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A computational theory of hippocampal function, and empirical tests of the theory

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Abstract

The main aim of the paper is to present an up-to-date computational theory of hippocampal function and the predictions it makes about the different subregions (dentate gyrus, CA3 and CA1), and to examine behavioral and electrophysiological data that address the functions of the hippocampus and particularly its subregions. Based on the computational proposal that the dentate gyrus produces sparse representations by competitive learning and via the mossy fiber pathway forces new representations on the CA3 during learning (encoding), it has been shown behaviorally that the dentate gyrus supports spatial pattern separation during learning. Based on the computational proposal that CA3–CA3 autoassociative networks are important for episodic memory, it has been shown behaviorally that the CA3 supports spatial rapid one-trial learning, learning of arbitrary associations where space is a component, pattern completion, spatial short-term memory, and sequence learning by associations formed between successive items. The concept that the CA1 recodes information from CA3 and sets up associatively learned backprojections to neocortex to allow subsequent retrieval of information to neocortex, is consistent with findings on consolidation. Behaviorally, the CA1 is implicated in processing temporal information as shown by investigations requiring temporal order pattern separation and associations across time; computationally this could involve temporal decay memory, and temporal sequence memory which might also require CA3. The perforant path input to DG is implicated in learning, to CA3 in retrieval from CA3, and to CA1 in retrieval after longer time intervals (''intermediate-term memory'').

Keywords: Autoassociation; Recall; Episodic memory; Cortical backprojections; CA3; CA1; Dentate granule cells

Contents

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1. Introduction

In this paper a computational theory of hippocampal function developed by Rolls (1987, 1989a, 1989b, 1989c, 1996b), Treves and Rolls (1992, 1994) and with other colleagues (Rolls and Stringer, 2005; Rolls et al., 2002) is refined and further developed, and tests of the theory based especially on subregion analysis of the hippocampal system are described, with further refinement of the theory then added. The relation of this theory to other computational approaches to hippocampal function is described.

The theory was originally developed as described next, and was preceded by work of Marr (1971) who developed a mathematical model, which although not applied to particular networks within the hippocampus and dealing with binary neurons and binary synapses which utilised heavily the properties of the binomial distribution, was important in utilizing computational concepts.[1] The model was assessed by Willshaw and Buckingham (1990). Early work of Gardner-Medwin (1976) showed how progressive recall could operate in a network of binary neurons with binary synapses. Rolls (1987) produced a theory of the hippocampus in which the CA3 neurons operated as an autoassociation memory to store episodic memories including object and place memories, and the dentate granule cells operated as a preprocessing stage for this by performing pattern separation so that the mossy fibres could act to set up different representations for each memory to be stored in the CA3 cells.[2] He suggested that the CA1 cells operate as a recoder for the information recalled from the CA3 cells to a partial memory cue, so that the recalled information would be represented more efficiently to enable recall, via the backprojection synapses, of activity in the neocortical areas similar to that which had been present during the original episode. This theory was developed further (Rolls, 1989a, 1989b, 1989c, 1989d, 1990a, 1990b), including further details about how the backprojections could operate (Rolls, 1989b, 1989d), and how the dentate granule cells could operate as a competitive network (Rolls, 1989a). Quantitative aspects of the theory were then developed with A. Treves, who brought the expertise of theoretical physics applied previously mainly to understand the properties of fully connected attractor networks

[1] Marr (1971) showed how a network with recurrent collaterals could complete a memory using a partial retrieval cue, and how sparse representations could increase the number of memories stored (see also Willshaw and Buckingham, 1990). The analysis of these autoassociation or attractor networks was developed by Kohonen (1977) and Hopfield (1982), and the value of sparse representations was quantified by Treves and Rolls (1991). Marr (1971) did not specify the functions of the dentate granule cells versus the CA3 cells versus the CA1 cells (which were addressed in the Rolls (1989a, 1989b, 1989c, 1989d) papers and by Treves and Rolls (1992, 1994)), nor how retrieval to the neocortex of hippocampal memories could be produced, for which a quantitative theory was developed by Treves and Rolls (1994). In addition, Treves and Rolls (1994) and Rolls and Treves (1998) have argued that approaches to neurocomputation which base their calculations on what would happen in the tail of an exponential, Poisson, or binomial distribution are very fragile.

[2] McNaughton and Morris (1987) at about the same time suggested that the CA3 network might be an autoassociation network, and that the mossy fibre to CA3 connections might implement 'detonator' synapses. However, the concepts that the diluted mossy fibre connectivity might implement selection of a new random set of CA3 cells for each new memory, and that a direct perforant path input to CA3 was needed to initiate retrieval, were introduced by Treves and Rolls (1992). Contributions by Levy (e.g. 1989), McNaughton (1991), Hasselmo et al. (1995), and many others, are described below.

with binary neurons (Amit, 1989; Hopfield, 1982), to bear on the much more diluted connectivity of the recurrent collaterals found in real biological networks (e.g. 2% between CA3 pyramidal cells in the rat), in networks of neurons with graded (continuously variable) firing rates, graded synaptic strengths, and sparse representations in which only a small proportion of the neurons is active at any one time, as is found in the hippocampus (Treves, 1990; Treves and Rolls, 1991). These developments in understanding quantitatively the operation of more biologically relevant recurrent networks with modifiable synapses were applied quantitatively to the CA3 region (Treves and Rolls, 1991), and to the issue of why there are separate mossy fibre and perforant path inputs to the CA3 cells of the hippocampus (Treves and Rolls, 1992). The whole model of the hippocampus was described in more detail, and a quantitative treatment of the theory of recall by backprojection pathways in the brain was provided by Treves and Rolls (1994). The speed of operation of the CA3 system, and of the cortico-cortical recall backprojections, was addressed in a number of new developments (Battaglia and Treves, 1998b; Panzeri et al., 2001; Simmen et al., 1996a; Treves, 1993). Rolls (1995) produced a simulation of the operation of the major parts of the hippocampus from the entorhinal cortex through the dentate, CA3, and CA1 cells back to the hippocampus, which established the quantitative feasibility of the whole theory, and raised a number of important issues considered in Section 2.2.7. Further developments of the theory, and new developments introduced here, are described below.

Tests of the theory including analysis of the functions of different subregions of the hippocampus are described in Section 3.

2. The theory

2.1. Systems-level functions of the hippocampus

Any theory of the hippocampus must state at the systems level what is computed by the hippocampus. Some of the relevant evidence comes from the effects of damage to the hippocampus, the responses of neurons in the hippocampus during behavior, and the systems-level connections of the hippocampus.

2.1.1. Evidence from the effects of damage to the hippocampus

Damage to the hippocampus or to some of its connections such as the fornix in monkeys produces deficits in learning about the places of objects and about the places where responses should be made (Buckley and Gaffan, 2000). For example, macaques and humans with damage to the hippocampal system or fornix are impaired in object–place memory tasks in which not only the objects seen, but where they were seen, must be remembered (Burgess et al., 2002; Crane and Milner, 2005; Gaffan, 1994; Gaffan and Saunders, 1985; Parkinson et al., 1988; Smith and Milner, 1981). Posterior parahippocampal lesions in macaques impair even a simple type of object–place learning in which the memory load is just one pair of trial-unique stimuli (Malkova and Mishkin, 2003). Further, neurotoxic lesions that selectively damage the primate hippocampus impair spatial scene memory (Murray et al., 1998). Also, fornix lesions impair conditional left–right discrimination learning, in which the visual appearance of an object specifies whether a response is to be made to the left or the right (Rupniak and Gaffan, 1987). A comparable deficit is found in humans (Petrides, 1985). Fornix sectioned monkeys are also impaired in learning on the basis of a spatial cue which object to choose (e.g. if two objects are on the left, choose object A, but if the two objects are on the right, choose object B) (Gaffan and Harrison, 1989a). Monkeys with fornix damage are also impaired in using information about their place in an environment. For example, Gaffan and Harrison (1989b) found learning impairments when which of two or more objects the monkey had to choose depended on the position of the monkey in the room. Rats with hippocampal lesions are impaired in using environmental spatial cues to remember particular places (Cassaday and Rawlins, 1997; Jarrard, 1993; Kesner et al., 2004; Martin et al., 2000; O'Keefe and Nadel, 1978), to utilize spatial cues or bridge delays (Kesner, 1998; Kesner et al., 2004; Kesner and Rolls, 2001; Rawlins, 1985), or to perform relational operations on remembered material (Eichenbaum, 1997).

One way of relating the impairment of spatial processing to other aspects of hippocampal function is to note that this spatial processing involves a snapshot type of memory, in which one whole scene must be remembered. This memory may then be a special case of episodic memory, which involves an arbitrary association of a particular set of events which describe a past episode. Further, the non-spatial tasks impaired by damage to the hippocampal system may be impaired because they are tasks in which a memory of a particular episode or context rather than of a general rule is involved (Gaffan et al., 1984). Further, the deficit in paired associate learning in humans may be especially evident when this involves arbitrary associations between words, for example window-lake. The right (spatial) left (word) dissociation in the human hippocampus (Burgess et al., 2002; Crane and Milner, 2005), with a less well developed hippocampal commissural system in humans, could be related to the fact that arbitrary associations between words and places are not required.

It is suggested that the reason why the hippocampus is used for the spatial and non-spatial types of memory described above, and the reason that makes these two types of memory so analogous, is that the hippocampus contains one stage, the CA3 stage, which acts as an autoassociation memory. It is suggested that an autoassociation memory implemented by the CA3 neurons equally enables whole (spatial) scenes or episodic memories to be formed, with a snapshot quality which depends on the arbitrary associations which can be made and the short temporal window which characterises the synaptic modifiability in this system (see below and Rolls, 1987, 1989b, 1989d, 1990a, 1990b). The hypothesis is that the autoassociation memory enables arbitrary sets of concurrent neuronal firings, representing for example the spatial context where an episode occurred, the people present during the episode, and what was

seen during the episode, to be associated together and stored as one event. (The associations are arbitrary in the sense that any representation within CA3 may be associated with any other representation in CA3.) The issue of the types of item, e.g. spatial, for which this type of associativity is hippocampus-dependent is considered below. Later recall of that episode from the hippocampus in response to a partial cue can then lead to reinstatement of the activity in the neocortex that was originally present during the episode. The theory described here shows how the episodic memory could be stored in the hippocampus, and later retrieved from the hippocampus and thereby to the neocortex using backprojections.

The extensive literature on the effects of hippocampal damage in rats is considered in Section 3, in particular the parts of it that involve selective lesions to different subregions of the hippocampus and allow the theory described here to be tested. The theory described here is intended to be as relevant to rodents as to primates, the main difference being that the spatial representation used in the hippocampus of rats is about the place where the rat is, whereas the spatial representation in primates includes a representation of space ''out there'', as represented by spatial view cells (see Section 2.1.3). Although it is argued that the hippocampus can form associations between places and other inputs rapidly to help form an episodic memory, it is shown in Section 3 that in addition some types of hippocampus-dependent learning may occur more slowly, including trace conditioning; paired associate learning; and the formation of spatial representations of a new environment (Wilson and McNaughton, 1993).

2.1.2. *The necessity to recall information from the hippocampus*

The information about episodic events recalled from the hippocampus could be used to help form semantic memories (Rolls, 1989b, 1989d, 1990a; Treves and Rolls, 1994). For example, remembering many particular journeys could help to build a geographic cognitive map in the neocortex. The hippocampus and neocortex would thus be complementary memory systems, with the hippocampus being used for rapid, ''on the fly'', unstructured storage of information involving activity potentially arriving from many areas of the neocortex; while the neocortex would gradually build and adjust on the basis of much accumulating information the semantic representation (McClelland et al., 1995; Rolls, 1989b; Treves and Rolls, 1994). A view close to this in which a hippocampal episodic memory trace helps to build a neocortical semantic memory has also been developed by Moscovitch et al. (2005). The quantitative evidence considered below (Section 2.2.3.1) and by Treves and Rolls (1994) on the storage capacity of the CA3 system indicates that episodic memories could be stored in the hippocampus for at least a considerable period.

This raises the issue of the possible gradient of retrograde amnesia following hippocampal damage, and of whether information originally hippocampus-dependent for acquisition gradually becomes ''consolidated'' in the neocortex and thereby becomes hippocampus-independent over time (Debiec et al., 2002; McGaugh, 2000). The issue of whether memories stored some time before hippocampal damage are less impaired than more recent memories, and whether the time course is minutes, hours, days, weeks or years is a debated issue (Gaffan, 1993; Squire, 1992). (In humans, there is evidence for a gradient of retrograde amnesia; in rats and monkeys, hippocampal damage in many studies appears to impair previously learned hippocampal-type memories, suggesting that in these animals, at least with the rather limited numbers of different memories that need to be stored in the tasks used, the information remains in the hippocampus for long periods.) If there is a gradient of retrograde amnesia related to hippocampal damage, then this suggests that information may be retrieved from the hippocampus if it is needed, allowing the possibility of incorporating the retrieved information into neocortical memory stores. If on the other hand there is no gradient of retrograde amnesia related to hippocampal damage, but old as well as recent memories of the hippocampal type are stored in the hippocampus, and lost if it is damaged, then again this implies the necessity of a mechanism to retrieve information stored in the hippocampus, and to use this retrieved information to affect neural circuits elsewhere (for if this were not the case, information stored in the hippocampus could never be used for anything). The current perspective is thus that whichever view of the gradient of retrograde amnesia is correct, information stored in the hippocampus will need to be retrieved and affect other parts of the brain in order to be used. The present theory shows how information could be retrieved within the hippocampus, and how this retrieved information could enable the activity in neocortical areas that was present during the original storage of the episodic event to be reinstated, thus implementing recall. The backprojections from the hippocampus to the neocortex are one of the two major outputs of the hippocampus (see Fig. 1). The backprojections are most likely to be involved in what is described by humans as recall, and in enabling information about an episode captured on the fly to be incorporated into long-term, possibly semantic, neocortical stores with a rich associative structure (cf. McClelland et al., 1995). As a result of such neocortical recall, action may be initiated.

