

Research report

Neurophysiological and computational analyses of the primate presubiculum, subiculum and related areas

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Abstract

Head direction cells are described in the presubiculum of the macaque, used as a model of what is likely to be present in humans. The firing rate of these cells is a function of the head direction of the monkey, with a response that is typically 10–100 times larger to the optimal as compared to the opposite head direction. The mean half-amplitude width of the tuning of the cells was 76°. The response of head direction cells in the presubiculum was not influenced by the place where the monkey was, by the ‘spatial view’ observed by the monkey, and also the position of the eyes in the head. The cells maintained their tuning for periods of at least several minutes when the view details were obscured or the room was darkened.

This representation of head direction could be useful together with the hippocampal spatial view cells and whole body motion cells in primates in such memory and spatial functions as episodic memory and path integration. Discrete and continuous attractor networks can be combined so that they contain both object and spatial information, and thus provide a model of episodic memory. Self-organizing continuous attractor neural networks that can perform path integration from velocity signals (e.g. head direction from head rotational velocity, and place from whole body motion) are described.

The role of the subiculum in the backprojection pathways from the hippocampus to the neocortex in a quantitative model of the recall of memories from the hippocampus is described.

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1. Introduction

The aims of this paper are to review the neurophysiology of the primate presubiculum, and to consider separately the possible computational functions of the subiculum.

The location of the primate subiculum and presubiculum in the primate temporal lobe are shown in Fig. 1. Topologically, the rat ventral hippocampus may be thought of as corresponding with the primate anterior hippocampus, and the rodent dorsal hippocampus as it rotates down into the primate temporal lobe as corresponding with the primate posterior hippocampus.

2. Presubiculum: head direction cells in primates

In this section, I will show that there are head direction cells in primates as well as rats; will describe their properties; will show that a new class of cell found in the primate hippocampus, spatial view cells, are different from head direction cells and from rat place cells; will show the utility of spatial view cells in forming episodic memories; will show how a single network can associate together both discrete representations about objects and continuous spatial representations to form episodic memories; and will show how path integration may be performed in continuous attractor networks to update their spatial representations by idiothetic (self-motion) cues in the dark.

While making recordings of spatial view cells (which respond to a location in space being viewed by the monkey, and are described below) in the actively locomoting monkey [12,31,36,44,47,52], Robertson et al. [32] discovered a popu-

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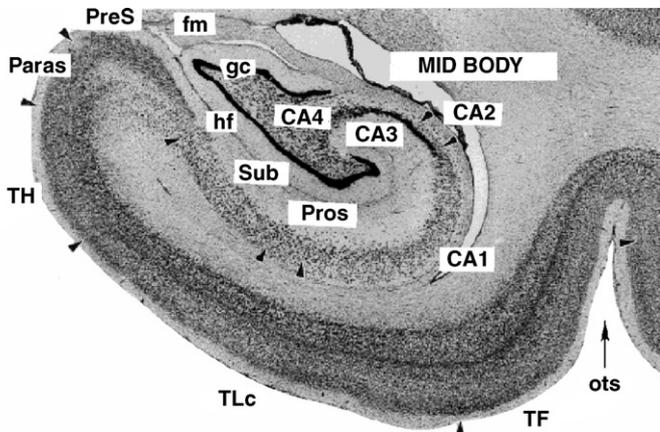


Fig. 1. Thionin-stained coronal section through the monkey hippocampal formation (HF), including the adjacent parahippocampal gyrus. CA1–CA4: hippocampal subfields; fm: fimbria; gc: granule cells in the dentate gyrus; hf: hippocampal formation; ProS: prosubiculum; Sub: subiculum; PreS: presubiculum (PreS); ParaS: parasubiculum; TF, TH, TL: areas of the parahippocampal gyrus; ots: occipitotemporal sulcus. (After Blatt and Rosene [4].)

lation of neurons not previously found in primates which we call head direction cells. We call these cells head direction cells because they have many similarities to head direction cells in rats. Rat head direction cells have a firing rate which is a simple function of head direction in the horizontal plane (see [22,62,66]). The firing does not depend on the place where the rat is located. The cells in the rat are found in the dorsal presubiculum (also referred to as the postsubiculum), and also in some other brain structures including the anterior thalamic

nuclei [62,66]. The rat head direction cells appear to be able to be influenced by vestibular (and/or other self-motion related) input, in that they maintain and update their tuning even when the rat is in darkness. The cells can be reset by visual landmarks. The discovery of head direction cells in primates is of interest, because it provides useful evidence with which to develop hypotheses of primate hippocampal function in the context of what is encoded in the primate hippocampus in terms of spatial view.

To perform the experiments we arranged for the monkey to see positions in space with different head directions, with different eye positions, and when the monkey was located at different positions in the laboratory. The recordings were made both during active locomotion with the monkey walking (on all 4 feet in a baby walker), and when the monkey was still for a few seconds visually exploring the environment by eye movements. The neuronal activity for a cell was sorted according to each hypothesis to be tested (head direction, allocentric view, place, and eye position), and an ANOVA was performed to determine whether the cell had significantly different firing rates when sorted according to each of the hypotheses. In addition, the quantitative measure of the information that was available in the firing rate of the cell about the different hypotheses was calculated. We were able to show for example that these cells convey much more information about head direction than about spatial view, the place where the monkey is, or about eye position. The transmitted information carried by neuronal firing rates about the stimuli was computed with the use of techniques that have been described fully previously [40,41,46,51].

An example of a head direction cell recorded in a macaque is shown in Fig. 2 (av070c2). The data for this diagram were

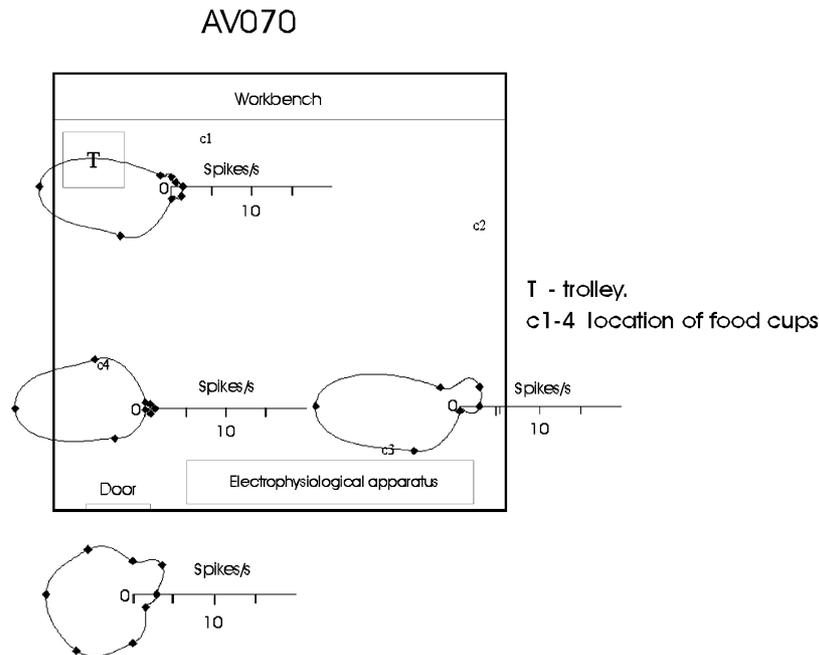


Fig. 2. The responses of a macaque head direction cell. Polar response plots of the firing rate (in spikes/s) when the monkey was stationary at different positions (shown at the 0 on the firing rate scale) in (and one outside) the room are shown. The monkey was rotated to face in each direction. The mean response of the cell from at least four different firing rate measurements in each head direction in pseudorandom sequence is shown. c1–c3: cups to which the monkey could walk on all fours to obtain food. Polar firing rate response plots are superimposed on an overhead view of the square room to show where the firing for each plot was recorded. The plot at the lower left was taken outside the room, in the corridor, where the same head direction firing was maintained.

obtained with the monkey stationary in the positions shown at the 0 on the firing rate scale. The mean response of the cell from at least four different firing rate measurements in each head direction is shown. The polar firing rate response plot shows that the cell had its maximum firing rate when the monkey was facing “west”. The polar response plots were remarkably similar for three different positions in the room. A one-way ANOVA for the different head directions showed highly significantly different firing for the different head directions ($F(1, 7) = 51.1, P < 0.0001$) (see Table 1). The average information over the eight head directions was 0.58 bits, and the maximal information about any one head direction was 2.26 bits (see Table 1). The cell showed the same head direction tuning outside the laboratory in the corridor (see Fig. 2), a place where the monkey had never been previously walking at floor level. When the data for the cell were cast to show how much information the cell firing provided about the place where the monkey was located, the information was low (0.16 bits), and the ANOVA across different places was not significant (see Table 1). The neuron conveyed little information about spatial view (0.08 bits), in that the firing rate of the cell was very similar inside and outside the room even though the spatial views were completely different. The cell was located in the presubiculum (see Fig. 4).

