalamic projection should show synaptic plasticity, and the strong possibility that potentiation of this pathway should lead to a collateral heterosynaptic depression of the subicular input to the same hypothalamic nuclei (assuming here the functional roles of prefrontal cortical and subicular projections to the hypothalamus are opposed: the prefrontal input is excitatory and the subicular input is inhibitory). A direct test of this hypothesis can be made by showing there is a double dissociation of function within the subiculum: dorsal subicular lesions should leave ventral subicular control of the HPA axis unaffected and ventral subicular lesions should leave the role of dorsal subiculum in spatial representation unaffected. Similarly, ventral lesions should leave synaptic transmission through the dorsal CA1-dorsal subiculum-entorhinal cortex axis unaffected, and dorsal lesions should leave synaptic transmission through the ventral CA1-ventral subiculum-entorhinal cortex axis unaffected.

The model presented here revolves around two key hypotheses: that there is a dorso-ventral segregation of function within subiculum and that the particular pattern of convergence of inputs to subicular neurons determines the functional/representational response properties of single subicular neurons. Are these hypotheses correct? A straightforward answer is not yet possible, because the neuroanatomy is as yet underdetermined, but the model clearly falls if the neuroanatomy turns out to be other than as predicted. The particular pattern of convergence of separate CA1 neurons (or neurons from other cortical areas) onto single subicular neurons has not yet been described; similarly, whether this projection is a straightforwardly feedforward monosynaptic excitatory projection (as assumed here), rather than a more complex polysynaptic or oligosynaptic projection involving complex feedforward and feedback elements is not yet known. Similarly, convergent projections from differing cortical areas leading to integrative and polymodal responses are assumed here to occur, but there are no data available yet to address this question in any meaningfully quantitative way. Another prediction here is that quantitative inputs to subiculum are segregated: the bulk of inputs to dorsal subiculum are either hippocampal or cortical in origin, whereas the bulk of inputs to ventral subiculum are subcortical in origin. The pattern of return projections is predicted to follow a similar fashion: the majority of dorsal subicular projections are returned to cortical sites, whereas the majority of ventral subicular projections are to subcortical sites. In respect of these latter projections, a further assumption is made: that projections from prefrontal cortex terminate directly in the same hypothalamic nuclei as those from ventral subiculum (allowing top-down cognitive control of the response to stress), whereas the projections from ventral subiculum to these neurons are mediated transynaptically via GABAergic neurons: thus, the PFC input is directly excitatory and the ventral subicular inputs are inhibitory.

A further unknown is the role that intrasubicular associational fibres play: do these intrinsic projection fibres converge on neurons across whole dorso-ventral subicular axis, and thus reduce segregation of function within the subiculum? Here it is assumed that such fibres have a role in maintaining neurophysiological tone and patency across the dorso-ventral subicular axis and that they have a functional role in information representation by allowing ventral subicular neurons some access to mnemonic information processed by dorsal CA1 and dorsal subiculum. The possibility that there is limited information transmission from dorsal to ventral subiculum and vice versa via these associational fibres appears reasonable, as this may in turn mean that mnemonic information in dorsal subiculum can prime activation in ventral subiculum, thereby contributing to or supporting in some limited way a direct effect of spatio-mnemonic processing on the HPA axis. A direct test of this hypothesis can be made by showing there is a double dissociation of function within the subiculum: dorsal subicular lesions should leave ventral subicular control of the HPA axis unaffected and ventral subicular lesions should leave the role of dorsal subiculum in spatial representation unaffected. Similarly, ventral lesions should leave synaptic transmission through the dorsal CA1-dorsal subiculum-entorhinal cortex axis unaffected, and dorsal lesions should leave synaptic transmission through the ventral CA1-ventral subiculum-entorhinal cortex axis unaffected. Finally, it may be the case that the whole subiculum participates in the temporal control of reinforced behaviour, and these fibres may contribute to this.

Acknowledgements

Supported by the Government of Ireland Higher Education Authority Programme for Research in Third-Level Institutions (SMOM); the (SMOM); EU FET project PRESENCCIA (IST-2006-27731) to MVSV.