The other major set of outputs from the hippocampus projects via the fimbria/fornix system to the anterior nucleus of the thalamus (both directly and via the mammillary bodies), which in turn projects to the cingulate cortex. This may provide an output for more action-directed use of information stored in the hippocampus, for example in the initiation of conditional spatial responses in a visual conditional spatial response task (Miyashita et al., 1989; Rupniak and Gaffan, 1987). In such a task, a rapid mapping must be learned between a visual stimulus and a spatial response, and a new mapping must be learned each day. The hippocampus is involved in this rapid visual to spatial response mapping (Rupniak and Gaffan, 1987), and the way in which hippocampal circuitry may be appropriate for this is that the CA3 region enables signals originating from very different parts of the cerebral cortex to be associated rapidly together (see below).

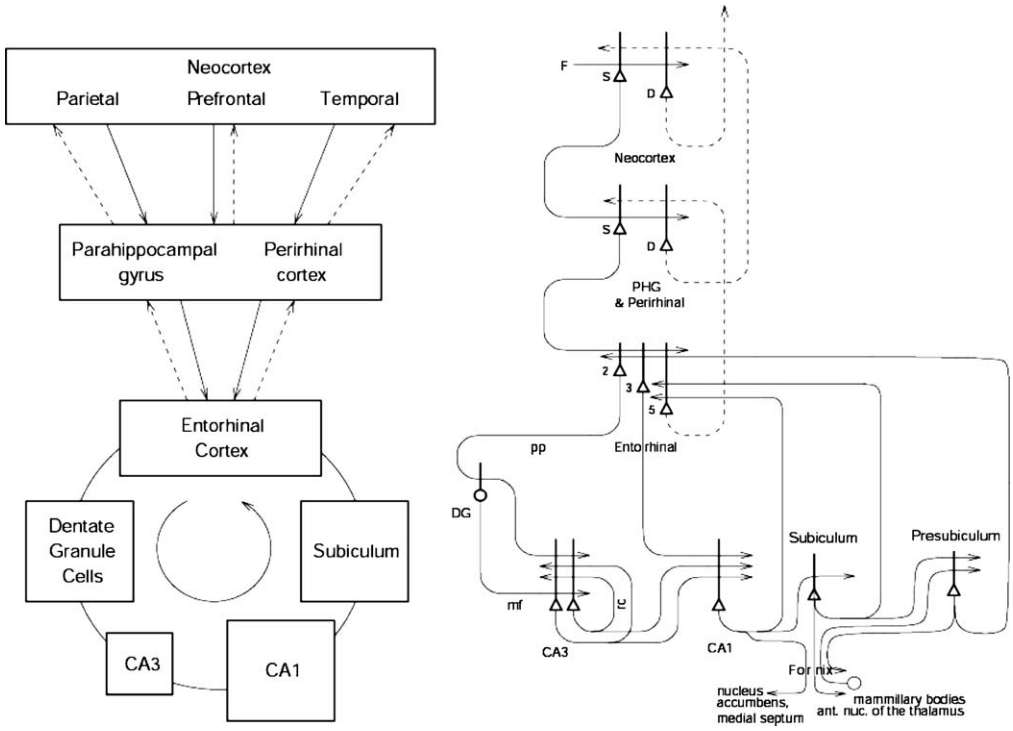

Fig. 1. Forward connections (solid lines) from areas of cerebral association neocortex via the parahippocampal gyrus and perirhinal cortex, and entorhinal cortex, to the hippocampus; backprojections (dashed lines) via the hippocampal CA1 pyramidal cells, subiculum, and parahippocampal gyrus to the neocortex. 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. Abbreviations: 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.

2.1.3. Systems-level neurophysiology of 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 recently by Rolls and Xiang (2006), and a brief summary is provided here because it provides a perspective relevant to understanding the function of the human hippocampus that is somewhat different from that provided by the properties of place cells in rodents, which have been reviewed elsewhere (see Jeffery et al., 2004; Jeffery and Hayman, 2004; McNaughton et al., 1983; Muller et al., 1991; O'Keefe, 1984).

The primate hippocampus contains spatial cells that respond when the monkey looks at a certain part of space, for example at one quadrant of a video monitor while the monkey is performing an object–place memory task in which he must remember where on the monitor he has seen particular images (Rolls et al., 1989). Approximately 9% of the hippocampal neurons have such spatial view fields, and about 2.4% combine information about the position in space with information about the object that is in that position in space (Rolls et al., 1989). The latter point shows that information from very different parts of the cerebral cortex (parietal for spatial information, and inferior temporal for visual information about objects) is brought together onto single neurons in the primate hippocampus. The representation of space is for the majority of hippocampal neurons in allocentric not egocentric coordinates (Feigenbaum and Rolls, 1991).

In rats, place cells are found, which respond depending on the place where the rat is in a spatial environment (see McNaughton et al., 1983; Muller et al., 1991; O'Keefe, 1984). To analyse whether such cells might be present in the primate hippocampus, Rolls and O'Mara (1993, 1995) recorded the responses of hippocampal cells when macaques were moved in a small chair or robot on wheels in a cue-controlled testing environment. The most common type of cell responded to the part of space at which the monkeys were looking, independently of the place where the monkey was. Ono et al. (1993) performed studies on the representation of space in the primate hippocampus while the monkey was moved in a cab to different places in a room. They found that 13.4% of hippocampal formation neurons fired more when the monkey was at some but not other places in the test area, but it was not clear whether the responses of these neurons occurred to the place where the monkey was independently of spatial view, or whether the responses of place-like cells were view dependent.

In rats, place cells fire best during active locomotion by the rat (Foster et al., 1989). To investigate whether place cells might be present in monkeys if active locomotion was being

performed, we (Georges-François et al., 1999; Robertson et al., 1998; Rolls et al., 1997a, 1998) recorded from single hippocampal neurons while monkeys move themselves round the test environment by walking (or running) on all fours. We found that these hippocampal "spatial view neurons" responded significantly differently for different allocentric spatial views and had information about spatial view in their firing rate, but did not respond differently just on the basis of eye position, head direction, or place. If the view details are obscured by curtains and darkness, then some spatial view neurons (especially those in CA1 and less those in CA3) continue to respond when the monkey looks towards the spatial view field. This experiment by Robertson et al. (1998) (see also Rolls et al., 1997b) shows that primate hippocampal spatial view neurons can be updated for at least short periods by idiothetic (self-motion) cues including eye position and head direction signals. Consistent with this, a small drift is sometimes evident after a delay when the view details are obscured, consistent with inaccuracies in the temporal path integration of these signals, which is then corrected by showing the visual scene again.

It is essential to measure the firing rate of a primate hippocampal cell with different head directions so that different spatial views can be compared, as testing with just one head direction (Matsumura et al., 1999) cannot provide evidence that will distinguish a place cell from a spatial view cell. These points will need to be borne in mind in future studies of hippocampal neuronal activity in primates including humans (cf. Ekstrom et al., 2003; Fried et al., 1997; Kreiman et al., 2000), and simultaneous recording of head position, head direction, and eye position, as described by Rolls and colleagues (Georges-François et al., 1999; Robertson et al., 1998; Rolls et al., 1997a, 1998) will be needed. To distinguish spatial view from place cells it will be important to test neurons while the primate or human is in one place with all the different spatial views visible from that place; and to also test the same neuron when the organism is in a different place, but at least some of the same spatial views are visible, as has been done in our primate recording.

A fundamental question about the function of the primate including human hippocampus is whether object as well as allocentric spatial information is represented. To investigate this, Rolls et al. (2005b) made recordings from single hippocampal formation neurons while macaques performed an object–place memory task which required the monkeys to learn associations between objects, and where they were shown in a room. Some neurons (10%) responded differently to different objects independently of location; other neurons (13%) responded to the spatial view independently of which object was present at the location; some neurons (12%) responded to a combination of a particular object and the place where it was shown in the room. These results show that there are separate as well as combined representations of objects and their locations in space in the primate hippocampus. This is a property required in an episodic memory system, for which associations between objects and the places where they are seen, is prototypical. The results thus show that a requirement for a human episodic memory system, separate and combined neuronal representations of objects and where they are seen "out there" in the environment, are present in the primate hippocampus (Rolls et al., 2005b). What may be a corresponding finding in rats is that some rat hippocampal neurons respond on the basis of the conjunction of location and odor (Wood et al., 1999).

Primate hippocampal neuronal activity has also been shown to be related to the recall of memories. In a one-trial object–place recall task, images of an object in one position on a screen, and of a second object in a different position on the screen, were shown successively. Then one of the objects was shown at the top of the screen, and the monkey had to recall the position in which it had been shown earlier in the trial, and to touch that location (Rolls and Xiang, 2006). In addition to neurons that responded to the objects or places, a new type of neuronal response was found in which 5% of hippocampal neurons had place-related responses when a place was being recalled by an object cue.

The primate anterior hippocampus (which corresponds to the rodent ventral hippocampus) receives inputs from brain regions involved in reward processing such as the amygdala and orbitofrontal cortex (Carmichael and Price, 1995; Pitkanen et al., 2002; Stefanacci et al., 1996; Suzuki and Amaral, 1994a). To investigate how this affective input may be incorporated into primate hippocampal function, Rolls and Xiang (2005) recorded neuronal activity while macaques performed a reward–place association task in which each spatial scene shown on a video monitor had one location which if touched yielded a preferred fruit juice reward, and a second location which yielded a less preferred juice reward. Each scene had different locations for the different rewards. Of 312 hippocampal neurons analyzed, 18% responded more to the location of the preferred reward in different scenes, and 5% to the location of the less preferred reward (Rolls and Xiang, 2005). When the locations of the preferred rewards in the scenes were reversed, 60% of 44 neurons tested reversed the location to which they responded, showing that the reward–place associations could be altered by new learning in a few trials. The majority (82%) of these 44 hippocampal reward–place neurons tested did not respond to object–reward associations in a visual discrimination object–reward association task. Thus the primate hippocampus contains a representation of the reward associations of places "out there" being viewed, and this is a way in which affective information can be stored as part of an episodic memory, and how the current mood state may influence the retrieval of episodic memories. There is consistent recent evidence that rewards available in a spatial environment can influence the responsiveness of rodent place neurons (Hölscher et al., 2003a; Tabuchi et al., 2003).

In another type of task for which the primate hippocampus is needed, conditional spatial response learning, in which the monkeys had to learn which spatial response to make to different stimuli, that is, to acquire associations between visual stimuli and spatial responses, 14% of hippocampal neurons responded to particular combinations of visual stimuli and spatial responses (Miyashita et al., 1989). The firing of these neurons could not be accounted for by the motor requirements

of the task, nor wholly by the stimulus aspects of the task, as demonstrated by testing their firing in related visual discrimination tasks. These results showed that single hippocampal neurons respond to combinations of the visual stimuli and the spatial responses with which they must become associated in conditional response tasks, and are consistent with the computational theory described above according to which part of the mechanism of this learning involves associations between visual stimuli and spatial responses learned by single hippocampal neurons. In a following study by Cahusac et al. (1993), it was found that during such conditional spatial response learning, 22% of this type of neuron analysed in the hippocampus and parahippocampal gyrus altered their responses so that their activity, which was initially equal to the two new stimuli, became progressively differential to the two stimuli when the monkey learned to make different responses to the two stimuli (Cahusac et al., 1993). These changes occurred for different neurons just before, at, or just after the time when the monkey learned the correct response to make to the stimuli, and are consistent with the hypothesis that when new associations between objects and places (in this case the places for responses) are learned, some hippocampal neurons learn to respond to the new associations that are required to solve the task. Similar findings have been described by Wirth et al. (2003).

2.1.4. Systems-level anatomy

The primate hippocampus receives inputs via the entorhinal cortex (area 28) and the highly developed parahippocampal gyrus (areas TF and TH) as well as the perirhinal cortex from the ends of many processing streams of the cerebral association cortex, including the visual and auditory temporal lobe association cortical areas, the prefrontal cortex, and the parietal cortex (Amaral, 1987; Amaral et al., 1992; Lavenex et al., 2004; Suzuki and Amaral, 1994b; Van Hoesen, 1982; Witter et al., 2000b) (see Fig. 1). The hippocampus is thus by its connections potentially able to associate together object and spatial representations. In addition, the entorhinal cortex receives inputs from the amygdala, and the orbitofrontal cortex, which could provide reward-related information to the hippocampus (Carmichael and Price, 1995; Pitkanen et al., 2002; Stefanacci et al., 1996; Suzuki and Amaral, 1994a). (The connections are analogous in the rat, although areas such as the temporal lobe visual cortex areas are not well developed in rodents, and the parahippocampal gyrus may be represented by the dorsal perirhinal cortex, Burwell et al., 1995.) Given that some topographic segregation is maintained in the afferents to the hippocampus through the perirhinal and parahippocampal cortices (Amaral and Witter, 1989), it may be that these areas are able to subserve memory within one of these topographically separated areas, of for example visual object, *or* spatial, *or* olfactory information. In contrast, the final convergence afforded by the hippocampus into one network in CA3 (see Fig. 1) may be especially appropriate for an episodic memory typically involving arbitrary associations between any of the inputs to the hippocampus, e.g. spatial, vestibular related to self-motion, visual object, olfactory, and auditory (see below). There are also direct subcortical inputs from for example the amygdala and septum (Amaral, 1986).

The primary output from the hippocampus to neocortex originates in CA1 and projects to subiculum, entorhinal cortex, and parahippocampal structures (areas TF-TH) as well as prefrontal cortex (Delatour and Witter, 2002; van Haeften et al., 2003; Van Hoesen, 1982; Witter, 1993). CA1 and subiculum also project to subcortical areas via the fimbria/fornix such as the mammillary bodies and anterior thalamic nuclei (see Fig. 1). In addition to the projections originating in CA1, projections out of Ammon's horn also originate in CA3. Many researchers have reported that CA3 projects to the lateral and medial septal nuclei (Amaral and Witter, 1995; Gaykema et al., 1991; Risold and Swanson, 1997). The lateral septum also has projections to the medial septum (Jakab and Leranth, 1995), which in turn projects to subiculum and eventually entorhinal cortex (Amaral and Witter, 1995; Jakab and Leranth, 1995).

2.1.5. Perirhinal cortex, recognition memory, and long-term familiarity memory

The functions of the perirhinal cortex are different to those of the hippocampus, and are reviewed briefly here partly because it provides afferents to the hippocampus via the entorhinal cortex, and partly to make it clear that there are memory functions at one time attributed to the hippocampus that a hippocampal theory need not account for, given the memory functions now known to be performed by the perirhinal cortex.