The results of an experiment in which the firing of a head direction cell was recorded for many minutes while the room was completely obscured by ceiling-to-floor curtains is shown in Fig. 3, curve b (av115c3). The head direction tuning was very similar when the curtains were drawn closed with the monkey in situ (compare to Fig. 3, curve a with the curtains open). When the room lights were subsequently extinguished so that the square space enclosed by the curtains (which could provide a minimal reference frame) was no longer visible, a head direction tuning curve was still present, though with no visual anchor at all, the peak of the tuning did drift a little during 5 min in darkness, as shown in Fig. 3, curve c. This is consistent with the hypothesis that visual cues can reset the cells, and prevent them from drifting over long periods. This is similar to the hypothesis for head direction cells in rats (see [22,62]).

The results over all head direction cells fully tested are shown in Tables 1 and 2 which summarizes the half-amplitude tuning widths of the cells, and the peak firing rates. For cells av070 and av115, data were not available (n.a.) for eye position. The first four cells in Table 1 were recorded in the presubiculum, and were among a set of 12 different cells analyzed in the presubiculum. The individual head direction cells shown in Table 1 had very highly significant head direction tuning, as shown.

It was also shown that the information about head direction increased approximately linearly as the number of cells in the sample was increased from one to four [32]. Thus, up to this number of cells, approximately independent information was conveyed by the neurons. (The application of information theory to analyzing neuronal responses is described by Rolls and Treves [40] and Rolls and Deco [41].)

The sites in the brain where the head direction cells were located are shown in Fig. 4. All the cells had low spon-

Table 1
Head direction cells

Cell	Head direction			Allocentric view			Eye position			Place		
	Information (bits)	I_{max} (bits)	ANOVA F (d.f.), P	Information (bits)	I_{max} (bits)	ANOVA F (d.f.), P	Information (bits)	I_{max} (bits)	ANOVA F (d.f.), P	Information (bits)	I_{max} (bits)	ANOVA F (d.f.), P
av070	0.58	2.26	51.1 (7), $<10^{-4}$	0.08	0.08	0.776 (1), 0.391				0.16	0.49	1.78 (3), 0.153
av115	0.62	2.59	23.5 (7), $<10^{-4}$	0.09	0.10	2.91 (1), 0.103		n.a.		0.03	0.05	1.08 (2), 0.342
av195	1.11	1.67	59.21 (23), 3×10^{-16}	0.55	1.74	49.31 (14), 0.0001	0.03	n.a.	3.56 (7), 0.001	0.16	0.19	26.12 (2), 0.0001
az080	0.41	1.14	19.26 (23), 3×10^{-13}	0.32	0.54	40.78 (7), 0.0001	0.01	0.21	2.17 (12), 0.011	0.05	0.12	10.36 (4), 0.0001
av192	0.38	0.99	13.98 (7), $<10^{-4}$	0.28	0.29	0.077 (1), 0.784	0.03	0.89	1.88 (14), 0.024	0.12	0.15	8.01 (2), 0.001
Average	0.64	1.71		0.27	0.55		0.02	0.39		0.10	0.20	

Note: Further details are provided by Robertson et al. [32]. The average information, and the maximum information about any one condition (I_{max}) with the data cast according to head direction, allocentric view, eye position and place.

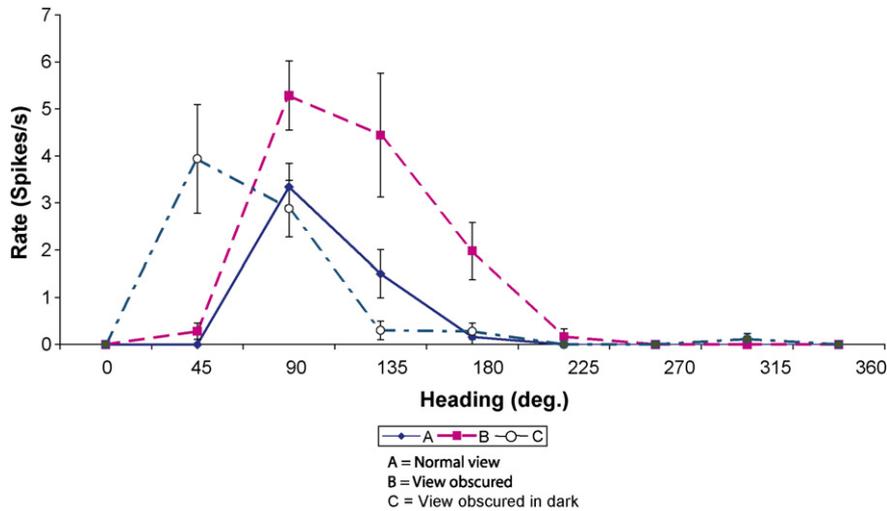


Fig. 3. (A) The firing of a head direction cell recorded with the normal view of the room. (B) The firing rate when the room was completely obscured by ceiling-to-floor curtains. (C) The responses of the same cell recorded not only with the blackout curtain, but also with the lights off. The mean and standard error of the mean response is shown.

Table 2
Head direction cells: firing rates

Location	Cell no.	Peak rate (spikes/s)	Half-amplitude width (°)	Null rate (spikes/s)
Presubiculum	(1) AV070c2	17.2	72	0.8
Presubiculum	(2) AV115c3	4.3	54	0.0
Presubiculum	(3) AV195	29.1	89	0.9
Presubiculum	(4) AZ080	2.3	90	0.0
	Mean	13.2	76.3	0.4
Parahippocampal gyrus	(5) AV192c4	15.7	139	2.2

taneous firing rates (mean=0.8 spikes/s, interquartile range 0–1.0). The peak firing rates were also relatively low (mean 10.0 spikes/s, interquartile range 6–13). These characteristics, together with the large amplitude and broad action poten-

tials indicate that these neurons are likely to be pyramidal cells. Four cells were in the presubiculum, and in addition, one neuron with head direction cell properties was recorded in the primate parahippocampal gyrus. (Further details about

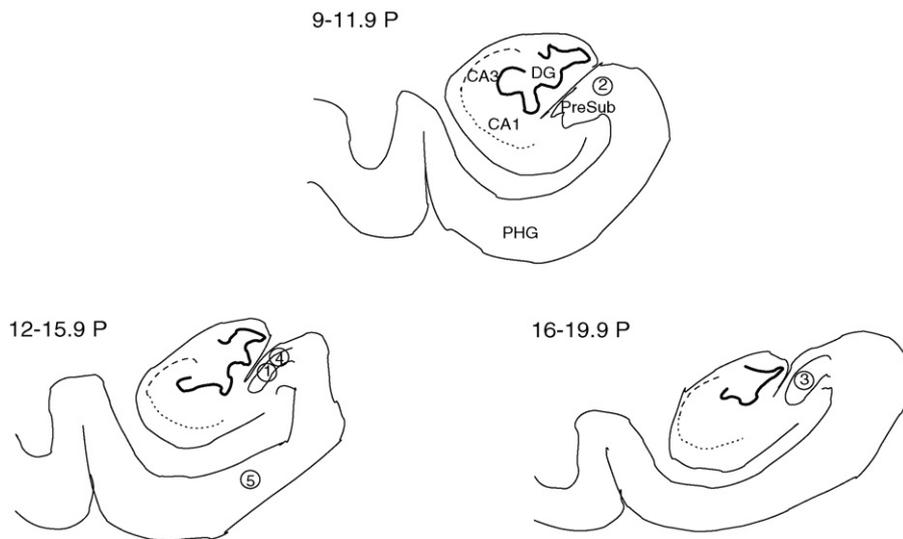


Fig. 4. The hippocampal and parahippocampal sites at which different head direction cells were recorded. Coronal sections at different distances in mm posterior (P) to the sphenoid reference are shown. The number inside each circle corresponds to the cell number shown in Table 1. CA3–CA3 hippocampal pyramidal cell field; CA1–CA1 hippocampal pyramidal cell field; DG: dentate gyrus; PHG: parahippocampal gyrus; Pre-s, PreSub: presubiculum.

the population of cells analyzed are provided by Robertson et al. [32].) We have not so far found head direction cells in the hippocampus itself (CA3 and CA1), nor in the dentate gyrus.