References

Amaral DG, Dolorfo C, Alvarez-Royo P. Organization of CA1 projections to the subiculum: a PHA-L analysis in the rat. Hippocampus 1991;1:415–35.
Amaral DG, Witter MP. Hippocampal formation. In: Paxinos G, editor. The Rat Nervous System. 2nd edn. New York: Academic Press; 1995. p. 247–91.
Anderson M, Commins S, O'Mara SM. The effects of low frequency and two-pulse stimulation protocols on synaptic transmission in the CA1-subiculum pathway in the anaesthetized rat. Neurosci Lett 2000;279:181–4.
Anderson M, O'Mara SM. Analysis of recordings of single-unit firing and population activity in the subiculum of unrestrained, freely-moving rats. J Neurophysiol 2003;90:655–65.
Anderson M, O'Mara SM. Activity of subicular units on a spatial and non-spatial version of an open-field object exploration task. Experiment Brain Res 2004;159:519–29.
Andrzejewski ME, Spencer RC, Kelley AE. Dissociating ventral dorsal subicular dopamine-D1 receptor involvement in instrumental learning spontaneous motor behavior motivation. Behav Neurosci 2006;120:542–53.
Barnes CA, McNaughton BL, Mizumori SJ, Leonard BW, Lin LH. Comparison of spatial and temporal characteristics of neuronal activity in sequential stages of hippocampal processing. Prog Brain Res 1990;83:287–300.
Barry C, Lever C, Hayman R, Hartley T, Burton S, O'Keefe J, et al. The boundary vector cell model of place cell firing and spatial memory. Rev Neurosci 2006;17:71–97.
Brotons J, O'Mara SM, Sanchez-Vives MV. Neural processing of spatial information: what we know about place cells and what they can tell us about presence. Presence: Teleoper Virtual Environ 2006;15:485–99.
Canteras NS, Swanson LW. Projections of the ventral subiculum to the amygdala, septum, and hypothalamus: a PHA-L anterograde tract-tracing study in the rat. J Comp Neurol 1992;324:180–94.
Cohen I, Navarro V, Clemenceau S, Baulac M, Miles R. On the origin of interictal activity in human temporal lobe epilepsy *in vitro*. Science 2002;298:1418–21.
Commins S, O'Mara SM. Interactions between paired-pulse facilitation, low-frequency stimulation and behavioral stress in the pathway from hippocampal area CA1 to the subiculum: dissociation of baseline synaptic transmission from paired-pulse facilitation and depression of the same pathway. Psychobiology 2000;28:1-11.
Commins S, Aggleton JP, O'Mara SM. Physiological evidence for a projection from the subiculum to hippocampal area CA1. Experimental Brain Research 2002;146:155–60.
Cooper DC, Moore SJ, Staff NP, Spruston N. Psychostimulant-induced plasticity of intrinsic neuronal excitability in ventral subiculum. J Neurosci. 2003 Oct 29;23 (30):9937–46.