The perirhinal cortex is involved in recognition memory in that damage to the perirhinal cortex produces impairments in recognition memory tasks in which several items intervene between the sample presentation of a stimulus and its presentation again as a match stimulus (Malkova et al., 2001; Zola-Morgan et al., 1989, 1994). Indeed, damage to the perirhinal cortex rather than to the hippocampus is believed to underlie the impairment in recognition memory found in amnesia in humans associated with medial temporal lobe damage (Brown and Aggleton, 2001; Buckley and Gaffan, 2000; Winters and Bussey, 2005). Neurophysiologically, it has been shown that many inferior temporal cortex (area TE) neurons (Rolls, 2000a; Rolls and Deco, 2002), which provide visual inputs to the perirhinal cortex (Suzuki and Amaral, 1994a, 1994b), respond more to the first, than to the second, presentation of a stimulus in a running recognition task with trial-unique stimuli (Baylis and Rolls, 1987). In this task, there is typically a presentation of a novel stimulus, and after a delay which may be in the order of minutes or more and in which other stimuli may be shown, the stimulus is presented again as ''familiar'', and the monkey can respond to obtain food reward. Most neurons responded more to the ''novel'' than to the ''familiar'' presentation of a stimulus, where ''familiar'' in this task reflects a change produced by seeing the stimulus typically once (or a few times) before. (A small proportion of neurons respond more to the familiar (second) than to the novel (first) presentation of each visual stimulus.) In the inferior temporal cortex this memory spanned up to one to two intervening stimuli between the first (novel) and second (familiar)

presentations of a given stimulus (Baylis and Rolls, 1987), and as recordings are made more ventrally, towards and within the perirhinal cortex, the memory span increases to several or more intervening stimuli (Brown and Xiang, 1998; Wilson et al., 1990; Xiang and Brown, 1998), allowing the perirhinal cortex to contribute to recognition memory over larger memory spans.

In a similar task though typically performed with non-trial-unique stimuli, a delayed matching-to-sample task with up to several intervening stimuli, some perirhinal cortex neurons respond more to the match stimulus than to the sample stimulus (Miller et al., 1998). This has been modelled by interaction with a prefrontal cortex attractor network that holds the first item in a short-term memory, and then shows enhanced responding when that item is repeated (Renart et al., 2001; Rolls and Deco, 2002). Many other neurons in this task respond more to the sample (''novel'') than to the match (''familiar'') presentations of the stimuli, and this short-term memory is reset at the start of the next trial (Hölscher and Rolls, 2002). The resetting at the start of each trial shows that the perirhinal cortex in actively involved in the task demands.

A third type of memory in which the perirhinal cortex is implicated is paired associate learning (a model of semantic long term memory), which is represented by a population of neurons in a restricted part of area 36 where the neuronal responses may occur to both members of a pair of pictures used in the paired association task (Miyashita et al., 1998, 1996).

Evidence that the perirhinal cortex is involved in a fourth type of memory, long-term familiarity memory, comes from a neuronal recording study in which it was shown that perirhinal cortex neuronal responses in the rhesus macaque gradually increase in magnitude to a set of stimuli as that set is repeated for 400 presentations each 1.3 s long (Hölscher et al., 2003b). The single neurons were recorded in the perirhinal cortex in monkeys performing a delayed matching-to-sample task with up to three intervening stimuli, using a set of very familiar visual stimuli used for several weeks. When a novel set of stimuli was introduced, the neuronal responses were on average only 47% of the magnitude of the responses to the familiar set of stimuli. It was shown that the responses of the perirhinal cortex neurons gradually increased over hundreds of presentations of the new set of (initially novel) stimuli to become as large as to the already familiar stimuli. The mean number of 1.3 s presentations to induce this effect was 400 occurring over 7–13 days. These results show that perirhinal cortex neurons represent the very long-term familiarity of visual stimuli. A representation of the long-term familiarity of visual stimuli may be important for many aspects of social and other behavior, and part of the impairment in temporal lobe amnesia may be related to the difficulty of building representations of the degree of familiarity of stimuli. It has been shown that long-term familiarity memory can be modelled by neurons with synapses with a small amount of long-term potentiation which occurs at every presentation of a given stimulus, but which also incorporate hetero-synaptic long-term depression to make the learning self-limiting (Rolls et al., 2005a).

The perirhinal cortex thus has visual representations of objects, and some at least of the perirhinal cortex neurons have view-invariant representations. The perirhinal cortex, via it projections to the lateral entorhinal cortex and lateral perforant path, could thus introduce object information into the hippocampus for object–place associations (see Fig. 1). The parahippocampal gyrus, in which cells with spatial information are present in macaques (Rolls and Xiang, 2006; Rolls et al., 2005b) could via connections to the medial entorhinal cortex introduce spatial information into the hippocampus (see Fig. 1), and there is evidence consistent with this in rodents (Hargreaves et al., 2005). In contrast to the perirhinal cortex, the final convergence afforded by the hippocampus into one network in CA3 (see Fig. 1) may enable the hippocampus proper to implement an event or episodic memory typically involving arbitrary associations between any of the inputs to the hippocampus, e.g. spatial, visual object, olfactory, and auditory (see below). In contrast to the hippocampus, the functions of the perirhinal cortex do not involve associations to spatial representations, and indeed many of the memory-related functions of the perirhinal cortex involve unimodal visual representations.

2.2. The operation of hippocampal circuitry as a memory system

Given the systems level hypothesis about what the hippocampus performs, and the neurophysiological evidence about what is represented in the primate hippocampus, the next step is to consider how using its internal connectivity and synaptic modifiability the hippocampus could store and retrieve many memories, and how retrieval within the hippocampus could lead to retrieval of the activity in the neocortex that was present during the original learning of the episode. To develop understanding of how this is achieved, we have developed a computational theory of the operation of the hippocampus (Rolls, 1987, 1989a, 1989b, 1989d, 1990a, 1990b; Treves and Rolls, 1991, 1992, 1994). This theory, and new developments of it, are outlined next.

2.2.1. Hippocampal circuitry (see Fig. 1 and Amaral, 1993; Amaral and Witter, 1989; Lavenex et al., 2004; Naber et al., 2001; Storm-Mathiesen et al., 1990; Witter et al., 2000b)

Projections from the entorhinal cortex layer 2 reach the granule cells (of which there are 10^6 in the rat) in the dentate gyrus (DG), via the perforant path (pp) (Witter, 1993). In the dentate gyrus there is a set of excitatory interneurons in the hilus that interconnect granule cells and a layer of inhibitory interneurons that provide recurrent inhibition. The granule cells project to CA3 cells via the mossy fibres (mf), which provide a *sparse* but possibly powerful connection to the 3×10^5 CA3 pyramidal cells in the rat. Each CA3 cell receives approximately 50 mossy fibre inputs, so that the sparseness of this connectivity is thus 0.005%. By contrast, there are many more – possibly weaker – direct perforant path inputs also from layer 2 of the entorhinal cortex onto each CA3 cell, in the rat of the order of 4×10^3. The largest number of synapses (about 1.2×10^4 in the rat) on the dendrites of CA3 pyramidal cells is,

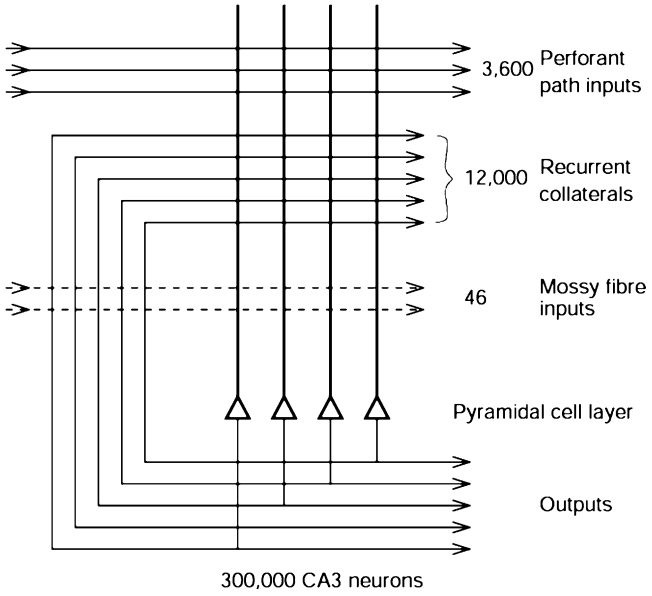

Fig. 2. The numbers of connections from three different sources onto each CA3 cell from three different sources in the rat (after Rolls and Treves, 1998; Treves and Rolls, 1992).

however, provided by the (recurrent) axon collaterals of CA3 cells themselves (rc) (see Fig. 2). It is remarkable that the recurrent collaterals are distributed to other CA3 cells throughout the hippocampus (Amaral et al., 1990; Amaral and Witter, 1989, 1995; Ishizuka et al., 1990), so that effectively the CA3 system provides a single network, with a connectivity of approximately 2% between the different CA3 neurons given that the connections are bilateral. The neurons that comprise CA3, in turn, project to CA1 neurons via the Schaffer collaterals. In addition, projections that terminate in the CA1 region originate in layer 3 of the entorhinal cortex (see Fig. 1).

2.2.2. *Dentate granule cells*

The theory is that the dentate granule cell stage of hippocampal processing which precedes the CA3 stage acts in a number of ways to produce during learning the sparse yet efficient (i.e. non-redundant) representation in CA3 neurons that is required for the autoassociation to perform well. Parts of the theory were developed elsewhere (Rolls, 1989a, 1989b, 1989d) (see also Treves and Rolls, 1992), and further developments are described here.

The first way is that the perforant path—dentate granule cell system with its Hebb-like modifiability is suggested to act as a competitive learning network to remove redundancy from the inputs producing a more orthogonal, sparse, and categorised set of outputs (Rolls, 1987, 1989a, 1989b, 1989d, 1990a, 1990b). The non-linearity in the NMDA receptors may help the operation of such a competitive net, for it ensures that only the most active neurons left after the competitive feedback inhibition have synapses that become modified and thus learn to respond to that input (Rolls, 1989a). We note that if the synaptic modification produced in the dentate granule cells lasts for a period of more than the duration of learning the episodic memory, then it could reflect the formation of codes for regularly occurring combinations of active inputs that might need to participate in different episodic memories. We note on the other hand that even with a single exposure to a new input, as might occur in episodic memory, a competitive network can usefully separate representations (cf. Hasselmo and Wyble, 1997). Because of the non-linearity in the NMDA receptors, the non-linearity of the competitive interactions between the neurons (produced by feedback inhibition and non-linearity in the activation function of the neurons), need not be so great (Rolls, 1989a). Because of the feedback inhibition, the competitive process may result in a relatively constant number of strongly active dentate neurons relatively independently of the number of active perforant path inputs to the dentate cells. The operation of the dentate granule cell system as a competitive network may also be facilitated by a Hebb rule of the form:

$$\delta w_{ij} = k \cdot r_i(r'_j - w_{ij}) \quad (1)$$

where k is a constant, r_i the activation of the dendrite (the postsynaptic term), r'_j the presynaptic firing rate, w_{ij} the synaptic weight, and r'_j and w_{ij} are in appropriate units (Rolls, 1989a). Incorporation of a rule such as this which implies heterosynaptic long-term depression as well as long-term potentiation (see Levy et al., 1990; Levy and Desmond, 1985) makes the sum of the synaptic weights on each neuron remain roughly constant during learning (cf. Oja, 1982; see Rolls, 1989a; Rolls and Deco, 2002; Rolls and Treves, 1998).

This functionality could be used to help build hippocampal place cells in rats from the grid cells present in the medial entorhinal cortex (Hafting et al., 2005). Each grid cell responds to a set of places in a spatial environment, with the places to which a cell responds set out in a regular grid. Different grid cells have different phases (positional offsets) and grid spacings (or frequencies) (Hafting et al., 2005). We (Rolls et al., 2006) have simulated the dentate granule cells as a system that receives as inputs the activity of a population of entorhinal cortex grid cells as the animal traverses a spatial environment, and have shown that the competitive net builds dentate-like place cells from such entorhinal grid cell inputs (see Fig. 3). This occurs because the firing states of entorhinal cortex cells that are active at the same time when the animal is in one place become associated together by the action of the competitive net, yet each dentate cell represents primarily one place because the dentate representation is kept sparse, thus helping to implement symmetry-breaking (Rolls et al., 2006).