The head direction cells are very different from the spatial view cells (described in more detail below), which are found in the primate hippocampus and parahippocampal gyrus. For example, for a given head direction, if the monkey is moved to different places in the environment where the spatial view is different, spatial view cells give different responses. In contrast, the response of head direction cells remains constant for a given head direction, even when the spatial view is very different, as the data shown in Fig. 2 and the tables show. To provide a simple concept to emphasize the difference, one can think of head direction cells as responding like a compass attached to the top of the head, which will signal head direction even when the compass is in different locations, including in a totally different, and even novel, spatial environment, as illustrated in Fig. 2.

Taken in the context of evidence on the neurophysiology and functions of the primate (including human) hippocampal system, head direction cells could perform a number of functions. One would be as part of a memory system. By remembering the compass bearing (head direction) and distance travelled, it is possible to find one's way back to the origin, even with a number of sectors of travel, and over a number of minutes. This is referred to as path integration, and can occur even without a view of the environment. Head direction cells provide part of the information to be remembered for such spatial memory functions. Complementary information also required for this is available in the whole body motion cells that we have described in the primate hippocampus [29]. These cells provide information about for example linear translation, or axial whole body rotation. Part of the way in which head direction cell firing could be produced is by taking into account axial movements, which is what is encoded by some of these whole body motion cells [29], and it is an interesting hypothesis that this function is performed by some of the structures related to the hippocampal system such as the presubiculum.

Spatial memory and navigation can also benefit from visual information about places being looked at, which can be used as landmarks, and spatial view cells added to the head direction cells and whole body motion cells would provide the basis for a memory system useful in navigation. Another possibility is that primate head direction cells are part of a system for computing during navigation which direction to head in next. For this, not only would a memory system be needed of the type just described and elaborated elsewhere [33,35,36,40,45,65] that can store spatial information of the type found in the hippocampus, but also an ability to use this information in spatial computation of the appropriate next bearing. Such a system might be implemented using a hippocampal memory system which associated together spatial views, whole body motion and head direction information [42,59]. The system would be different from that in the rat [6,19], in that spatial view is represented in the primate hippocampus.

3. Presubiculum and hippocampus: attractor networks modelling continuous (e.g. spatial) with discrete (object) information

3.1. Continuous attractor networks for spatial information

A class of network that can maintain the firing of its neurons to represent any location along a continuous physical dimension such as spatial position, head direction, etc., is a 'Continuous Attractor' neural network (CANN) (see references provided below and Chapter 7 in Rolls and Deco [41]). It uses excitatory recurrent collateral connections with associative modifiability between the neurons to reflect the distance between the neurons in the state space of the animal (e.g. head direction space). These networks can maintain the packet or bubble of neural activity constant for long periods wherever it is started to represent the current state (head direction, position, etc.) of the animal, and are likely to be involved in many aspects of spatial processing and memory, including spatial vision. Global inhibition (implemented by feedback inhibitory interneurons) is used to keep the number of neurons in a bubble or packet of actively firing neurons relatively constant, and to help to ensure that there is only one activity packet. Continuous attractor networks can be thought of as very similar to autoassociation or discrete attractor networks [40,41] and have the same architecture, as illustrated in Fig. 5. The main difference is that the patterns stored in a CANN are continuous patterns, with each neuron having broadly tuned firing which decreases with for example a Gaussian function as the distance from the optimal firing location of the cell is varied, and with different neurons having tuning that overlaps

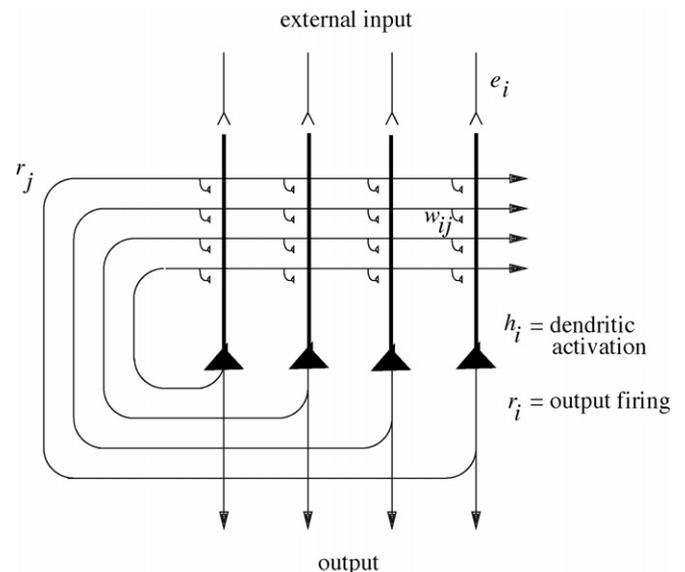


Fig. 5. The architecture of a continuous attractor neural network (CANN). Recurrent collateral axons with associatively modifiable synaptic connections make contact with the excitatory pyramidal cells in the network. The vertical lines are the dendrites, the cell bodies are triangles, and the axons extend out of the bottom of each cell body. The synaptic weight or strength for axon j to the dendrite of neuron i is w_{ij} . The external firing rate input to the network is conveyed by axons e_i . Feedback inhibitory interneurons are not shown. (For details see Rolls et al. [48] and Rolls and Deco [41].)

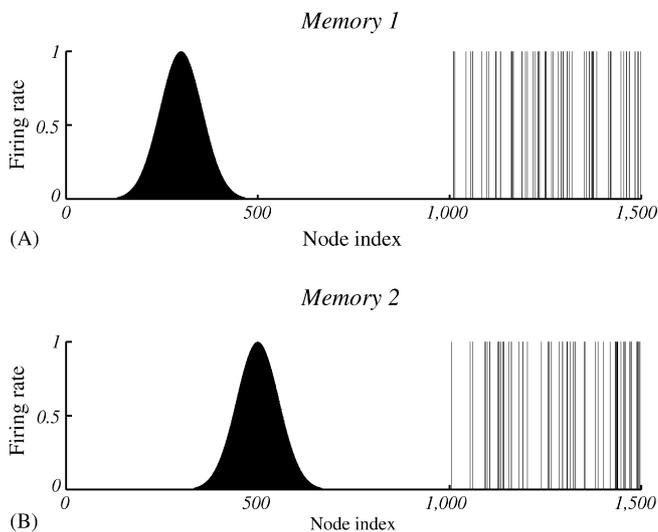


Fig. 6. The types of firing patterns stored in continuous attractor networks are illustrated for the patterns present on neurons 1–1000 for Memory 1 (when the firing is that produced when the spatial state represented is that for location 300), and for Memory 2 (when the firing is that produced when the spatial state represented is that for location 500). The continuous nature of the spatial representation results from the fact that each neuron has a Gaussian firing rate that peaks at its optimal location. This particular mixed network also contains discrete representations that consist of discrete subsets of active binary firing rate neurons in the range 1001–1500. The firing of these latter neurons can be thought of as representing the discrete events that occur at the location. Continuous attractor networks by definition contain only continuous representations, but this particular network can store mixed continuous and discrete representations, and is illustrated to show the difference of the firing patterns normally stored in separate continuous attractor and discrete attractor networks. For this particular mixed network, during learning, Memory 1 is stored in the synaptic weights, then Memory 2, etc., and each memory contains part that is continuously distributed to represent physical space, and part that represents a discrete event or object.

throughout the space. Such tuning is illustrated in Fig. 6, together with the examples of discrete (separate) patterns (each pattern implemented by the firing of a particular subset of the neurons), with no continuous distribution of the patterns throughout the space, that are useful for storing arbitrary events or objects. A consequent difference is that the CANN can maintain its firing at any location in the trained continuous space, whereas a discrete attractor or autoassociation network moves its population of active neurons towards one of the previously learned attractor states, and thus implements the recall of a particular previously learned pattern from an incomplete or noisy (distorted) version of one of the previously learned patterns.