Cooper DC, Klipec WD, Fowler MA, Ozkan ED. A role for the subiculum in the brain motivation/reward circuitry. Behav Brain Res. 2006 Nov 11;174(2):225–31.
Deadwyler SA, Hampson RE. Differential but complementary mnemonic functions of the hippocampus and subiculum. Neuron 2004;42:465–76.
Deadwyler SA, Hampson RE. Temporal coupling between subicular and hippocampal neurons underlies retention of trial-specific events. Behav Brain Res 2006;174:272–80.
Galani R, Jarrard LE, Will BE, Kelche C. Effects of postoperative housing conditions on functional recovery in rats with lesions of the hippocampus, subiculum or entorhinal cortex. Neurobiol Learn Mem 1997;67:43–56.
Galani R, Coutureau E, Kelche C. Effects of enriched postoperative housing conditions on spatial memory deficits in rats with selective lesions of either the hippocampus, subiculum or entorhinal cortex. Resto Neurol Neurosci 1998;13:173–84.
Gigg J, Finch DM, O'Mara SM. Responses of morphologically characterized rat subicular neurons to stimulation of CA1 and lateral entorhinal cortex *in vivo*. Brain Res 2000;884:35–50.
Hafting T, Fyhn M, Molden S, Moser MB, Moser EI. Microstructure of a spatial map in the entorhinal cortex. Nature 2005;436:801–6.
Hartley T, Burgess N, Lever C, Cacucci F, O'Keefe J. Modeling place fields in terms of the cortical inputs to the hippocampus. Hippocampus 2000;10:369–79.
Hampson RE, Deadwyler SA. Temporal firing characteristics and the strategic role of subicular neurons in short-term memory. Hippocampus 2003;13:529–41.
Herman JP, Mueller NK. Role of the ventral subiculum in stress integration. Behavioural Brain Research 2006;174:215–24.
Jung MW, McNaughton BL. Spatial selectivity of unit activity in the hippocampal granular layer. Hippocampus 1993;3:165–82.
Kohler C. Subicular projections to the hypothalamus and brainstem: some novel aspects revealed in the rat by the anterograde PHA-L tracing method. Prog Brain Res 1990;83:59–69.
Lowry CA. Functional subsets of serotonergic neurones: implications for control of the hypothalamic–pituitary–adrenal axis. J Neuroendocrinology 2002;14:911–23.
Markus EJ, Barnes CA, McNaughton BL, Gladden VL, Skaggs WE. Spatial information content and reliability of hippocampal CA1 neurons: effects of visual input. Hippocampus. 1994 Aug;4(4):410–21.
Maren S. Neurotoxic or electrolytic lesions of the ventral subiculum produce deficits in the acquisition and expression of Pavlovian fear conditioning in rats. Behav Neurosci. 1999 Apr;113(2):283–90.
Martin PD. Locomotion towards a goal alters the synchronous firing of neurons recorded simultaneously in the subiculum and nucleus accumbens of rats. Behav Brain Res. 2001 Sep 28;124(1):19–28.
Martin PD, Ono T. Effects of reward anticipation, reward presentation, and spatial parameters on the firing of single neurons recorded in the subiculum and nucleus accumbens of freely moving rats. Behav Brain Res. 2000 Nov 15;116(1):23–38.
McNaughton BL, Barnes CA, Gerrard JL, Gothard K, Jung MW, Knierim JJ, et al. Deciphering the hippocampal polyglot: the hippocampus as a path integration system. J Exp Biol 1996;199:173–85.
Menendez de la Prida L, Totterdell S, Gigg J, Miles R. The subiculum comes of age. Hippocampus 2006;16:916–23.
Morris RG, Schenk F, Tweedie F, Jarrard LE. Ibotenate lesions of hippocampus and/or subiculum: dissociating components of allocentric spatial learning. Eur J Neurosci 1990;2:1016–28.
Muller RU, Kubie JL, Bostock EM, Taube JS, Quirk GJ. Spatial firing correlates of neurons in the hippocampal formation of freely-moving rats. In: Paillard J, editor. Brain Space. Oxford: Oxford University Press; 1991.
Mueller NK, Dolgas CM, Herman JP. Stressor-selective role of the ventral subiculum in regulation of neuroendocrine stress responses. Endocrinology. 2004 Aug;145(8):3763–8.
O'Keefe J. A review of the hippocampal place cells. Prog Neurobiol 1979;13(4):419–39.
O'Keefe J, Nadel L. The hippocampus as a cognitive map. Oxford: Clarendon Press; 1978.
O'Mara SM. Spatially selective firing properties of hippocampal formation neurons in rodents and primates. Prog Neurobiol 1995;45:253–74.
O'Mara SM. The subiculum: what it does, what it might do, and what neuroanatomy has yet to tell us. J Anatom 2005;207:271–82.