The second way is also a result of the competitive learning hypothesized to be implemented by the dentate granule cells (Rolls, 1987, 1989a, 1989b, 1989d, 1990a, 1990b, 1994). It is proposed that this allows overlapping (or very similar) inputs to the hippocampus to be separated, in the following way (see also Rolls, 1996b). Consider three patterns B, W and BW where BW is a linear combination of B and W. (To make the example very concrete, we could consider binary patterns where B = 10, W = 01 and BW = 11.) Then the memory system is required to associate B with reward, W with reward, but BW with

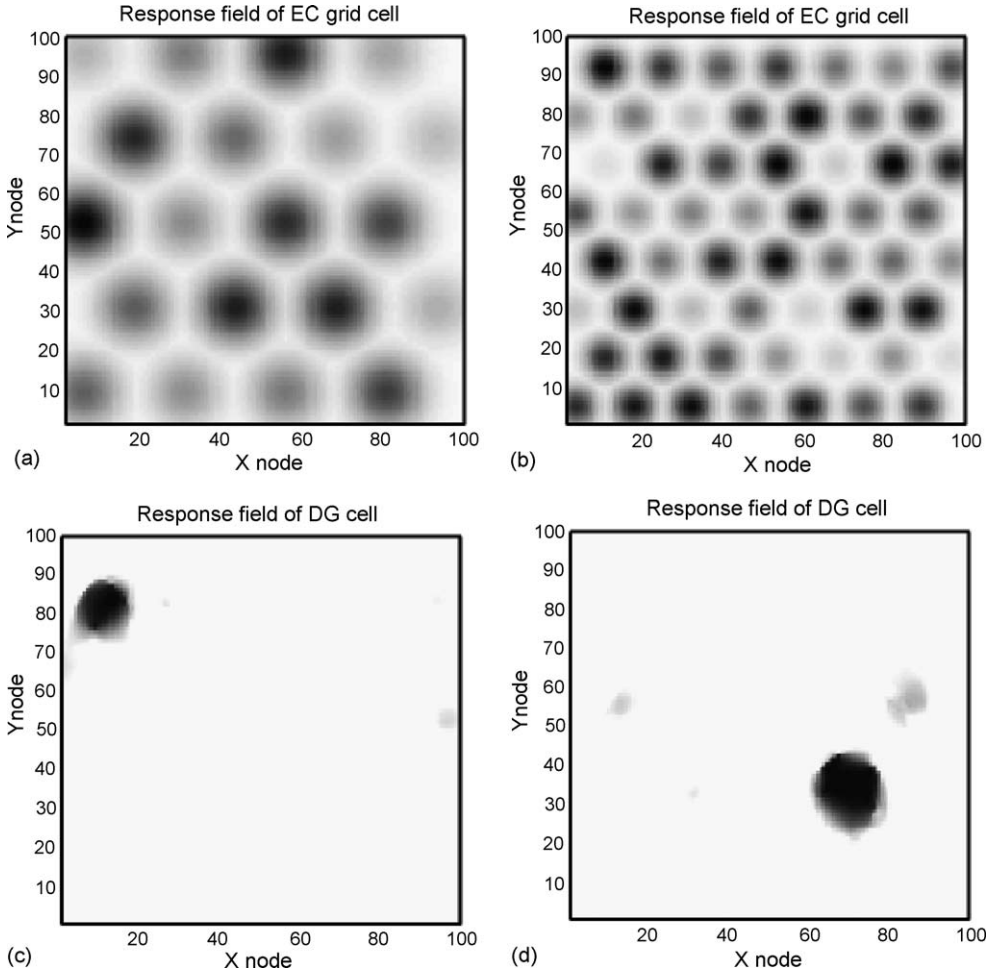

Fig. 3. Simulation of competitive learning in the dentate gyrus to produce place cells from the entorhinal cortex grid cell inputs. (a and b) Firing rate profiles of two entorhinal cortex grid cells with frequencies of four and seven cycles. In the simulation, cells with frequencies of 4–7 cycles were used, and with 25 phases or spatial offsets. (A phase is defined as an offset in the *X* and *Y* directions, and five offset values were used in each direction.) The standard deviation of the peak heights was set to 0.6. (c and d) Firing rate profiles of two dentate gyrus cells after competitive network training with the Hebb rule (after Rolls et al., 2006).

punishment. Without the hippocampus, rats might have more difficulty in solving such problems, particularly when they are spatial, for the dentate/CA3 system in rodents is characterized by being implicated in spatial memory. However, it is a property of competitive neuronal networks that they can separate such overlapping patterns, as has been shown elsewhere (Rolls, 1989a; Rolls and Treves, 1998); normalization of synaptic weight vectors is required for this property. It is thus an important part of hippocampal neuronal network architecture that there is a competitive network that precedes the CA3 autoassociation system. Without the dentate gyrus, if a conventional autoassociation network were presented with the mixture BW having learned B and W separately, then the autoassociation network would produce a mixed output state, and would therefore be incapable of storing separate memories for B, W and BW. It is suggested therefore that competition in the dentate gyrus is one of the powerful computational features of the hippocampus, and that could enable it to help solve spatial pattern separation tasks. Consistent with this, rats with dentate gyrus lesions are impaired at a metric spatial pattern separation task (Gilbert et al., 2001; Goodrich-Hunsaker et al., 2005). The recoding of grid cells in the entorhinal cortex (Hafting et al., 2005) into small place field cells in the dentate granule cells that was modelled by Rolls et al. (2006) can also be considered to be a case where overlapping inputs must be recoded so that different spatial components can be treated differently. We note that Sutherland and Rudy's configural learning hypothesis was similar, but was not tested with spatial pattern separation. Instead, when tested with for example tone and light combinations, it was not consistently found that the hippocampus was important (O'Reilly and Rudy, 2001; Sutherland and Rudy, 1991). We suggest that application of the configural concept, but applied to spatial pattern separation, may capture part of what the dentate gyrus acting as a competitive network could perform, particularly when a large number of such overlapping spatial memories must be stored and retrieved.

The third way in which the dentate gyrus is hypothesized to contribute to the sparse and relatively orthogonal representations in CA3 arises because of the very low contact probability in the mossy fibre-CA3 connections, and is described in Section 2.2.3.8 and by Treves and Rolls (1992).

A fourth way is that as suggested and explained in Section 2.2.3.8, the dentate granule cell—mossy fibre input to the CA3

cells may be powerful and its use particularly during learning would be efficient in forcing a new pattern of firing onto the CA3 cells during learning.

In the ways just described, the dentate granule cells could be particularly important in helping to build and prepare spatial representations for the CA3 network. The actual representation of space in the primate hippocampus includes a representation of spatial view, whereas in the rat hippocampus it is of the place where the rat is. The representation in the rat 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. However, the spatial representations in the rat and primate could arise from essentially the same computational process as follows (de Araujo et al., 2001; Rolls, 1999). The starting assumption is that in both the rat and the primate, the dentate granule cells (and the CA3 and CA1 pyramidal cells) respond to combinations of the inputs received. In the case of the primate, a combination of visual features in the environment will, because of the fovea providing high spatial resolution over a typical viewing angle of perhaps 10–20°, result in the formation of a spatial view cell, the effective trigger for which will thus be a combination of visual features within a relatively small part of space. In contrast, in the rat, given the very extensive visual field subtended by the rodent retina, which may extend over 180–270°, a combination of visual features formed over such a wide visual angle would effectively define a position in space that is a place. The actual processes by which the hippocampal formation cells would come to respond to feature combinations could be similar in rats and monkeys, involving for example competitive learning in the dentate granule cells. This competitive learning has the required properties, of associating together co-occurrent features, and of ensuring by the competition that each feature combination (representing a place or spatial view) is very different from that of other places or spatial views (pattern separation, and orthogonalizing effect), and is also a sparse representation. Consistent with this, dentate place fields in rats are small (Jung and McNaughton, 1993). Although this computation could be performed to some extent also by autoassociation learning in CA3 pyramidal cells, and competitive learning in CA1 pyramidal cells (Rolls and Treves, 1998; Treves and Rolls, 1994), the combined effect of the dentate competitive learning and the mossy fibre low probability but strong synapses to CA3 cells would enable this part of the hippocampal circuitry to be especially important in separating spatial representations, which as noted above are inherently continuous. The prediction thus is that during the learning of spatial tasks in which the spatial discrimination is difficult (for example because the places are close together), then the dentate system should be especially important. Tests of this prediction are described below.

Although spatial view cells are present in the parahippocampal areas (Georges-François et al., 1999; Robertson et al., 1998; Rolls et al., 1997a, 1998), and neurons with place-like fields (though in some cases as a grid (Hafting et al., 2005)) are found in the medial entorhinal cortex (Brun et al., 2002; Fyhn et al., 2004; Moser, 2004; Moser and Moser, 1998), there are backprojections from the hippocampus to the entorhinal cortex and thus to parahippocampal areas, and these backprojections could enable the hippocampus to influence the spatial representations found in the entorhinal cortex and parahippocampal gyrus. On the other hand, as described above, the grid-like place cells in the medial entorhinal cortex could if transformed by the competitive net functionality of the dentate cells result in the place cell activity (without a repeating grid) that is found in dentate and rat hippocampal neurons.

2.2.3. CA3 as an autoassociation memory

2.2.3.1. Arbitrary associations, and pattern completion in recall. Many of the synapses in the hippocampus show associative modification as shown by long-term potentiation, and this synaptic modification appears to be involved in learning (see Lynch, 2004; Morris, 1989, 2003; Morris et al., 2003). On the basis of the evidence summarized above, Rolls (1987, 1989a, 1989b, 1989d, 1990a, 1990b, 1991) has suggested that the CA3 stage acts as an autoassociation memory which enables episodic memories to be formed and stored in the CA3 network, and that subsequently the extensive recurrent collateral connectivity allows for the retrieval of a whole representation to be initiated by the activation of some small part of the same representation (the cue). The crucial synaptic modification for this is in the recurrent collateral synapses. (A description of the operation of autoassociative networks is provided by Hertz et al. (1991), by Rolls and Treves (1998), and by Rolls and Deco (2002). The architecture of an autoassociation network is shown in Fig. 4, and the learning rule is as shown in Eq. (1) except that the subtractive term could be the presynaptic firing rate (Rolls and Deco, 2002; Rolls and Treves, 1998). As described in footnotes 1 and 2, a number of investigators have contributed to the development of this hypothesis, including Marr (1971), McNaughton and Morris (1987), Levy (1989), and McNaughton (1991).)

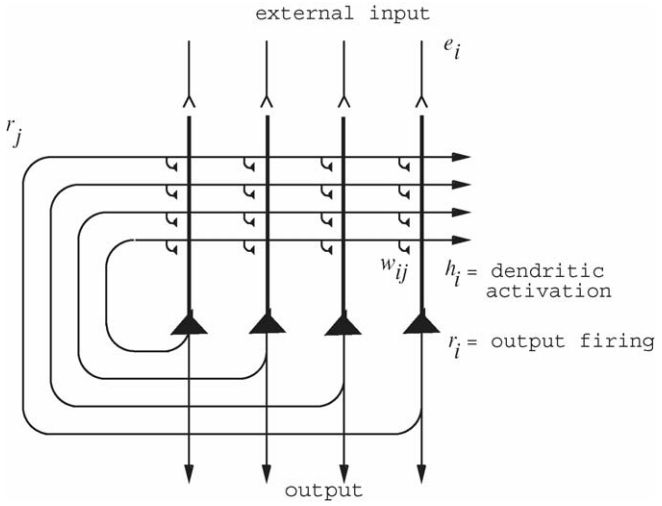

Fig. 4. The architecture of a continuous attractor neural network (CANN). The architecture is the same as that of a discrete attractor neural network.

The hypothesis is that because the CA3 operates effectively as a single network, it can allow arbitrary associations between inputs originating from very different parts of the cerebral cortex to be formed. These might involve associations between information originating in the temporal visual cortex about the presence of an object, and information originating in the parietal cortex about where it is. We note that although there is some spatial gradient in the CA3 recurrent connections, so that the connectivity is not fully uniform (Ishizuka et al., 1990), nevertheless the network will still have the properties of a single interconnected autoassociation network allowing associations between arbitrary neurons to be formed, given the presence of many long-range connections which overlap from different CA3 cells.

Crucial issues include how many memories could be stored in this system (to determine whether the autoassociation hypothesis leads to a realistic estimate of the number of memories that the hippocampus could store); whether the whole of a memory could be completed from any part; whether the autoassociation memory can act as a short-term memory, for which the architecture is inherently suited, and whether the system could operate with spatial representations, which are essentially continuous because of the continuous nature of space. These and related issues are considered in the remainder of Section 2.2.3.

2.2.3.1.1. Storage capacity. We have performed quantitative analyses of the storage and retrieval processes in the CA3 network (Treves and Rolls, 1991, 1992). We have extended previous formal models of autoassociative memory (see Amit, 1989) by analyzing a network with graded response units, so as to represent more realistically the continuously variable rates at which neurons fire, and with incomplete connectivity (Treves, 1990; Treves and Rolls, 1991). We have found that in general the maximum number $p_{\max}$ of firing patterns that can be (individually) retrieved is proportional to the number C^{RC} of (associatively) modifiable recurrent collateral synapses per cell, by a factor that increases roughly with the inverse of the sparseness a of the neuronal representation.[3] The sparseness of response (or selectivity) of a single cell to a set of stimuli (which in the brain has approximately the same value as the sparseness of the response of the population of neurons to any one stimulus, which can in turn be thought of as the proportion of neurons that is active to any one stimulus if the neurons had binary responses, see Franco et al., 2006) is defined as

$$a = \frac{\left(\sum r_i/n\right)^2}{\sum (r_i^2/n)} \tag{2}$$

where r_i is the firing rate to the ith stimulus in the set of n stimuli. The sparseness ranges from $1/n$, when the cell responds to only one stimulus, to a maximal value of 1.0, attained when the cell responds with the same rate to all stimuli. Approximately

$$p_{\max} \cong \frac{C^{RC}}{a \ln(1/a)} k \tag{3}$$

where 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 (Treves and Rolls, 1991). [The sparseness a in this equation is strictly the population sparseness (Franco et al., 2006; Treves and Rolls, 1991). The population sparseness a^p would be measured by measuring the distribution of firing rates of all neurons to a single stimulus at a single time. The single cell sparseness or selectivity a^s would be measured by the distribution of firing rates to a set of stimuli, which would take a long time. These concepts are elucidated by Franco et al. (2006). The sparseness estimates obtained by measuring early gene changes, which are effectively population sparsenesses, would thus be expected to depend greatly on the range of environments or stimuli in which this was measured. If the environment was restricted to one stimulus, this would reflect the population sparseness. If the environment was changing, the measure from early gene changes would be rather undefined, as all the populations of neurons activated in an undefined number of testing situations would be likely to be activated.] For example, for $C^{RC} = 12{,}000$ and $a = 0.02$, $p_{\max}$ is calculated to be approximately 36,000. This analysis emphasizes the utility of having a sparse representation in the hippocampus, for this enables many different memories to be stored. Third, in order for most associative networks to store information efficiently, heterosynaptic Long Term Depression (as well as LTP) is required (Fazeli and Collingridge, 1996; Rolls and Deco, 2002; Rolls and Treves, 1990, 1998; Treves and Rolls, 1991). Simulations that are fully consistent with the analytic theory are provided by Simmen et al. (1996b) and Rolls et al. (1997b).

We have also indicated how to estimate I, the total amount of information (in bits per synapse) that can be retrieved from the network. I is defined with respect to the information i_p (in bits per cell) contained in each stored firing pattern, by subtracting the amount i_l lost in retrieval and multiplying by p/C^{RC}:

$$I = \frac{p}{C^{RC}}(i_p - i_l) \tag{4}$$

The maximal value $I_{\max}$ of this quantity was found (Treves and Rolls, 1991) to be in several interesting cases around 0.2–0.3 bits per synapse, with only a mild dependency on parameters such as the sparseness of coding a.