3.2. Continuous attractor networks and path integration

We have considered how spatial representations could be stored in continuous attractor networks, and how the activity can be maintained at any location in the state space in a form of short term memory when the external (e.g. visual) input is removed [41]. However, many networks with spatial representations in the brain can be updated by internal, self-motion (i.e. idiothetic), cues even when there is no external (e.g. visual) input. Examples are head direction cells in the presubiculum of rats and macaques, place cells in the rat hippocampus, and spa-

tial view cells in the primate hippocampus. The major question arises about how such idiothetic inputs could drive the activity packet in a continuous attractor network, and in particular, how such a system could be set up biologically by self-organizing learning.

One approach to simulating the movement of an activity packet produced by idiothetic cues (which is a form of path integration whereby the current location is calculated from recent movements) is to employ a look-up table that stores (taking head direction cells as an example), for every possible head direction and head rotational velocity input generated by the vestibular system, the corresponding new head direction [54]. Another approach involves modulating the strengths of the recurrent synaptic weights in the continuous attractor on one but not the other side of a currently represented position, so that the stable position of the packet of activity, which requires symmetric connections in different directions from each node, is lost, and the packet moves in the direction of the temporarily increased weights, although no possible biological implementation was proposed of how the appropriate dynamic synaptic weight changes might be achieved [69]. Another mechanism (for head direction cells) [56] relies on a set of cells, termed (head) rotation cells, which are co-activated by head direction cells and vestibular cells and drive the activity of the attractor network by anatomically distinct connections for clockwise and counter-clockwise rotation cells, in what is effectively a look-up table. However, no proposal was made about how this could be achieved by a biologically plausible learning process, and this has been the case until recently for most approaches to path integration in continuous attractor networks, which rely heavily on rather artificial pre-set synaptic connectivities.

Stringer et al. [60] introduced a proposal with more biological plausibility about how the synaptic connections from idiothetic inputs to a continuous attractor network can be learned by a self-organizing learning process. The essence of the hypothesis is described with Fig. 7. The continuous attractor synaptic weights w^{RC} are set up under the influence of the external visual inputs I^{V} [41]. At the same time, the idiothetic synaptic weights w^{ROT} (in which the ROT refers to the fact that they are in this case produced by idiothetic inputs, produced by cells that fire to represent the velocity of clockwise and anticlockwise head rotation), are set up by associating the change of head direction cell firing that has just occurred (detected by a trace memory mechanism described below) with the current firing of the head rotation cells r^{ROT} . (Neurons that reflect head rotation are found in the primate hippocampus [29]; neurons influenced by head rotation are also found in the parietal cortex [15].) For example, when the trace memory mechanism incorporated into the idiothetic synapses w^{ROT} detects that the head direction cell firing is at a given location (indicated by the firing r^{HD}) and is moving clockwise (produced by the altering visual inputs I^{V}) and there is simultaneous clockwise head rotation cell firing, the synapses w^{ROT} learn the association, so that when that rotation cell firing occurs later without visual input, it takes the current head direction firing in the continuous attractor into account, and moves the location of the head direction attractor in the appropriate direction.

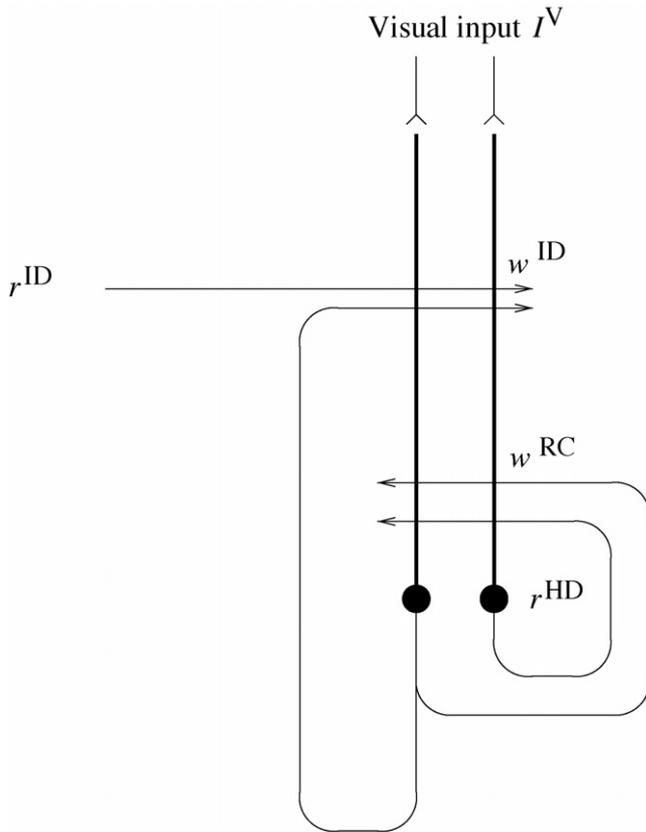


Fig. 7. General network architecture for a one-dimensional continuous attractor model of head direction cells which can be updated by idiothetic inputs produced by head rotation cell firing r^{ID} . The head direction cell firing is r^{HD} , the continuous attractor synaptic weights are w^{RC} , the idiothetic synaptic weights are w^{ID} , and the external visual input is I^{V} . (For details see Stringer et al. [60].)

For the learning to operate, the idiothetic synapses onto head direction cell i with firing r_i^{HD} need two inputs: the short term memory traced term from other head direction cells \bar{r}_j^{HD} (which is just an average over, e.g. the preceding 1 s), and the head rotation cell input with firing r_k^{ID} ; the learning rule can be written

$$\delta w_{ijk}^{\text{ROT}} = k r_i^{\text{HD}} \bar{r}_j^{\text{HD}} r_k^{\text{ID}} \quad (1)$$

where k is the learning rate associated with this type of synaptic connection.

After learning, the firing of the head direction cells would be updated in the dark (when $I_i^{\text{V}} = 0$) by idiothetic head rotation cell firing r_k^{ROT} as follows

$$\begin{aligned} \tau \frac{dh_i^{\text{HD}}(t)}{dt} = & -h_i^{\text{HD}}(t) + \frac{\phi_0}{C} \sum_j (w_{ij} - w^{\text{INH}}) r_j^{\text{HD}}(t) + I_i \\ & + \frac{\phi_1}{C_{\text{HD} \times \text{ROT}}} \sum_{jk} w_{ijk}^{\text{ROT}} r_j^{\text{HD}} r_k^{\text{ROT}} \end{aligned} \quad (2)$$

The last term introduces the effects of the idiothetic synaptic weights w_{ijk}^{ROT} , which effectively specify that the current firing of head direction cell i , r_i^{HD} , must be updated by the previously learned combination of the particular head rotation now occurring indicated by r_k^{ROT} , and the current head direction indicated by the firings of the other head direction cells r_j^{HD} indexed

through j . This makes it clear that the idiothetic synapses operate using combinations of inputs, in this case of two inputs. Neurons that sum the effects of such local products are termed Sigma–Pi neurons. Although such synapses are more complicated than the two-term synapses often used, such three-term synapses (with two axons connecting to the dendrite) appear to be useful to solve the computational problem of updating representations based on idiothetic inputs in the way described. Synapses that operate according to Sigma–Pi rules might be implemented in the brain by a number of mechanisms described by Koch [16], and Stringer et al. [60], including having two inputs close together on a thin dendrite, so that local synaptic interactions would be emphasized. However, in a recent development we have shown that the Sigma–Pi synapses in this class of network could be replaced with a simple competitive network that learns by self-organization to respond to combinations of velocity and position (e.g. head direction, or place), making the system more biologically plausible [58].