O'Mara SM, Commins S, Anderson M. Synaptic plasticity in the hippocampal area CA1-subiculum projection: implications for theories of memory. Hippocampus 2000;10:447–56.
O'Mara SM, Commins S, Anderson M, Gigg J. The subiculum: a review of form, physiology and function. Prog Neurobiol. 2001 Jun;64(2):129–55.
O'Mara SM, Walsh V. Experimental neuropsychology: the logic of, and lessons from, lesions. In: Lynch MA, O'Mara SM, editors. Neuroscience Labfax. London: Academic Press; 1997.
Oswald CJP, Good M. The effects of combined lesions of the subicular complex and the entorhinal cortex on two forms of spatial navigation in the water maze. Behav Neurosci 2000;114:211–7.
Pearce JM, Roberts ADL, Good M. Hippocampal lesions disrupt navigation based on cognitive maps but not heading vectors. Nature 1998;396:75–7.
Poucet B. Object exploration, habituation, and response to a spatial change in rats following septal or medial frontal cortical damage. Behav Neurosci. 1989 Oct;103(5):1009–16.
Quirk GJ, Muller RU, Kubie JL. The firing of hippocampal place cells in the dark depends on the rat's recent experience. J Neurosci. 1990 Jun;10(6):2008–17.
Quirk GJ, Muller RU , Kubie JL , Ranck Jr JB. The positional firing properties of medial entorhinal neurons: description and comparison with hippocampal place cells J. Neurosci., May 1992;12:1945–1963.
Rawlins JN, Feldon J, Tonkiss J, Coffey PJ. The role of subicular outputs in the development of the partial reinforcement extinction effect. Exp Brain Res 1989;77:153–60.
Risold PY, Thompson RH, Swanson LW. The structural organization of connections between hypothalamus and cerebral cortex. Brain Res Rev 1997;19:197–254.
Ross RS, Eichenbaum H. Dynamics of hippocampal and cortical activation during consolidation of a nonspatial memory. J Neurosci 2006;26:4852–9.
Save E, Nerad L, Poucet B. Contribution of multiple sensory information to place field stability in hippocampal place cells. Hippocampus 2000;10(1):64–76.
Schenk F, Morris RG. Dissociation between components of spatial memory in rats after recovery from the effects of retrohippocampal lesions. Exp Brain Res 1985;58:11–28.
Segal M. Hippocampal unit responses to perforant path stimulation. Exp. Neurol 1972;35:541–6.
Sharp PE. Complimentary roles for hippocampal versus subicular/entorhinal place cells in coding place, context, and events. Hippocampus 1999;9(4):432–43.
Sharp PE. Subicular cells generate similar spatial firing patterns in two geometrically and visually distinctive environments: comparison with hippocampal place cells. Behav Brain Res 1997;85:71–92.
Sharp PE, Green C. Spatial correlates of firing patterns of single cells in the subiculum of the freely moving rat. J. Neurosci 1994;14:2339–56.
Staff NP, Jung HY, Thiagarajan T, Yao M, Spruston N. Resting and active properties of pyramidal neurons in subiculum and CA1 of rat hippocampus. J Neurophysiol 2000;84:2398–408.
Stewart M, Wong RK. Intrinsic properties and evoked responses of guinea pig subicular neurons in vitro. J Neurophysiol 1993;70:232–45.
Swanson LW, Kohler C, Bjorklund A. The limbic region. I. The septohippocampal system. In: Bjorklund A, Hokfelt T, Swanson LW, editors. Handbook of Chemical Neuroanatomy, Integrated Systems of the CNS, vol. 5. Amsterdam: Elsevier; 1987. p. 125–227.
Sun W, Rebec GV. Lidocaine inactivation of ventral subiculum attenuates cocaine-seeking behavior in rats. J Neurosci. 2003 Nov 12;23(32):10258–64.
Tonkiss J, Rawlins JN. Mammillary body lesions and restricted subicular output lesions produce long-lasting DRL performance impairments in rats. Exp Brain Res 1992;90:572–82.
Vorel SR, Liu X, Hayes RJ, Spector JA, Gardner EL. Relapse to cocaine-seeking after hippocampal theta burst stimulation. Science 2001;292:1175–8.
Witter MP, Groenewegen HJ, Lopes da Silva FH, Lohman AH. Functional organization of the extrinsic and intrinsic circuitry of the parahippocampal region. Prog Neurobiol. 1989;33(3):161–253.
Witter MP, Groenewegen HJ. The subiculum: cytoarchitectonically a simple structure, but hodologically complex. In understanding the brain through the hippocampus. In: Storm-Mathisen J, Zimmer J, Otterson OP, editors. Progress in Brain Research. Amsterdam: Elsevier; 1990. p. 47–58.
Zeineh MM, Engel SA, Thompson PM, Bookheimer SY. Dynamics of the hippocampus during encoding and retrieval of face-name pairs. Science 2003;299:577–80.