We may then estimate (Treves and Rolls, 1992) how much information has to be stored in each pattern for the network to efficiently exploit its information retrieval capacity $I_{\max}$. The estimate is expressed as a requirement on i_p:

$$i_p > a \ln\left(\frac{1}{a}\right) \tag{5}$$

As the information content of each stored pattern i_p depends on the storage process, we see how the retrieval capacity analysis, coupled with the notion that the system is organized so as to be

[3] Each memory is precisely defined in the theory: it is a set of firing rates of the population of neurons (which represent a memory) that can be stored and later retrieved, with retrieval being possible from a fraction of the originally stored set of neuronal firing rates.

an efficient memory device in a quantitative sense, leads to a constraint on the storage process.

A number of points deserve comment. First, if it is stated that a certain number of memories is the upper limit of what could be stored in a given network, then the question is sometimes asked, what constitutes a memory? The answer is precise. Any one memory is represented by the firing rates of the population of neurons that are stored by the associative synaptic modification, and can be correctly recalled later. The firing rates in the primate hippocampus might be constant for a period of for example 1 s in which the monkey was looking at an object in one position in space; synaptic modification would occur in this time period (cf. the time course of LTP, which is sufficiently rapid for this); the memory of the event would have been stored. The quantitative analysis shows how many such random patterns of rates of the neuronal population can be stored and later recalled correctly. If the rates were constant for 5 s while the rat was at one place or monkey was looking at an object at one position in space, then the memory would be for the pattern of firing of the neurons in this 5 s period. (The pattern of firing of the population refers to the rate at which each neuron in the population of CA3 neurons is firing.)

Second, the question sometimes arises of whether the CA3 neurons operate as an attractor network. An attractor network is one in which a stable pattern of firing is maintained once it has been started. Autoassociation networks trained with modified Hebb rules can store the number of different memories, each one expressed as a stable attractor, indicated in Eq. (3). However, the hippocampal CA3 cells do not necessarily have to operate as a stable attractor: instead, it would be sufficient for the present theory if they can retrieve stored information in response to a partial cue initiating retrieval. The partial cue would remain on during recall, so that the attractor network would be operating in the clamped condition (see Rolls and Treves, 1998). The completion of the partial pattern would then provide more information than entered the hippocampus, and the extra information retrieved would help the next stage to operate. Demonstrations of this by simulations that are fully consistent with the analytic theory are provided by Rolls (1995), Simmen et al. (1996b), and Rolls et al. (1997b).

Third, in order for most associative networks to store information efficiently, heterosynaptic Long Term Depression (as well as LTP) is required (Rolls, 1996a; Rolls and Treves, 1990; Treves and Rolls, 1991). Without heterosynaptic LTD, there would otherwise always be a correlation between any set of positively firing inputs acting as the input pattern vector to a neuron. LTD effectively enables the average firing of each input axon to be subtracted from its input at any one time, reducing the average correlation between different pattern vectors to be stored to a low value (Rolls, 1996a).

Given that the memory capacity of the hippocampal CA3 system is limited, it is necessary to have some form of forgetting in this store, or other mechanism to ensure that its capacity is not exceeded. (Exceeding the capacity can lead to a loss of much of the information retrievable from the network.) Heterosynaptic LTD could help this forgetting, by enabling new memories to overwrite old memories (Rolls, 1996a). The limited capacity of the CA3 system does also provide one of the arguments that some transfer of information from the hippocampus to neocortical memory stores may be useful (see Treves and Rolls, 1994). Given its limited capacity, the hippocampus might be a useful store for only a limited period, which might be in the order of days, weeks, or months. This period may well depend on the acquisition rate of new episodic memories. If the animal were in a constant and limited environment, then as new information is not being added to the hippocampus, the representations in the hippocampus would remain stable and persistent. These hypotheses have clear experimental implications, both for recordings from single neurons and for the gradient of retrograde amnesia, both of which might be expected to depend on whether the environment is stable or frequently changing. They show that the conditions under which a gradient of retrograde amnesia might be demonstrable would be when large numbers of new memories are being acquired, not when only a few memories (few in the case of the hippocampus being less than a few hundred) are being learned.

The potential link to the gradient of retrograde amnesia is that the retrograde memories lost in amnesia are those not yet consolidated in longer term storage (in the neocortex). As they are still held in the hippocampus, their number has to be less than the storage capacity of the (presumed) CA3 autoassociative memory. Therefore the time gradient of the amnesia provides not only a measure of a characteristic time for consolidation, but also an upper bound on the rate of storage of new memories in CA3. For example, if one were to take as a measure of the time gradient in the monkey, say, 5 weeks (about 50,000 min, Squire, 1992) and as a reasonable estimate of the capacity of CA3 in the monkey, e.g. $p = 50{,}000$, then one would conclude that there is an upper bound on the rate of storage in CA3 of not more than one new memory per minute, on average. (This might be an average over many weeks; the fastest rate might be closer to 1 per s, see Treves and Rolls, 1994). These quantitative considerations are consistent with the concept described in Section 2.1 that retrieval of episodic memories from the hippocampus for a considerable time after they have been stored would be useful in helping the neocortex to build a semantic memory (McClelland et al., 1995; Moscovitch et al., 2005; Rolls, 1989b, 1989d, 1990a; Treves and Rolls, 1994).

2.2.3.1.2. Completion. A fundamental property of the autoassociation model of the CA3 recurrent collateral network is that the recall can be symmetric, that is, the whole of the memory can be retrieved from any part. For example, in an object–place autoassociation memory, an object could be recalled from a place retrieval cue, and vice versa. This is not the case with a pattern association network. If for example the CA3 activity represented a place/spatial view, and perforant path inputs with associative synapses to CA3 neurons carried object information (consistent with evidence that the lateral perforant path (LPP) may reflect inputs from the perirhinal cortex connecting via the lateral entorhinal cortex (Hargreaves et al., 2005)), then an object could recall a place, but a place could not recall an object.

Another fundamental property is that the recall can be complete even from a small fragment. Thus, it is a prediction

that when an incomplete retrieval cue is given, CA3 may be especially important in the retrieval process. Tests of this prediction are described in Section 3.

2.2.3.1.3. CA3 as a short-term attractor memory. Another fundamental property of the autoassociation model of the CA3 recurrent collateral network is that it can implement a short-term memory by maintaining the firing of neurons using the excitatory recurrent collateral connections. A stable attractor can maintain one memory active in this way for a considerable period, until a new input pushes the attractor to represent a new location or memory. For example, if one place were being held in a CA3 place short-term memory, then if the rat moved to a new place, the CA3 representation would move to represent the new place, and the short-term memory held in the CA3 network would be lost. It is thus predicted that when the hippocampus is used as a short-term memory with ongoing neuronal activity used to represent the short-term memory, than maintenance of the memory will be very dependent on what happens in the delay period. If the animal is relatively isolated from its environment and does not move around in a well defined spatial environment (as can be achieved by placing a vertical cylinder/bucket around a rat in the delay period), then the memory may be maintained for a considerable period in the CA3 (and even updated by idiothetic, self-motion, inputs as described below). However, the CA3 short-term memory will be very sensitive to disruption/interference, so that if the rat is allowed to move in the spatial environment during the delay period, then it is predicted that CA3 will not be able to maintain correctly the spatial short-term memory. In the circumstances where a representation must be kept active while the hippocampus (or inferior temporal visual cortex or parietal cortex) must be updating its representation to reflect the new changing perceptual inputs, which must be represented in these brain areas for the ongoing events to have high-level representations, the prefrontal cortex is thought computationally to provide an off-line buffer store (see pp. 406–412, Rolls and Deco, 2002). The predictions are thus that if there is no task in a delay period (and no need for an off-line buffer store), the hippocampus may be sufficient to perform the short-term memory function (such as remembering a previous location), provided that there is little distraction in the delay period. On the other hand, short-term memory deficits are predicted to be produced by prefrontal cortex lesions if there are intervening stimuli in the delay period.

2.2.3.2. Continuous, spatial, patterns and CA3 representations. The fact that spatial patterns, which imply continuous representations of space, are represented in the hippocampus has led to the application of continuous attractor models to help understand hippocampal function. This has been necessary, because space is inherently continuous, because the firing of place and spatial view cells is approximately Gaussian as a function of the distance away from the preferred spatial location, because these cells have spatially overlapping fields, and because the theory is that these cells in CA3 are connected by Hebb-modifiable synapses. This specification would inherently lead the system to operate as a continuous attractor network. Continuous attractor network models have been developed by Samsonovich and McNaughton (1997), Battaglia and Treves (1998a), Stringer et al. (2002b), Stringer et al. (2002a), Stringer et al. (2004), and Stringer and Rolls (2002) (see Rolls and Deco, 2002), and are described next.

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). It uses excitatory recurrent collateral connections between the neurons (as are present in CA3) to reflect the distance between the neurons in the state space of the animal (e.g. place or head direction). These networks can maintain the 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 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 (see Rolls and Deco, 2002), and have the same architecture, as illustrated in Fig. 4. 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 throughout the space. Such tuning is illustrated in Fig. 5. For comparison, autoassociation networks normally have 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 (see Fig. 5). 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. The energy landscape of a discrete attractor network (see Rolls and Deco, 2002) has separate energy minima, each one of which corresponds to a learned pattern, whereas the energy landscape of a continuous attractor network is flat, so that the activity packet remains stable with continuous firing wherever it is started in the state space. (The state space refers to the set of possible spatial states of the animal in its environment, e.g. the set of possible places in a room.) Continuous attractor networks are described next, as they are very likely to apply to the operation of systems with spatial representations and recurrent connections, such as the CA3 neurons. Continuous attractor networks have been studied by for example Amari (1977), Zhang (1996), Taylor (1999), and Stringer et al. (2002b).

The generic model of a continuous attractor is as follows. (The model is described in the context of head direction cells, which represent the head direction of rats (Muller et al., 1996; Taube et al., 1996) and macaques (Robertson et al., 1999), and

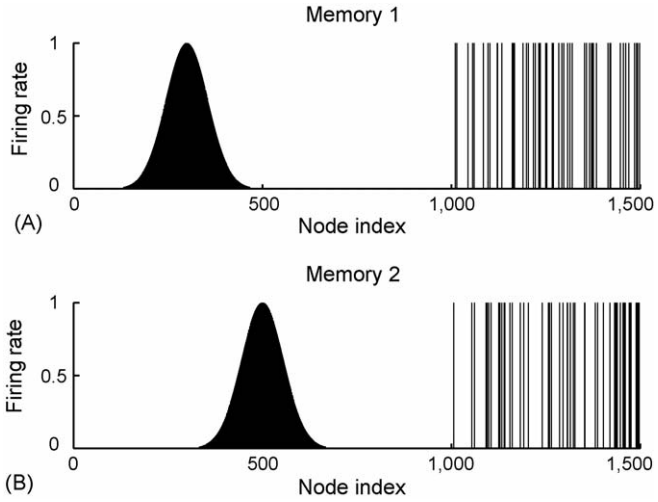

Fig. 5. The types of firing patterns stored in continuous attractor networks are illustrated for the patterns present on neurons 1–1000 for Memory 1 (when the firing is that produced when the spatial state represented is that for location 300), and for Memory 2 (when the firing is that produced when 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.

can be reset by visual inputs after gradual drift in darkness.) The model is a recurrent attractor network with global inhibition. It is different from a Hopfield attractor network (Hopfield, 1982) primarily in that there are no discrete attractors formed by associative learning of discrete patterns. Instead there is a set of neurons that are connected to each other by synaptic weights w_{ij} that are a simple function, for example Gaussian, of the distance between the states of the agent in the physical world (e.g. head directions) represented by the neurons. Neurons that represent similar states (locations in the state space) of the agent in the physical world have strong synaptic connections, which can be set up by an associative learning rule, as described in Section 2.2.3.2. The network updates its firing rates by the following "leaky-integrator" dynamical equations (where head direction is used as a prototypical example, but could be replaced by place, or spatial view). The continuously changing activation h_i^{HD} of each head direction cell i is governed by the equation

$$\frac{\mathrm{d}h_i^{\mathrm{HD}}(t)}{\mathrm{d}t} = -h_i^{\mathrm{HD}}(t) + \frac{\phi_0}{C^{\mathrm{HD}}} \sum_j (w_{ij} - w^{\mathrm{inh}}) r_j^{\mathrm{HD}}(t) + I_i^{\mathrm{V}}, \qquad (6)$$

where r_j^{HD} is the firing rate of head direction cell j, w_{ij} the excitatory (positive) synaptic weight from head direction cell j to cell i, w^{inh} a global constant describing the effect of inhibitory interneurons, and τ is the time constant of the system.[4] The term $-h_i^{\mathrm{HD}}(t)$ indicates the amount by which the activation decays (in the leaky integrator neuron) at time t. (The network is updated in a typical simulation at much smaller timesteps than the time constant of the system, τ.) The next term in Eq. (6) is the input from other neurons in the network r_j^{HD} weighted by the recurrent collateral synaptic connections w_{ij} (scaled by a constant ϕ_0 and C^{HD} which is the number of synaptic connections received by each head direction cell from other head direction cells in the continuous attractor). The term I_i^{V} represents a visual input to head direction cell i. Each term I_i^{V} is set to have a Gaussian response profile in most continuous attractor networks, and this sets the firing of the cells in the continuous attractor to have Gaussian response profiles as a function of where the agent is located in the state space (see e.g. Fig. 5), but the Gaussian assumption is not crucial. (It is known that the firing rates of head direction cells in both rats (Muller et al., 1996; Taube et al., 1996) and macaques (Robertson et al., 1999) is approximately Gaussian.) When the agent is operating without visual input, in memory mode, then the term I_i^{V} is set to zero. The firing rate r_i^{HD} of cell i is determined from the activation h_i^{HD} and the sigmoid function:

$$r_i^{\mathrm{HD}}(t) = \frac{1}{1 + \mathrm{e}^{-2\beta(h_i^{\mathrm{HD}}(t) - \alpha)}}, \qquad (7)$$

where α and β are the sigmoid threshold and slope, respectively.