Simulations demonstrating the operation of this self-organizing learning to produce movement of the location being represented in a continuous attractor network were described by Stringer et al. [60]. They also showed that, after training with just one value of the head rotation cell firing, the network showed the desirable property of moving the head direction being represented in the continuous attractor by an amount that was proportional to the value of the head rotation cell firing. Stringer et al. [60] also describe a related model of the idiothetic cell update of the location represented in a continuous attractor, in which the rotation cell firing directly modulates in a multiplicative way the strength of the recurrent connections in the continuous attractor in such a way that clockwise rotation cells modulate the strength of the synaptic connections in the clockwise direction in the continuous attractor, and vice versa. Although it is possible that path integration for head direction is performed in brainstem regions such as the dorsal tegmental nucleus and lateral mammillary nucleus [57], the general proposal for path integration in a self-organizing attractor/competitive network system could be useful for other types of path integration including that for place and spatial view [58].

3.3. Continuous and discrete attractor networks, and episodic memory

It has now been shown that attractor networks can store both continuous patterns and discrete patterns, and can thus be used to store for example the location in (continuous, physical) space (e.g. the place “out there” in a room represented by spatial view cells) where an object (a discrete item) is present [48] (cf. [33,35]). Such associations between an object and the place where it is located are prototypical of episodic or event memory, and may be implemented in the primate hippocampus [49]. In this network, when events are stored that have both discrete (object) and continuous (spatial) aspects, then the whole place can be retrieved later by the object, and the object can be retrieved by using the place as a retrieval cue. Such networks are likely to be present in parts of the brain such as the hippocampus which receive and combine inputs both from sys-

tems that contain representations of continuous (physical) space, and from brain systems that contain representations of discrete objects, such as the inferior temporal visual cortex. The combined continuous and discrete attractor network described by Rolls et al. [48] shows that in brain regions where the spatial and object processing streams are brought together, then a single network can represent and learn associations between both types of input. Indeed, in brain regions such as the hippocampal system, it is essential that the spatial and object processing streams are brought together in a single network, for it is only when both types of information are in the same network that spatial information can be retrieved from object information, and vice versa, which is a fundamental property of episodic memory [40,41,44,45].

4. The subiculum in the context of a theory of hippocampal function

4.1. Introduction

Information reaches the primate hippocampus via a number of cortical stages, including from the inferior temporal visual cortex to the perirhinal cortex and from the parietal cortex to the parahippocampal cortex, which in turn project to the entorhi-

nal cortex, which then projects to the hippocampus (see Fig. 8). These are typical forward projections, in that they tend to project to the next stage from pyramidal cells in layers 2 and 3. Once information has reached the hippocampus, it must be capable of leaving if it is to be useful in any way. There are two main exit routes. One is via the fimbria/fornix to the anterior thalamus and mammillary bodies. The second is from CA1 via subiculum, entorhinal cortex and backprojections to the cortical areas that originally sent inputs to the hippocampus. These are backprojections, in that in the cortical stages, the projections are mainly from cortical pyramidal cells in layers 5 and 6, and end on dendrites in layers 1 and 2 of the preceding cortical stage. The aim of this part of the paper is to consider the functions of the hippocampo-cortical backprojections, and the role of the subiculum in these.

4.2. The information represented in the primate hippocampus

The systems-level neurophysiology of the hippocampus shows what information could be stored or processed by the hippocampus. To understand how the hippocampus works it is not sufficient to state just that it can store information—one needs to know what information. The systems-level neurophysiology of the primate hippocampus has been reviewed in more detail by

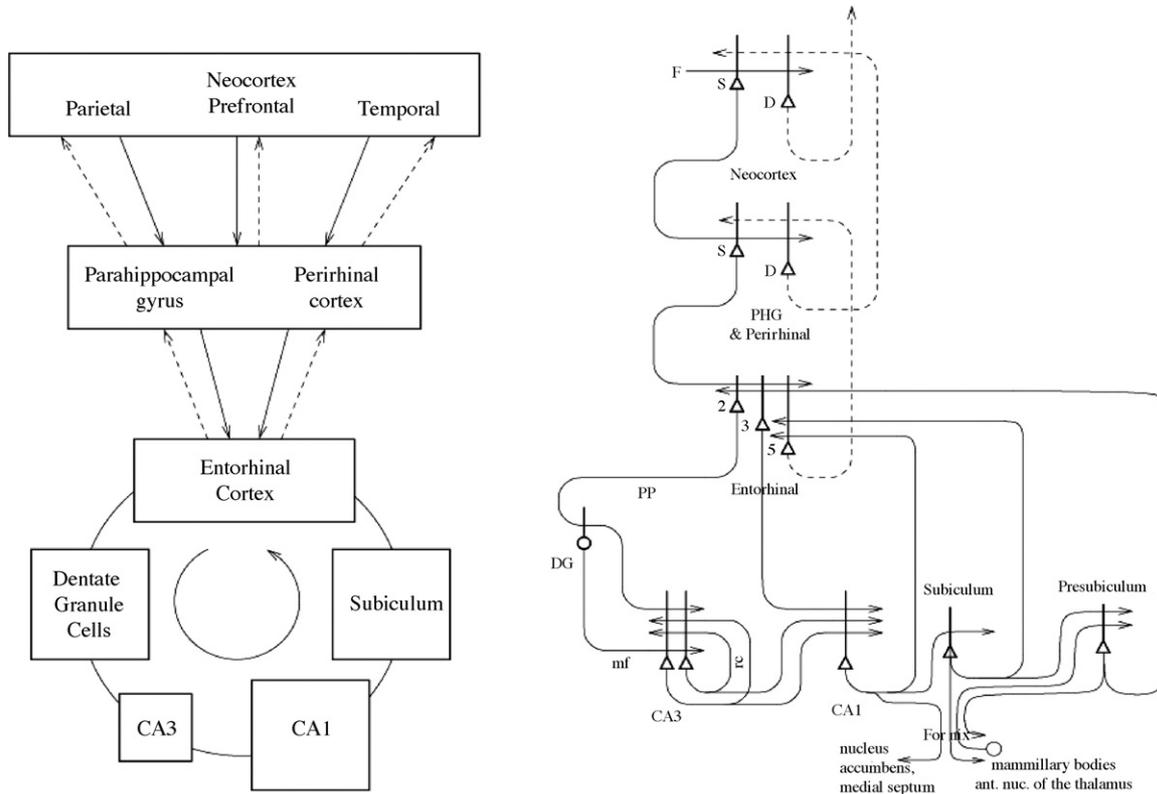


Fig. 8. Forward connections (solid lines) from areas of cerebral association neocortex via the parahippocampal gyrus and perirhinal cortex, and entorhinal cortex, to the hippocampus; backprojections (dashed lines) via the hippocampal CA1 pyramidal cells, subiculum, and parahippocampal gyrus to the neocortex. There is great convergence in the forward connections down to the single network implemented in the CA3 pyramidal cells; great divergence again in the backprojections. Left: block diagram; right: more detailed representation of some of the principal excitatory neurons in the pathways. D: deep pyramidal cells; DG: dentate granule cells; F: forward inputs to areas of the association cortex from preceding cortical areas in the hierarchy; mf: mossy fibres; PHG: parahippocampal gyrus and perirhinal cortex; pp: perforant path; rc: recurrent collateral of the CA3 hippocampal pyramidal cells; S: superficial pyramidal cells; 2: pyramidal cells in layer 2 of the entorhinal cortex; 3: pyramidal cells in layer 3 of the entorhinal cortex. The thick lines above the cell bodies represent the dendrites.

Rolls [36] and Rolls and Xiang [44], and only a brief summary is provided here.