So far we have said that the neurons in the continuous attractor network are connected to each other by synaptic weights w_{ij} that are a simple function, for example Gaussian, of the distance between the states of the agent in the physical world (e.g. head directions, spatial views, etc.) represented by the neurons. In many simulations, the weights are set by formula to have weights with these appropriate Gaussian values. However, Stringer et al. (2002b) showed how the appropriate weights could be set up by learning. They started with the fact that since the neurons have broad tuning that may be Gaussian in shape, nearby neurons in the state space will have overlapping spatial fields, and will thus be co-active to a degree that depends on the distance between them. They postulated that therefore the synaptic weights could be set up by associative learning based on the co-activity of the neurons produced by external stimuli as the animal moved in the state space. For example, head direction cells are forced to fire during learning by visual cues in the environment that produce Gaussian firing as a function of head direction from an optimal head direction for each cell. The learning rule is simply that the weights w_{ij} from head direction cell j with firing rate r_j^{HD} to head direction cell i with firing rate r_i^{HD} are updated according to an associative (Hebb) rule:

$$\delta w_{ij} = k r_i^{\mathrm{HD}} r_j^{\mathrm{HD}} \qquad (8)$$

[4] Note that here we use r rather than y to refer to the firing rates of the neurons in the network, remembering that, because this is a recurrently connected network (see Fig. 3), the output from a neuron y_i might be the input x_j to another neuron.

where δw_{ij} is the change of synaptic weight and k is the learning rate constant. During the learning phase, the firing rate r_i^{HD} of each head direction cell i might be the following Gaussian function of the displacement of the head from the optimal firing direction of the cell:

$$r_i^{HD} = e^{-s_{HD}^2/2\sigma_{HD}^2}, \quad (9)$$

where s_{HD} is the difference between the actual head direction x (in °) of the agent and the optimal head direction x_i for head direction cell i, and σ_{HD} is the standard deviation.

Stringer et al. (2002b) showed that after training at all head directions, the synaptic connections develop strengths that are an almost Gaussian function of the distance between the cells in head direction space. Interestingly if a non-linearity is introduced into the learning rule that mimics the properties of NMDA receptors by allowing the synapses to modify only after strong postsynaptic firing is present, then the synaptic strengths are still close to a Gaussian function of the distance between the connected cells in head direction space. They showed that after training, the continuous attractor network can support stable activity packets in the absence of visual inputs provided that global inhibition is used to prevent all the neurons becoming activated. (The exact stability conditions for such networks have been analyzed by Amari (1977).) Thus Stringer et al. (2002b) demonstrated biologically plausible mechanisms for training the synaptic weights in a continuous attractor using a biologically plausible local learning rule.

2.2.3.3. Combined continuous and discrete memory representations in the same (e.g. CA3) network, and episodic memory. Space is continuous, and object representations are discrete. If these representations are to be combined in for example an object–place memory, then we need to understand the operation of networks that combine these representations.

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 (Rolls et al., 2002). 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 (see Fig. 5). The combined continuous and discrete attractor network described by Rolls et al. (2002) 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 (Rolls and Deco, 2002; Rolls and Treves, 1998).

2.2.3.4. The capacity of a continuous attractor network, and multiple charts. If spatial representations are stored in the hippocampus, the important issue arises in terms of understanding memories that include a spatial component or context of how many such spatial representations could be stored in a continuous attractor network.

The capacity of a continuous attractor network can be approached on the following bases. First, as there are no discrete attractor states, but instead a continuous physical space is being represented, some concept of spatial resolution must be brought to bear, that is the number of different positions in the space that can be represented. Second, the number of connections per neuron in the continuous attractor will directly influence the number of different spatial positions (locations in the state space) that can be represented. Third, the sparseness of the representation can be thought of as influencing the number of different spatial locations (in the continuous state space) that can be represented, in a way analogous to that described for discrete attractor networks (Battaglia and Treves, 1998a). That is, if the tuning of the neurons is very broad, then fewer locations in the state space may be represented. Fourth, and very interestingly, if representations of different continuous state spaces, for example maps or charts of different environments, are stored in the same network, there may be little cost of adding extra maps or charts. The reason for this is that a large part of the interference between the different memories stored in such a network arises from the correlations between the different positions in any one map, which are typically relatively high because quite broad tuning of individual cells is common. In contrast, there are in general low correlations between the representations of places in different maps or charts, and thus many different maps can be simultaneously stored in a continuous attractor network (Battaglia and Treves, 1998a).

2.2.3.5. Idiothetic update by 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. 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. The way in which path integration could be implemented in recurrent networks such as the CA3 system in the hippocampus or in related systems is described next. Single-cell recording studies have shown that some neurons represent the current position along a continuous physical dimension or space even when no inputs are available, for example in darkness. Examples include neurons that represent the positions of the eyes (i.e. eye direction with respect to the head), the place where the animal is looking in space, head direction, and the place where the animal is located. In particular, examples of such classes of cells include head direction cells in rats (Muller et al., 1996; Ranck, 1985; Taube et al., 1996, 1990) and primates (Robertson et al., 1999), which respond maximally when the animal's head is facing in a particular preferred direction; place cells in rats

(Markus et al., 1995; McNaughton et al., 1983; Muller et al., 1991; O'Keefe, 1984; O'Keefe and Dostrovsky, 1971) that fire maximally when the animal is in a particular location; and spatial view cells in primates that respond when the monkey is looking towards a particular location in space (Georges-François et al., 1999; Robertson et al., 1998; Rolls et al., 1997a).

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 (Samsonovich and McNaughton, 1997). 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 (Zhang, 1996). Another mechanism (for head direction cells) (Skaggs et al., 1995) 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, these proposals did not show how the synaptic weights for this path integration could be achieved by a biologically plausible learning process.

Stringer et al. (2002b) 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 mechanism associates a short-term memory trace of the firing of the neurons in the attractor network reflecting recent movements in the state space (e.g. of places), with an idiothetic velocity of movement input (see Fig. 6). This has been applied to head direction cells (Stringer et al., 2002b), rat place cells (Stringer et al., 2002a, 2002b), and primate spatial view cells (Rolls and Stringer, 2005; Stringer et al., 2004, 2005). These attractor networks provide a basis for understanding cognitive maps, and how they are updated by learning and by self-motion. The implication is that to the extent that path integration of place or spatial view representations is performed within the hippocampus itself, then the CA3 system is the most likely part of the hippocampus to be involved in this, because it has the appropriate recurrent collateral connections. Consistent with this, Whishaw and colleagues (Maaswinkel et al., 1999; Wallace and Whishaw, 2003; Whishaw et al., 2001) have shown that path integration is impaired by hippocampal lesions. Path integration of head direction is reflected in the firing of neurons in the presubiculum, and mechanisms outside the hippocampus probably implement path integration for head direction.

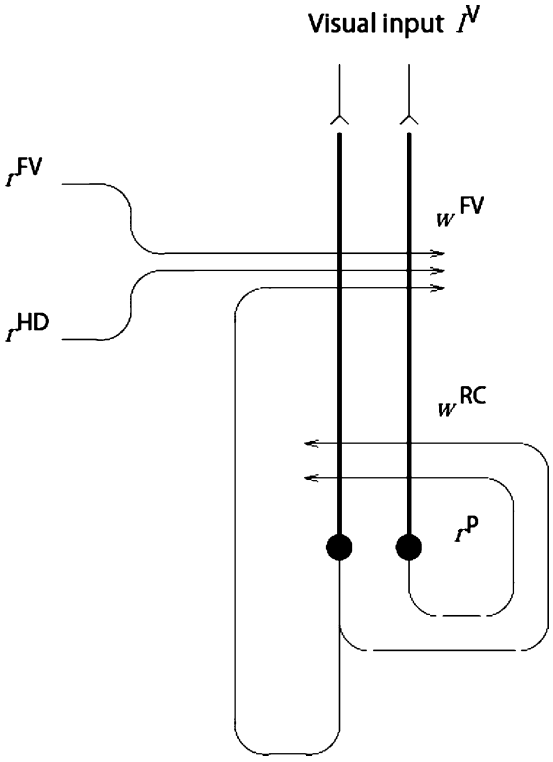

Fig. 6. Neural network architecture for two-dimensional continuous attractor models of place cells. There is a recurrent network of place cells with firing rates r^P, which receives external inputs from three sources: (i) the visual system, (ii) a population of head direction cells with firing rates r^{HD}, and (iii) a population of forward velocity cells with firing rates r^{FV}. The recurrent weights between the place cells are denoted by w^{RC}, and the idiothetic weights to the place cells from the forward velocity cells and head direction cells are denoted by w^{FV}.

2.2.3.6. The dynamics of the recurrent network. The analysis described above of the capacity of a recurrent network such as the CA3 considered steady state conditions of the firing rates of the neurons. The question arises of how quickly the recurrent network would settle into its final state. With reference to the CA3 network, how long does it take before a pattern of activity, originally evoked in CA3 by afferent inputs, becomes influenced by the activation of recurrent collaterals? In a more general context, recurrent collaterals between the pyramidal cells are an important feature of the connectivity of the cerebral neocortex. How long would it take these collaterals to contribute fully to the activity of cortical cells? If these settling processes took in the order of hundreds of ms, they would be much too slow to contribute usefully to cortical activity, whether in the hippocampus or the neocortex (Panzeri et al., 2001; Rolls, 1992, 2003; Rolls and Deco, 2002).

It has been shown that if the neurons are treated not as McCulloch–Pitts neurons which are simply "updated" at each iteration, or cycle of time steps (and assume the active state if the threshold is exceeded), but instead are analyzed and modelled as "integrate-and-fire" neurons in real continuous time, then the network can effectively "relax" into its recall state very rapidly, in one or two time constants of the synapses (Battaglia and Treves, 1998b; Rolls and Deco, 2002; Rolls and Treves, 1998; Treves, 1993). This corresponds to perhaps 20 ms in the brain. One factor in this rapid dynamics of

autoassociative networks with brain-like 'integrate-and-fire' membrane and synaptic properties is that with some spontaneous activity, some of the neurons in the network are close to threshold already before the recall cue is applied, and hence some of the neurons are very quickly pushed by the recall cue into firing, so that information starts to be exchanged very rapidly (within 1–2 ms of brain time) through the modified synapses by the neurons in the network. The progressive exchange of information starting early on within what would otherwise be thought of as an iteration period (of perhaps 20 ms, corresponding to a neuronal firing rate of 50 spikes/s), is the mechanism accounting for rapid recall in an autoassociative neuronal network made biologically realistic in this way. Further analysis of the fast dynamics of these networks if they are implemented in a biologically plausible way with ''integrate-and-fire'' neurons, is provided in Section 7.7 of Rolls and Deco (2002), in Appendix A5 of Rolls and Treves (1998), by Treves (1993), and by Panzeri et al. (2001).

2.2.3.7. Memory for sequences. Evidence from rodents that the hippocampus is involved in the memory for spatial sequences is described in Section 3.3.1. Ways in which the recurrent collateral connections in CA3 might contribute to this are described in this section.

One of the first extensions of the standard autoassociator paradigm that has been explored in the literature is the capability to store and retrieve not just individual patterns, but whole sequences of patterns (Kohonen, 1977; Kohonen et al., 1981; Willshaw, 1981). Hopfield (1982) suggested that this could be achieved by adding to the standard connection weights, which associate a pattern with itself, a new, asymmetric component, that associates a pattern with the next one in the sequence. In practice this scheme does not work very well, unless the new component is made to operate on a slower time scale than the purely autoassociative component (Kleinfeld, 1986; Sompolinsky and Kanter, 1986). With two different time scales, the autoassociative component can stabilize a pattern for a while, before the heteroassociative component moves the network, as it were, into the next pattern. The heteroassociative retrieval cue for the next pattern in the sequence is just the previous pattern in the sequence. A particular type of ''slower'' operation occurs if the asymmetric component acts after a delay τ. In this case, the network sweeps through the sequence, staying for a time of order τ in each pattern.

One can see how the necessary ingredient for the storage of sequences is only a minor departure from purely Hebbian learning: in fact, the (symmetric) autoassociative component of the weights can be taken to reflect the Hebbian learning of strictly simultaneous conjunctions of pre- and post-synaptic activity, whereas the (asymmetric) heteroassociative component can be implemented by Hebbian learning of each conjunction of postsynaptic activity with presynaptic activity shifted a time τ in the past. Both components can then be seen as resulting from a generalized Hebbian rule, which increases the weight whenever postsynaptic activity is paired with presynaptic activity occurring within a given time range, which may extend from a few hundred milliseconds in the past up to include strictly simultaneous activity. This is similar to a trace rule (see Chapter 8 of Rolls and Deco, 2002), which itself matches very well the observed conditions for induction of Long-Term Potentiation, and appears entirely plausible. The learning rule necessary for learning sequences, though, is more complex than a simple trace rule in that the time-shifted conjunctions of activity that are encoded in the weights must in retrieval produce activations that are time-shifted as well (otherwise one falls back into the Hopfield (1982) proposal, which does not quite work). The synaptic weights should therefore keep separate ''traces'' of what was simultaneous and what was time-shifted during the original experience, and this is not very plausible. Levy and colleagues (Levy et al., 1995; Wu et al., 1996) have investigated these issues further, and the temporal asymmetry that may be present in LTP has been suggested as a mechanism that might provide some of the temporal properties that are necessary for the brain to store and recall sequences (Abbott and Blum, 1996; Abbott and Nelson, 2000; Markram et al., 1998; Minai and Levy, 1993). A problem with this suggestion is that, given that the temporal dynamics of attractor networks are inherently very fast when the networks have continuous dynamics, and that the temporal asymmetry in LTP may be in the order of only milliseconds to a few tens of milliseconds, the recall of the sequences would be very fast, perhaps 10–20 ms per step of the sequence, with every step of a 10-step sequence effectively retrieved and gone in a quick-fire session of 100–200 ms.

Rolls and Stringer (in preparation) have suggested that the over-rapid replay of a sequence of memories stored in an autoassociation network such as CA3 if it included asymmetric synaptic weights to encode a sequence could be controlled by the physical inputs from the environment. If a sequence of places 1, 2, and 3 had been learned by the use of an asymmetric trace learning rule implemented in the CA3 network, then the firing initiated by place 1 would reflect (by the learned association) a small component of place 2 (which might be used to guide navigation to place 2, and which might be separated out from place 1 better by the competitive network action in CA1), but would not move fully away from representing place 1 until the animal moved away from place 1, because of the clamping effect on the CA3 firing of the external input representing place 1 to the recurrent network. In this way, the physical constraints of movements between the different places in the environment would control the speed of readout from the sequence memory. A simulation to illustrate this is shown in Fig. 7. The CA1 neurons might thus make a useful contribution to this sequential recall by acting as a competitive network that would separate out the patterns represented in CA3 for the current and the next place, and this has been tested in the simulation by Rolls and Stringer (in preparation). What has been found is that if the representation is set to be less sparse in the CA1 than the CA3, and the CA1 neurons operate on the upper part of a sigmoid activation function, then the next step in the sequence can be represented by a population of neurons in the CA1 better than it can in CA3. (This allows the CA3 representation to be kept sparse, which helps to maximize the

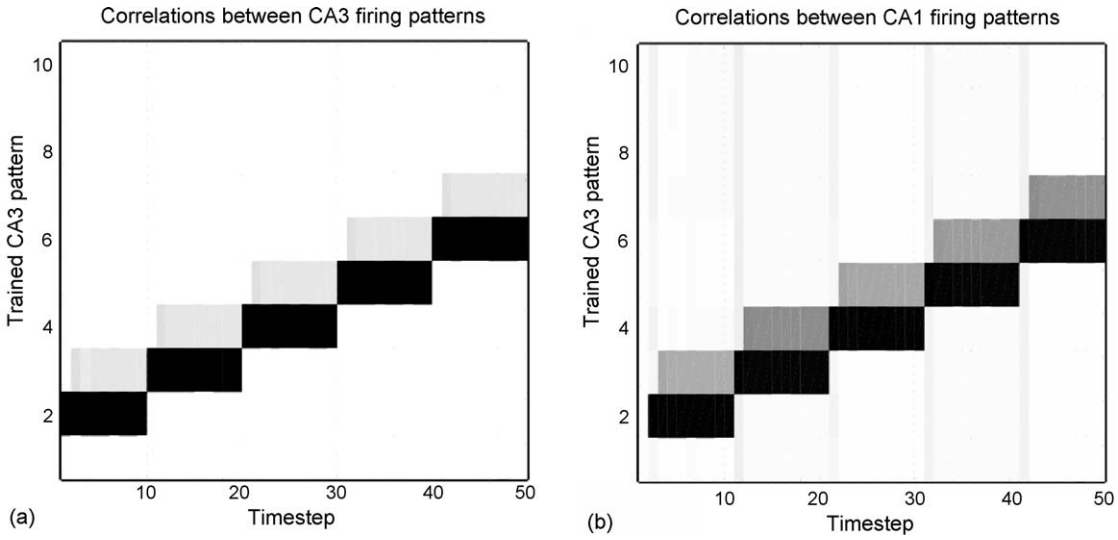

Fig. 7. (a) Simulation of sequence learning in an attractor network such as CA3. The 100 neuron network was trained on a sequence of orthogonal patterns, each represented by 10 active binary neurons. In the first 10 timesteps the agent was at place 2, and the firing of the network was correlated mainly with place 2, but also place 3 was being recalled to some extent. (The darkness of the shading represents the correlation with each of the patterns as indicated on the ordinate.) The network did not move fully to place 3 during timesteps 2–10, because the external place cue for place 2 was still present, providing a weak clamping input effected by scaling down the external input corresponding to place 2. At timestep 10 the agent was allowed to reach position 3 by moving the clamping input to position 3. The network then maintained its firing for position 3 due to the autoassociation in the network and the weak clamping input, but also now recalled in part the pattern of firing for step 4 in the sequence, as shown by the grey level of the correlation with pattern 4. Thus use of a weak clamping input representing the current position, which can only change gradually as the agent moves from place to place in the environment, illustrates how autoassociation in the network can help to maintain activity representing the current place, but can also recall weakly the next step in the sequence, which could help the agent to navigate to the next place. The synapses in the network were update by the normal Hebb rule to implement the autoassociation, and by the temporally asymmetric associative learning rule $\delta w_{ij} = k r_i^{\tau} r_j^{\tau-1}$ when the successive steps in the sequence were being pairwise associated, where τ is the current timestep. (b) The corresponding activity in the CA1 network, which operated as a competitive network with an activation function that emphasized low firing rates relative to high firing rates, as can be achieved by a sigmoid activation function. (A square root function was used in the simulations to convert the activations into the firing rates.) The results show that CA1 could represent the next step in the sequence more explicitly than CA3, as shown by the fact that the correlation with the representation of the next step in the sequence is higher than in CA3, as shown by the increased darkness for the next step. Thus, neurons in CA1 could be more useful than CA3 neurons in leading the agent to the next step in the sequence. CA3 neurons, cannot, in these simulations, represent the next step too strongly relative to the current step, as otherwise the network cycles very rapidly through all steps in the sequence.

number of memories that can be stored.) The CA1 neurons representing the next place in the sequence would be the basis for the animal navigating to that next place. There could be weaker heteroassociative firing of the third item in a sequence, but this would be much weaker. This functionality however could help the disambiguation of long sequences with overlapping parts (cf. Jensen and Lisman, 1996).

In the network of Rolls and Stringer (in preparation), CA3 might by the continuing firing implemented by autoassociation allow one item to be held in STM until the next item arrives for heteroassociation. This would enable long time gaps within the sequence during training to be bridged. This has also been confirmed in the simulation (see Fig. 7).

The heteroassocative (asymmetric) long term potentiation (LTP) could work as follows: If the effect of input 1 remains at every synapse activated by input 1 for e.g. 100 ms (e.g. as a result of the NMDA receptor glutamate unbinding time constant), then when input 2 drives firing of any neuron with these activated synapses, these input 1-related activated synapses will show LTP. This provides a mechanism for presynaptic firing which precedes postsynaptic firing to be effective in implementing LTP. The mechanism is effectively a short-term memory trace in the presynaptic term, and this presynaptic trace will occur for any synapse from a strongly firing neuron independently of whether the synapse is on a postsynaptic neuron that is firing. This occurs because it is the unbinding time constant of the glutamate from the NMDA receptor that implements the presynaptic trace term, and this unbinding time constant (which is long—in the order of 100 or more ms) may not be affected by whether the postsynaptic neuron is firing or not (Erreger et al., 2004; Lester et al., 1990; Lester and Jahr, 1992). Then during recall, a presentation of stimulus 1 will make the neurons activated by stimulus 2 fire, and thus stimulus 1 will lead to the neurons representing stimulus 2 firing, recalling the sequence correctly.

We note that if an episodic memory is thought to consist of a temporally linked sequence of event memories, then the mechanism for sequence memory just described could implement this type of multiple sequential item episodic memory.

Lisman and colleagues (Jensen et al., 1996; Jensen and Lisman, 1996, 2005; Lisman and Idiart, 1995; Lisman et al., 2005) have suggested that sequences might be encoded by utilizing the neuronal after-depolarization which follows a spike from a neuron by approximately 200 ms to tend to make neurons fire again after they are activated. Interaction with theta oscillations (5–8 Hz) and gamma oscillations (30–80 Hz) in the model would make a set of neurons coding for one item tend to

fire first in a new theta cycle. Neurons encoding a second item in a sequence would tend to fire in the next gamma cycle 20 ms later. Neurons encoding a third item in a sequence would tend to fire in the next gamma cycle 20 ms later. To keep the neurons representing one item synchronized, LTP associated with NMDA receptors with a short time constant of e.g. 12 ms is needed. Every theta cycle, the whole sequence is replayed by the model with 20 ms between items. In one version of the model (Jensen and Lisman, 2005) this is suggested to be implemented in the neocortex. To form associations between successive items in a sequence, LTP associated with NMDA receptors with a long time constant of e.g. 150 ms is needed, and this it is suggested might be implemented in the hippocampus (Jensen and Lisman, 2005; Lisman et al., 2005). It is a difficulty of the model that every theta cycle, the whole sequence is replayed by the model with 20 ms between items, for if the next item in a sequence is needed (e.g. the third), then the model just replays at this high speed all the following items in a sequence, so a special decoding system would be needed to know which the next item is. The model is also very susceptible to noise. The model also only works if there is great regularity in the spike trains of the neurons, which should repeat at very regular intervals locked to theta, and this is inconsistent with the almost Poisson nature of the spike trains of single neurons found in most brain areas. Further, no experimental evidence has been found that successive items in a remembered sequence are replayed at gamma frequency every theta cycle.

Another way in which a delay could be inserted in a recurrent collateral path in the brain is by inserting another cortical area in the recurrent path. This could fit in with the cortico-cortical backprojection connections described in Fig. 1 with return projections to the entorhinal cortex, which might then send information back into the hippocampus, which would introduce some conduction delay (see Panzeri et al., 2001). Another possibility is that the connections between the deep and the superficial layers of the entorhinal cortex help to close a loop from entorhinal cortex through hippocampal circuitry and back to the entorhinal cortex (van Haeften et al., 2003). Another suggestion is that the CA3 system holds by continuing firing a memory for event 1, which can then be associated with event 2 at the CA3–CA1 synapses if event 2 activates CA1 neurons by the direct entorhinal input (Levy, 1989).

Another type of sequence memory uses synaptic adaptation to effectively encode the order of the items in a sequence (Deco and Rolls, 2005c). Whenever the system is quenched into inactivity, the next member of the sequence emerges out of the spontaneous activity, because the least recently activated member of the sequence has the least synaptic or neuronal adaptation. This could be implemented in recurrent networks such as the CA3 or the prefrontal cortex.

For recency short-term memory, the sequence type of memory would be possible, but difficult because once a sequence has been recalled, a system has to ''manipulate'' the items, picking out which is later (or earlier) in the sequence. A simpler possibility is to use a short term form of long term potentiation (LTP) which decays, and then the latest of two items can be picked out because when it is seen again, the neuronal response is larger than to the earlier items (Renart et al., 2001; Rolls and Deco, 2002). This type of memory does not explicitly encode sequences, but instead reflects just how recently an item occurred. This could be implemented at any synapses in the system (e.g. in CA3 or CA1), and does not require recurrent collateral connectivity.

2.2.3.8. Mossy fibre inputs to the CA3 cells. We hypothesize that the mossy fibre inputs force efficient information storage by virtue of their strong and sparse influence on the CA3 cell firing rates (Rolls, 1987, 1989b, 1989d; Treves and Rolls, 1992). (The strong effects likely to be mediated by the mossy fibres were also emphasized by McNaughton and Morris (1987) and McNaughton and Nadel (1990).) We hypothesize that the mossy fibre input appears to be particularly appropriate in several ways. First of all, the fact that mossy fiber synapses are large and located very close to the soma makes them relatively powerful in activating the postsynaptic cell (this should not be taken to imply that a CA3 cell can be fired by a single mossy fiber EPSP). Second, the firing activity of dentate granule cells appears to be very sparse (Jung and McNaughton, 1993) and this, together with the small number of connections on each CA3 cell, produces a sparse signal, which can then be transformed into an even sparser firing activity in CA3 by a threshold effect.[5] Third, nonassociative plasticity of mossy fibres (see Brown et al., 1989, 1990) might have a useful effect in enhancing the signal-to-noise ratio, in that a consistently firing mossy fibre would produce nonlinearly amplified currents in the postsynaptic cell, which would not happen with an occasionally firing fibre (Treves and Rolls, 1992). This plasticity, and also learning in the dentate, would also have the effect that similar fragments of each episode (e.g. the same environmental location) recurring on subsequent occasions would be more likely to activate the same population of CA3 cells, which would have potential advantages in terms of economy of use of the CA3 cells in different memories, and in making some link between different episodic memories with a common feature, such as the same location in space. Fourth, with only a few, and powerful, active mossy fibre inputs to each CA3 cell, setting a given sparseness of the representation provided by CA3 cells would be simplified, for the EPSPs produced by the mossy fibres would be Poisson distributed with large membrane potential differences for each active mossy fiber. Setting the average firing rate of the dentate granule cells would effectively

[5] For example, if only 1 granule cell in 100 were active in the dentate gyrus, and each CA3 cell received a connection from 50 randomly placed granule cells, then the number of active mossy fibre inputs received by CA3 cells would follow a Poisson distribution of average 50/100 = 1/2, i.e. 60% of the cells would not receive any active input, 30% would receive only one, 7.5% two, little more than 1% would receive three, and so on. (It is easy to show from the properties of the Poisson distribution and our definition of sparseness, that the sparseness of the mossy fibre signal as seen by a CA3 cell would be $x/(1+x)$, with $x = C^{MF}a_{DG}$, assuming equal strengths for all mossy fibre synapses.) If three mossy fibre inputs were required to fire a CA3 cell and these were the only inputs available, we see that the activity in CA3 would be roughly as sparse, in the example, as in the dentate gyrus. C^{MF} is the number of mossy fibre connections to a CA3 neuron, and a_{DG} is the sparseness of the representation in the dentate granule cells.

set the sparseness of the CA3 representation, without great precision being required in the threshold setting of the CA3 cells (Rolls et al., 1997b). Part of what is achieved by the mossy fiber input may be setting the sparseness of the CA3 cells correctly, which, as shown above, is very important in an autoassociative memory store. Fifth, the non-associative and sparse connectivity properties of the mossy fibre connections to CA3 cells may be appropriate for an episodic memory system which can learn very fast, in one trial. The hypothesis is that the sparse connectivity would help arbitrary relatively uncorrelated sets of CA3 neurons to be activated for even somewhat similar input patterns without the need for any learning of how best to separate the patterns, which in a self-organizing competitive network would take several repetitions (at least) of the set of patterns. The mossy fibre solution may thus be adaptive in a system that must learn in one trial, and for which the CA3 recurrent collateral learning requires uncorrelated sets of CA3 cells to be allocated for each (one-trial) episodic memory. The hypothesis is that the mossy fibre sparse connectivity solution performs the appropriate function without the mossy fibre system having to learn by repeated presentations of how best to separate a set of training patterns.

The argument based on information suggests, then, that an input system with the characteristics of the mossy fibres is essential during learning, in that it may act as a sort of (unsupervised) teacher that effectively strongly influences which CA3 neurons fire based on the pattern of granule cell activity. This establishes an information-rich neuronal representation of the episode in the CA3 network (see further Treves and Rolls, 1992). The perforant path input would, the quantitative analysis shows, not produce a pattern of firing in CA3 that contains sufficient information for learning (Treves and Rolls, 1992).

On the basis of these points, we predict that the mossy fibres may be necessary for new learning in the hippocampus, but may not be necessary for recall of existing memories from the hippocampus. Experimental evidence consistent with this prediction about the role of the mossy fibres in learning has been found in rats with disruption of the dentate granule cells (Lassalle et al., 2000) (see below).