4.2.1. Spatial view cells in primates

In the rat, many hippocampal pyramidal cells fire when the rat is in a particular place, as defined for example by the visual spatial cues in an environment such as a room [17,24,25]. It has been discovered that in the primate hippocampus, many spatial cells have responses not related to the place where the monkey is, but instead related to the place where the monkey is looking [12,31,36,39,47,52]. These are called “spatial view cells”, an example of which is shown in Fig. 9.

These “spatial view” neurons, now analyzed in the actively locomoting monkey, are different from place cells, in that their activity is dependent not on the place where the monkey is, but on the place where the monkey is looking in space [47]. It can be

shown with the monkey stationary that these cells respond when the monkey’s eye position results in him looking at a particular part of space [12]. These cells thus encode information in allocentric (world-based, as contrasted with egocentric, body-related) coordinates [12,52]. Some of these spatial view cells respond when the view details are obscured by curtains or darkness, when the monkey’s eyes look towards the spatial view field of the neuron [31]. In this situation, it is suggested that the neurons are responding to the recalled spatial view, with the recall triggered by the partial idiothetic information provided about the spatial view by eye and head position information, which these experiments clearly do show influence primate hippocampal neurons. Another idiothetic input that drives some primate hippocampal neurons is linear and axial whole body motion [29]. Many of the “spatial view” cells are hippocampal pyramidal cells, with very low spontaneous firing rates and low peak fir-

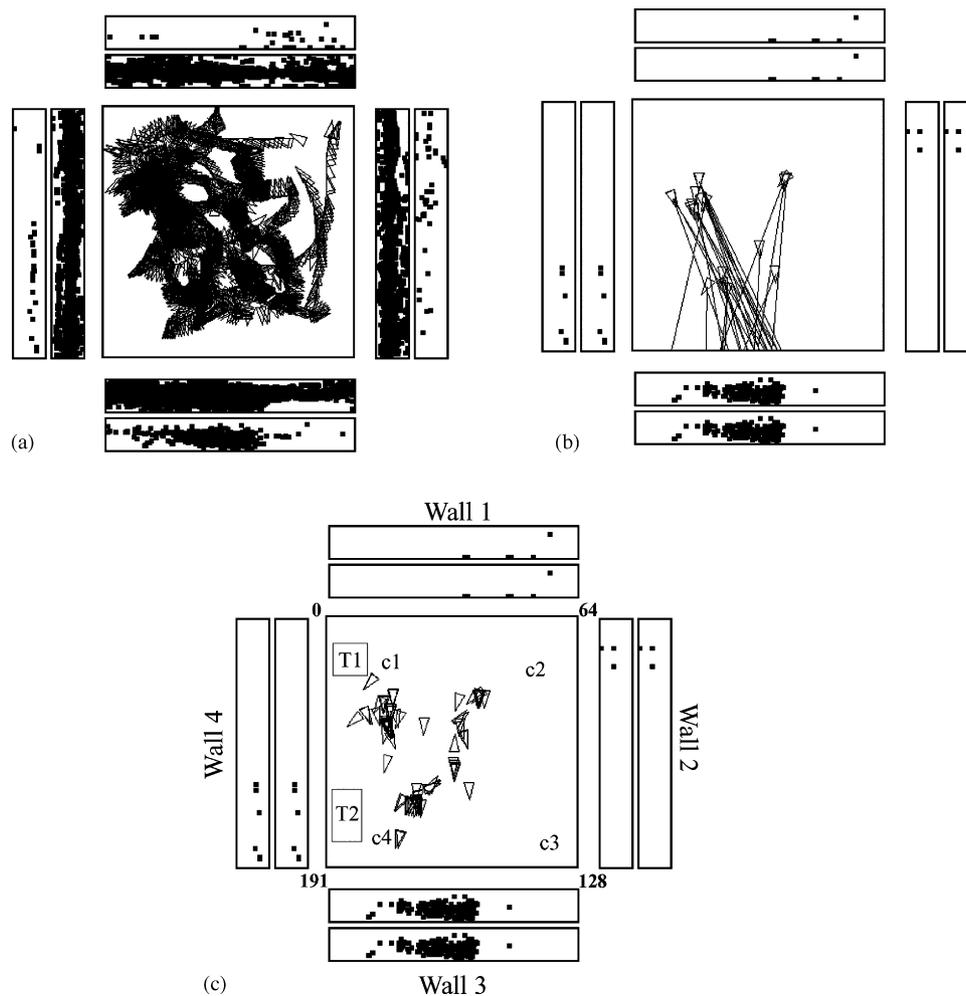


Fig. 9. Examples of the firing of a hippocampal spatial view cell when the monkey was walking around the laboratory. (a) The firing of the cell is indicated by the spots in the outer set of four rectangles, each of which represents one of the walls of the room. There is one spot on the outer rectangle for each action potential. The base of the walls is towards the centre of the diagram. The positions on the walls fixated during the recording sessions are indicated by points in the inner set of four rectangles, each of which also represents a wall of the room. The central square is a plan view of the room, with a triangle printed every 250 ms to indicate the position of the monkey, thus showing that many different places were visited during the recording sessions. (b) A similar representation of the same recording sessions as in (a), but modified to indicate some of the range of monkey positions and horizontal gaze directions when the cell fired at more than 12 spikes/s. (c) A similar representation of the same recording sessions as in (a), but modified to indicate more fully the range of places (and head directions) when the cell fired. The triangle indicates the current position of the monkey, and the line projected from it shows which part of the wall is being viewed at any one time while the monkey is walking. One spot is shown for each action potential. The neuron fires when the monkey looks at a particular position on the walls, even if to look at that position the monkey adopts a different head direction because of the place of the monkey in the room. (After Georges-François et al. [12].)

ing rates, and they implement a sparse representation. Although there is some evidence for place cells in the hippocampus of the monkey driving a cab [30], such place cells are not at all obvious in the actively locomoting monkey in a situation in which place cells would be found in rats [36,44].

Part of the interest of spatial view cells is that they could provide the spatial representation required to enable primates to perform object-place memory, for example remembering where they saw a person or object, which is an example of an episodic memory, and indeed similar neurons in the hippocampus respond in object-place memory tasks [44,49,53]. Associating together such a spatial representation with a representation of a person or object could be implemented by an autoassociation network implemented by the recurrent collateral connections of the CA3 hippocampal pyramidal cells [33,35,40,45,65]. Some other primate hippocampal neurons respond in the object-place memory task to a combination of spatial information and information about the object seen [53]. Further evidence for this convergence of spatial and object information in the hippocampus is that in another memory task for which the hippocampus is needed, learning where to make spatial responses conditional on which picture is shown, some primate hippocampal neurons respond to a combination of which picture is shown, and where the response must be made [7,20]. It has also been proposed that a related function of spatial view cells may be to form associations between spatial locations being viewed and the rewards or goals present at those locations, and indeed macaque neurons that respond to and learn the locations of rewards in scenes have been described [43].

These primate spatial view cells are thus unlike place cells found in the rat [17,23–25,67]. Primates, with their highly developed visual and eye movement control systems, can explore and remember information about what is present at places in the environment without having to visit those places. Such spatial view cells in primates would thus be useful as part of a memory system, in that they would provide a representation of a part of space that would not depend on exactly where the monkey or human was, and that could be associated with items that might be present in those spatial locations [43,44,49]. An example of the utility of such a representation in humans would be remembering where a particular person had been seen. The primate spatial representations would also be useful in remembering trajectories through environments, of use for example in short-range spatial navigation [29,41].

The representation of space in the rat hippocampus, which is of the place where the rat is, may be related to the fact that with a much less developed visual system than the primate, the rat's representation of space may be defined more by the olfactory and tactile as well as distant visual cues present, and may thus tend to reflect the place where the rat is. A hypothesis on how this difference could arise from essentially the same computational process in rats and monkeys is related to the large visual field seen by rats, and the foveate vision of primates [8,36]. Although the representation of space in rats therefore may be in some ways analogous to the representation of space in the primate hippocampus, the difference does have implications for theories, and modelling, of hippocampal function.

In rats, the presence of place cells has led to theories that the rat hippocampus is a spatial cognitive map, and can perform spatial computations to implement navigation through spatial environments [5,6,25,26]. The details of such navigational theories could not apply in any direct way to what is found in the primate hippocampus. Instead, what is applicable to both the primate and rat hippocampal recordings is that hippocampal neurons contain a representation of space (for the rat, primarily where the rat is, and for the primate primarily of positions “out there” in space) which is a suitable representation for an episodic memory system. In primates, this would enable one to remember, for example, where an object was seen. In rats, it might enable memories to be formed of where particular objects (for example those defined by olfactory, tactile, and taste inputs) were found. Thus, at least in primates, and possibly also in rats, the neuronal representation of space in the hippocampus may be appropriate for forming memories of events (which usually in these animals have a spatial component). Such memories would be useful for spatial navigation, for which according to the present hypothesis the hippocampus would implement the memory component but not the spatial computation component. Evidence that what neuronal recordings have shown is represented in the non-human primate hippocampal system may also be present in humans is that regions of the hippocampal formation can be activated when humans look at spatial views [11,27].

Other neurons in the primate hippocampus respond to combinations of visual object and spatial response information in associative learning tasks in which conditional spatial responses must be learned to visual images [7,20]. The presence of these neurons provides additional evidence that information represented in different parts of the cerebral cortex (visual temporal cortex and parietal cortex) is brought together on the same neurons in the hippocampus, in tasks in which those types of information must be rapidly associated. Other primate hippocampal neurons respond to (idiothetic) whole body motion [28]. These neurons represent information that it would be necessary to store in order to remember recent body movements made in short range navigation (so that one could perform path integration and for example return to the starting place); to determine whether one was facing towards a particular location in space, that is they would provide an important input for “spatial view” neurons. Indeed, when spatial view neurons respond in the dark as a monkey is rotated towards a spatial view [32], their activity may be triggered by whole body motion cell input into the CA3 autoassociative network. Other neurons that may help with this process are head direction cells, which have been found in primates in the primate presubiculum [32].

4.2.2. *Computational theories of the hippocampus*

One function performed by the primate hippocampus may be the association to form a memory of the activity of one population of neurons representing spatial position “out there”, with other neurons providing information about the object seen or the reward available at that location (see above) [43,44,49,45].

Part of a theory of how this is performed is that the CA3 neurons provide an autoassociative network appropriate for rapidly

(in one trial) learning such associations [33,35,45,65]. The theory is also compatible with the existence of place cells in rats, which might be formed by associating together a particular combination of spatial cues to define a place; which would be useful in a memory system, for associating objects with the place where the rat found them. Indeed, it is suggested that part of the difference between rat place cells and primate spatial view cells is that with a wide field of view (in the order of 270°) in the rat, the association of widely spaced visual environmental cues might result in the formation of place cells; whereas in primates, the association of closely spaced visual cues given the much smaller field of view could result in spatial view cells [8].

Under the hypothesis that the CA3 forms an autoassociative memory, the theory developed for attractor networks [2] with sparse representations and incomplete connectivity [63,64] can be applied, and it can be shown that the maximum number of memory CA3 firing patterns p that can be (individually) retrieved is proportional to the number C^{RC} of (associatively) modifiable recurrent collateral (RC) synapses per cell, by a factor that increases roughly with the inverse of the sparseness a of the neuronal representation. The sparseness is defined as

$$a = \frac{(\sum_{i=1,N} r_i / N)^2}{\sum_{i=1,N} (r_i^2 / N)} \quad (3)$$

where r_i is the firing rate of the i th neuron in the set of N neurons. The sparseness is within the range 0–1, and assumes the value 0.5 for a fully distributed representation with binary encoding; $1/N$ for a local or grandmother cell representation with binary encoding. The number p of different patterns that can be stored and retrieved correctly is approximately:

$$p \approx \frac{C^{\text{RC}} k}{a \ln(1/a)} \quad (4)$$

where C^{RC} is the number of synapses on the dendrites of each neuron devoted to the recurrent collaterals from other neurons in the network, and k is a factor that depends weakly on the detailed structure of the rate distribution, on the connectivity pattern, etc., but is roughly in the order of 0.2–0.3 [64]. For example, for $C^{\text{RC}} = 12,000$ and $a = 0.02$ (realistic estimates for the rat), p is calculated to be approximately 36,000. Simulations that are fully consistent with the analytic theory are provided by Rolls [50], and by a fuller computational model in Rolls [34].

Another hypothesis is that the CA3 cells might provide a continuous attractor, that is an attractor network in which the synaptic strengths are a function of the distance between positions in a continuum [54]. The synaptic strengths in such a network might be formed by Hebbian associative learning based on the overlapping firing rate response profiles of nearby hippocampal place [54] or spatial view cells [40,59,61]. The position in such a network would be represented by a group of firing cells (or activity packet), and the activity packet can move continuously from position to position in the continuous attractor. It has also been shown how multiple charts of place cells different in different environments could be stored in the CA3 network using a continuous attractor (cf. [3]).

The computational differences between the discrete and continuous attractor theories are interesting. In the discrete autoassociation theory, discrete representations of, for example, spatial view and object are associated together, and there are discrete memory states (minima in the energy landscape) to which the attractor settles to retrieve the memory. In contrast, with the continuous spatial attractor model, the energy landscape is flat, and the problem is how to move the firing rate activity packet from one location to another, using idiothetic cues. When the continuous attractor is accessed by visual cues, the neurons which represent a given spatial view can be accessed much more simply by associative lookup as in discrete attractor models in for example the way described by Treves and Rolls [64] and Rolls et al. [48]. One solution currently being explored is that the CA3 system may be kept stable in whatever position it is currently firing (if there is no idiothetic input), thus performing a short term memory of spatial location which could still operate in the dark, by virtue of being an amalgam of the two types of attractor network. This would allow for some bumps in the energy landscape for stability produced by virtue of discrete associations to visual cues, but nevertheless sufficient continuity so that idiothetic inputs can move the activity pattern to another position [40,59,61].

4.2.3. Backprojections to the neocortex and the role of the subiculum

Given that some information is represented by the firing of hippocampal neurons, we now consider how that information could influence the neocortex via backprojections.

It is suggested that the modifiable connections from the CA3 neurons to the CA1 neurons allow the information present in CA3 to be produced efficiently in CA1 [55,65]. The representation may be in a different form to that which is needed in CA3 for the recurrent collaterals to function correctly (see [35,45]). The CA1 neurons would then activate, partly via the subiculum, and by direct projections to the deep layers of the entorhinal cortex, at least the pyramidal cells in the deep layers of the entorhinal cortex (see Fig. 8). The subiculum may thus be important as part of the expansion process of cell numbers required to address the whole of the cerebral cortex; as well as an important source of hippocampal outputs via the fornix. These entorhinal cortex neurons would then, by virtue of their backprojections to the parts of cerebral cortex that originally provided the inputs to the hippocampus, terminate in the superficial layers of those neocortical areas, where synapses would be made onto the distal parts of the dendrites of the cortical pyramidal cells (see [33,45]). The areas of cerebral neocortex in which this recall would be produced could include multimodal cortical areas (e.g. the cortex in the superior temporal sulcus which receives inputs from temporal, parietal and occipital cortical areas), and also areas of unimodal association cortex (e.g. inferior temporal visual cortex). In addition to these backprojection pathways from CA1 directly and via the subiculum to the entorhinal cortex [38,40], there are some direct connections from CA1 and the subiculum to some of the neocortical areas that receive backprojections from the entorhinal cortex [4,45,68].

The hypothesis of the architecture with which this would be achieved is shown in Fig. 8. The feedforward connections from association areas of the cerebral neocortex (solid lines in Fig. 8), show major convergence as information is passed to CA3, with the CA3 autoassociation network having the smallest number of neurons at any stage of the processing. The backprojections allow for divergence back to neocortical areas. The way in which we suggest that the backprojection synapses are set up to have the appropriate strengths for recall is as follows [33,35,65]. During the setting up of a new input to the hippocampus (perhaps for episodic memory), there would be strong feedforward activity progressing towards the hippocampus. During the episode, the CA3 synapses would be modified, and via the CA1 neurons and the subiculum, a pattern of activity would be produced on the backprojecting synapses to the entorhinal cortex. Here the backprojecting synapses from active backprojection axons onto pyramidal cells being activated by the forward inputs to entorhinal cortex would be associatively modified. A similar process would be implemented at preceding stages of neocortex, in the parahippocampal gyrus/perirhinal cortex stage, and in association cortical areas, as shown in Fig. 8. The timing of the backprojecting activity would be sufficiently rapid for this, in that for example inferior temporal cortex neurons become activated by visual stimuli with latencies of 90–110 ms and may continue firing for several hundred milliseconds [37]; hippocampal pyramidal cells are activated in visual object-and-place and conditional spatial response tasks with latencies of 120–180 ms [20,53]. Thus, backprojected activity from the hippocampus might be expected to reach association cortical areas such as the inferior temporal visual cortex within 60–100 ms of the onset of their firing, and there would be a several hundred milliseconds period in which there would be conjunctive feedforward activation present with simultaneous backprojected signals in the association cortex. During recall implemented by backprojections, the backprojection connections onto the distal synapses of cortical pyramidal cells would be helped in their efficiency in activating the pyramidal cells by virtue of two factors. The first is that with no forward input to the neocortical pyramidal cells, there would be little shunting of the effects received at the distal dendrites by the more proximal effects on the dendrite normally produced by the forward synapses. Further, without strong forward activation of the pyramidal cells, there would not be very strong feedback and feedforward inhibition via GABA cells, so that there would not be a further major loss of signal due to (shunting) inhibition on the cell body and (subtractive) inhibition on the dendrite. (The converse of this is that when forward inputs are present, as during normal processing of the environment rather than during recall, the forward inputs would, appropriately, dominate the activity of the pyramidal cells, which would be only influenced, not determined, by the backprojecting inputs [9,10,33].)

The synapses receiving the backprojections would have to be Hebb-modifiable, as suggested by Rolls [33]. This would solve the de-addressing problem of how the hippocampus is able to bring into activity during recall just those cortical pyramidal cells that were active when the memory was originally being stored. The solution hypothesized [33,65] arises because modification

occurs during learning of the synapses from active backprojecting neurons from the hippocampal system onto the dendrites of only those neocortical pyramidal cells active at the time of learning. Without this modifiability of cortical backprojections during learning, it is difficult to see how exactly the correct cortical pyramidal cells active during the original learning experience would be activated during recall. Consistent with this hypothesis [33], there are NMDA receptors present especially in superficial layers of the cerebral cortex [21], implying Hebb-like learning just where the backprojecting axons make synapses with the apical dendrites of cortical pyramidal cells.

If the backprojection synapses are associatively modifiable, we may consider the duration of the period for which their synaptic modification should persist. What would be optimal would be to arrange for the associative modification of the backprojecting synapses to remain for as long as any associatively modified synapses remain in the hippocampus. This suggests that a similar mechanism for the associative modification would be appropriate both within the hippocampus and for that of at least one stage of the backprojecting synapses. It is suggested that the presence of high concentrations of NMDA synapses in the distal parts of the dendrites of neocortical pyramidal cells and within the hippocampus may reflect the similarity of the synaptic modification processes in these two regions (cf. [14]). It is noted that it would be appropriate to have this similarity of time course for at least one stage in the series of backprojecting stages from the CA3 region to the neocortex. Such stages might include the CA1 region, subiculum, entorhinal cortex, and perhaps the parahippocampal gyrus. However, from multimodal cortex (e.g. the parahippocampal gyrus) back to earlier cortical stages, it might be desirable for the backprojecting synapses to persist for a long period, so that some types of recall and top-down processing (see [33,45]) mediated by the operation of neocortico-neocortical backprojecting synapses could be stable.

An alternative hypothesis to that above is that rapid modifiability of backprojection synapses would be required only at the beginning of the backprojecting stream. Relatively fixed associations from higher to earlier neocortical stages would serve to activate the correct neurons at earlier cortical stages during recall. For example, there might be rapid modifiability from CA3 to CA1 neurons, but relatively fixed connections from there back [18]. For such a scheme to work, one would need to produce a theory not only of the formation of semantic memories in the neocortex, but also of how the operations performed according to that theory would lead to recall by setting up appropriately the backprojecting synapses.

4.2.4. Backprojections to the neocortex—quantitative aspects

How many backprojecting fibres does one need to synapse onto any given neocortical pyramidal cell, in order to implement the mechanism outlined above? Consider a polysynaptic sequence of backprojecting stages, from hippocampus to neocortex, as a string of simple (hetero-) associative memories in which, at each stage, the input connections are those coming from the previous stage (closer to the hippocampus). Implicit in this framework is the assumption that the synapses at each stage

are modifiable according to some Hebbian associative plasticity rule. A plausible requirement for a successful hippocampodirected recall operation, is that the signal generated from the hippocampally retrieved pattern of activity, and carried backwards towards neocortex, remain undegraded when compared to the noise due, at each stage, to the interference effects caused by the concurrent storage of other patterns of activity on the same backprojecting synaptic systems. That requirement is equivalent to that used in deriving the storage capacity of such a series of heteroassociative memories, and it was shown in Treves and Rolls [64] that the maximum number of independently generated activity patterns that can be retrieved is given, essentially, by the same formula as (4) above

$$p \approx \frac{Ck'}{a \ln(1/a)} \quad (5)$$

where, however, a is now the sparseness of the representation at any given stage, and C is the average number of (back-) projections each cell of that stage receives from cells of the previous one. (k' is a similar slowly varying factor to that introduced above.) If one assumes that a certain number of different attractor states can be determined by the CA3 recurrent collateral axons, then in order for all those states to be retrievable via the backprojecting synapses, there would need to be in the same order of backprojection connections to each cell in the backprojecting pathway as there are recurrent collateral connections per neuron in the hippocampus (but dependent to some extent on the sparseness of the representation in the CA3 neurons and in the backprojecting pathways, see Treves and Rolls [65]).

One consequence is that one could not possibly rely on a set of monosynaptic CA3-to-neocortex backprojections. This would imply that, to make a sufficient number of synapses on each of the vast number of neocortical cells, each cell in CA3 has to generate a disproportionate number of synapses (i.e. the number of backprojections received by a final cortical target cell times the ratio between the number of neocortical and of CA3 cells). The required divergence can be kept within reasonable limits only by assuming that the backprojecting system is polysynaptic, provided that the number of cells involved grows gradually at each stage, from CA3 back to neocortical association areas (cf. Fig. 8).

This theory provides what may be fundamental insight into why there are approximately as many backprojections as forward projecting neurons (between connected cortical areas, and between the hippocampus and the neocortex). However, not all cortical backprojections might reflect backprojection signals originating from the hippocampus, for there are backprojections which might be considered to originate in the amygdala (see [1]) or in multimodal cortical areas (allowing for example for recall of a visual image by an auditory stimulus with which it has been regularly associated). In this situation, one may consider whether the backprojections from any one of these systems would be sufficiently numerous to produce recall. One factor which may help here is that when recall is being produced by the backprojections, it may be assisted by the local recurrent collaterals between nearby (~ 1 mm) pyramidal cells which are a feature of neocortical connectivity. These would tend to complete a partial

neocortical representation being recalled by the backprojections into a complete recalled pattern.

There is evidence that the rat hippocampus is involved in some short term spatial working memory tasks [13,45], and when it is, the retrieval of information from the hippocampus may involve the types of process described here.

5. Conclusion

This paper has described the discovery of head direction cells in the primate presubiculum, placed them in the context of spatial view cells found in the primate hippocampus, suggested a computational explanation for the presence of spatial view cells in the primate hippocampus but place cells in the rat hippocampus, shown how both spatial and discrete (e.g. object or event) representations could be combined in a single attractor network suitable for episodic memory, and shown how path integration might be implemented in self-organizing neural networks for head direction or spatial position in the brain. The role of the subiculum in a model of how the backprojection system from the hippocampus to the neocortex is involved in the recall of episodic memories has also been described.

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