As acetylcholine turns down the efficacy of the recurrent collateral synapses between CA3 neurons (Hasselmo et al., 1995), then cholinergic activation also might help to allow external inputs rather than the internal recurrent collateral inputs to dominate the firing of the CA3 neurons during learning, as the current theory proposes. If cholinergic activation at the same time facilitated LTP in the recurrent collaterals (as it appears to in the neocortex), then cholinergic activation could have a useful double role in facilitating new learning at times of behavioral activation, when presumably it may be particularly relevant to allocate some of the limited memory capacity to new memories.

2.2.3.9. Perforant path inputs to CA3 cells. By calculating the amount of information that would end up being carried by a CA3 firing pattern produced solely by the perforant path input and by the effect of the recurrent connections, we have been able to show (Treves and Rolls, 1992) that an input of the perforant path type, alone, is unable to direct efficient information storage. Such an input is too weak, it turns out, to drive the firing of the cells, as the ''dynamics'' of the network is dominated by the randomizing effect of the recurrent collaterals. This is the manifestation, in the CA3 network, of a general problem affecting storage (i.e. learning) in *all* autoassociative memories. The problem arises when the system is considered to be activated by a set of input axons making synaptic connections that have to compete with the recurrent connections, rather than having the firing rates of the neurons artificially clamped into a prescribed pattern.

An autoassociative memory network needs afferent inputs also in the other mode of operation, i.e. when it retrieves a previously stored pattern of activity. We have shown (Treves and Rolls, 1992) that the requirements on the organization of the afferents are in this case very different, implying the necessity of a second, separate input system, which we have identified with the perforant path to CA3. In brief, the argument is based on the notion that the cue available to initiate retrieval might be rather small, i.e. the distribution of activity on the afferent axons might carry a small correlation, $q \ll 1$, with the activity distribution present during learning. In order not to lose this small correlation altogether, but rather transform it into an input current in the CA3 cells that carries a sizable signal – which can then initiate the retrieval of the full pattern by the recurrent collaterals – one needs a large number of associatively modifiable synapses. This is expressed by the formulas that give the specific signal S produced by sets of associatively modifiable synapses, or by nonassociatively modifiable synapses: if C^{AFF} is the number of afferents per cell:

$$S_{\mathrm{ASS}} \sim \frac{\sqrt{C^{\mathrm{AFF}}}}{\sqrt{p}} q, \qquad S_{\mathrm{NONASS}} \sim \frac{1}{\sqrt{C^{\mathrm{AFF}}}} q. \tag{10}$$

Associatively modifiable synapses are therefore needed, and are needed in a number C^{AFF} of the same order as the number of concurrently stored patterns p, so that small cues can be effective; whereas nonassociatively modifiable synapses – or even more so, nonmodifiable ones – produce very small signals, which decrease in size the larger the number of synapses. In contrast with the storage process, the average strength of these synapses does not play now a crucial role. This suggests that the perforant path system is the one involved in relaying the cues that initiate retrieval.

Before leaving the CA3 cells, it is suggested that separate scaling of the three major classes of excitatory input to the CA3 cells (recurrent collateral, mossy fibre, and perforant path, see Fig. 1) could be independently scaled, by virtue of the different classes of inhibitory interneuron which receive their own set of inputs, and end on different parts of the dendrite of the CA3 cells (cf. for CA1 Buhl et al., 1994; Gulyas et al., 1993). This possibility is made simpler by having these major classes of input terminate on different segments of the dendrites. Each of these inputs, and the negative feedback produced through inhibitory interneurons when the CA3 cells fire, should for optimal functioning be separately regulated (Rolls, 1995), and

the anatomical arrangement of the different types of inhibitory interneuron might be appropriate for achieving this.

2.2.4. CA1 cells

2.2.4.1. Associative retrieval at the CA3–CA1 (Schaffer collateral) synapses. The CA3 cells connect to the CA1 cells by the Schaeffer collateral synapses. The following arguments outline the advantage of this connection being associatively modifiable, and apply independently of the relative extent to which the CA3 or the direct entorhinal cortex inputs to CA1 drive the CA1 cells during the learning phase.

The amount of information about each episode retrievable from CA3 has to be balanced off against the number of episodes that can be held concurrently in storage. The balance is regulated by the sparseness of the coding. Whatever the amount of information per episode in CA3, one may hypothesize that the organization of the structures that follow CA3 (i.e., CA1, the various subicular fields, and the return projections to neocortex) should be optimized so as to preserve and use this information content in its entirety. This would prevent further loss of information, after the massive but necessary reduction in information content that has taken place along the sensory pathways and before the autoassociation stage in CA3. We have proposed (Treves, 1995; Treves and Rolls, 1994) that the need to preserve the full information content present in the output of an autoassociative memory, requires an intermediate recoding stage (CA1) with special characteristics. In fact, a calculation of the information present in the CA1 firing pattern, elicited by a pattern of activity retrieved from CA3, shows that a considerable fraction of the information is lost if the synapses are non-modifiable, and that this loss can be prevented only if the CA3–CA1 synapses are associatively modifiable. Their modifiability should match the plasticity of the CA3 recurrent collaterals. The additional information that can be retrieved beyond that retrieved by CA3 because the CA3–CA1 synapses are associatively modifiable is strongly demonstrated by the hippocampal simulation described by Rolls (1995), and quantitatively analyzed by Schultz and Rolls (1999).

2.2.4.2. Recoding in CA1 to facilitate retrieval to the neocortex. If the total amount of information carried by CA3 cells is redistributed over a larger number of CA1 cells, less information needs to be loaded onto each CA1 cell, rendering the code more robust to information loss in the next stages. For example, if each CA3 cell had to code for 2 bits of information, e.g. by firing at one of four equiprobable activity levels, then each CA1 cell (if there were twice as many as there are CA3 cells) could code for just 1 bit, e.g. by firing at one of only two equiprobable levels. Thus the same information content could be maintained in the overall representation while reducing the sensitivity to noise in the firing level of each cell. In fact, there are more CA1 cells than CA3 cells in rats (2.5×10^5). There are even more CA1 cells (4.6×10^6) in humans (and the ratio of CA1–CA3 cells is greater). The CA1 cells may thus provide the first part of the expansion for the return projections to the enormous numbers of neocortical cells in primates, after the bottleneck of the single network in CA3, the number of neurons in which may be limited because it has to operate as a single network.

Another argument on the operation of the CA1 cells is also considered to be related to the CA3 autoassociation effect. In this, several arbitrary patterns of firing occur together on the CA3 neurons, and become associated together to form an episodic or ''whole scene'' memory. It is essential for this CA3 operation that several different sparse representations are present conjunctively in order to form the association. Moreover, when completion operates in the CA3 autoassociation system, all the neurons firing in the original conjunction can be brought into activity by only a part of the original set of conjunctive events. For these reasons, a memory in the CA3 cells consists of several different simultaneously active ensembles of activity. To be explicit, the parts A–E of a particular episode would each be represented, roughly speaking, by its own population of CA3 cells, and these five populations would be linked together by autoassociation. It is suggested that the CA1 cells, which receive these groups of simultaneously active ensembles, can detect the conjunctions of firing of the different ensembles that represent the episodic memory, and allocate by competitive learning neurons to represent at least larger parts of each episodic memory (Rolls, 1987, 1989a, 1989b, 1989d, 1990a, 1990b). In relation to the simple example above, some CA1 neurons might code for ABC, and others for BDE, rather than having to maintain independent representations in CA1 of A–E. This implies a more efficient representation, in the sense that when eventually after many further stages, neocortical neuronal activity is recalled (as discussed below), each neocortical cell need not be accessed by all the axons carrying each component A, B, C, D and E, but instead by fewer axons carrying larger fragments, such as ABC, and BDE. This process is performed by competitive networks, which self-organize to find categories in the input space, where each category is represented by a set of simultaneously active inputs (Rolls, 2000b; Rolls and Deco, 2002; Rolls and Treves, 1998).

Concerning the details of operation of the CA1 system, we note that although competitive learning may capture part of how it is able to recode, the competition is probably not global, but instead would operate relatively locally within the domain of the connections of inhibitory neurons. This simple example is intended to show how the coding may become less componential and more conjunctive in CA1 than in CA3, but should not be taken to imply that the representation produced becomes more sparse. An example of what might be predicted follows. Given that objects and the places in which they are seen may be associated by learning in the hippocampus, we might predict that relatively more CA3 neurons might be encoding either objects or places (the components to be associated), and relatively more CA1 neurons might be encoding conjunctive combinations of objects and places. Although object, spatial view, and object–spatial view combination neurons have now been shown to be present in the primate hippocampus during a room-based object–spatial view task (Rolls et al., 2005b), the relative proportions of the types of

neuronal response in CA3 versus CA1 have not yet been analyzed.

The conjunctive recoding just described applies to any one single item in memory. Successive memory items would be encoded by a temporal sequence of such conjunctively encoded representations. To the extent that CA1 helps to build conjunctively encoded separate memory items, this could help a sequence of such memories (i.e. memory items) to be distinct (i.e. orthogonal to each other). This may be contrasted with successive memory items as encoded in CA3, in which there might be more overlap because each memory would be represented by its components, and some of the components might be common to some of the successive memory items. Episodic memory has been used here to refer to the memory of a single event or item. It can also be used to describe a succession of items that occurred close together in time, usually at one place. CA1 could help the encoding of these successive items that are parts of a multi-item episodic memory by making each item distinct from the next, due to the conjunctive encoding of each item (Rolls and Stringer, in preparation). These arguments suggest that the CA1 could be useful in what is described as temporal pattern separation in Section 3.3.3.

2.2.4.3. CA1 inputs from CA3 versus direct entorhinal inputs. Another feature of the CA1 network is its double set of afferents, with each of its cells receiving most synapses from the Schaeffer collaterals coming from CA3, but also a proportion (about 1/6, Amaral et al., 1990) from direct perforant path projections from entorhinal cortex. Such projections appear to originate mainly in layer 3 of entorhinal cortex (Witter et al., 1989b), from a population of cells only partially overlapping with that (mainly in layer 2) giving rise to the perforant path projections to DG and CA3. This suggests that it is useful to include in CA1 not only what it is possible to recall from CA3, but also the detailed information present in the retrieval cue itself (see Treves and Rolls, 1994).

Another possibility is that the perforant path input provides the strong forcing input to the CA1 neurons during learning, and that the output of the CA3 system is associated with this forced CA1 firing during learning (McClelland et al., 1995). During recall, an incomplete cue could then be completed in CA3, and the CA3 output would then produce firing in CA1 that would correspond to that present during the learning. This suggestion is essentially identical to that of Treves and Rolls (1994) about the backprojection system and recall, except that McClelland et al. (1995) suggest that the output of CA3 is associated at the CA3–CA1 (Schaeffer collateral) synapses with the signal present during training in CA1, whereas in the theory of Treves and Rolls (1994), the output of the hippocampus consists of CA1 firing which is associated in the entorhinal cortex and earlier cortical stages with the firing present during learning, providing a theory of how the correct recall is implemented at every backprojection stage though the neocortex (see below).

2.2.4.4. Subcortical versus neocortical backprojection outputs from CA1. The CA1 network is on anatomical grounds thought to be important for the hippocampus to access the neocortex, and the route by which retrieval to the neocortex would occur (see Fig. 1). However, as also shown in Fig. 1, there are direct subcortical outputs of the hippocampus. One route is that outputs that originate from CA3 project via the fimbria directly to the medial septum (Gaykema et al., 1991) or indirectly via the lateral septum to the medial septum (Saper et al., 1979; Swanson and Cowan, 1977). The medial septum in turn provides cholinergic and GABAergic inputs back to the hippocampus, especially the CA3 subregion. In addition to projecting back to the hippocampus, the medial septum also projects to subiculum, entorhinal cortex and mammillary bodies. In turn, the mammillary bodies project to the anterior thalamus which projects to the cingulate cortex, and also to the entorhinal cortex via the pre and parasubiculum. The outputs from CA3 in the fimbria can thus potentially send information to the entorhinal cortex via direct projections from the medial septum, and via the anterior thalamus. A second subcortical output route is provided by the subiculum and CA1 projections via the fimbria/fornix to the lateral septum, and to the mammillary bodies and anterior thalamic nuclei, which in turn project to the cingulate cortex as well as to the prelimbic cortex (rat), which could provide a potential output to behavior (Vann and Aggleton, 2004), and to the entorhinal cortex. A third subcortical output route is that the subiculum and CA1 also project to the nucleus accumbens (Swanson and Cowan, 1977). How might the CA1 to entorhinal cortico-cortical back-projection system, and the different subcortical output routes from the hippocampus, implement different functions?

First, we note that the CA1 to entorhinal cortico-cortical backprojection system is numerically in terms of the number of connections involved large, and this as developed below is likely to be crucial in allowing large numbers of memories to be retrieved from the hippocampus back to the neocortex. This recall operation to the neocortex is described below, but we note here that once a memory has been retrieved to the neocortex, the neocortex then provides a way for hippocampal function to influence behavior. For example, in a place–object recall task, a place cue used to initiate recall of the whole place–object memory in the CA3 would then lead via the backprojections to the object being retrieved (via entorhinal cortex layer 5 and perirhinal cortex) back to the inferior temporal visual cortex (see Fig. 1 left), and this object representation could then guide behavior via the other outputs of the inferior temporal visual cortex (see Rolls and Deco, 2002). As objects are represented in the neocortex, it is a strong prediction of the theory that place–object recall will involve this CA1 backprojection pathway back to the neocortex. Backprojections from CA1 via entorhinal cortex to parahippocampal gyrus and thus to parietal cortex or other parts of the neocortex with spatial representations could allow spatial representations to be retrieved in for example an object–place recall task, and this provides a possible route to spatial action (though an alternative subcortical route for spatial action is described below). In addition, there are more direct CA1, subicular, and entorhinal connections to the prefrontal cortex (Jay and Witter, 1991; Witter et al., 1989a), which could allow the hippocampus to

provide inputs to prefrontal cortex networks involved in short-term memory and in planning actions (Deco and Rolls, 2003, 2005a).

Second, we note that the part of the second subcortical pathway that projects from CA1 and subiculum to the mammillary bodies and anterior thalamus is also numerically large, with in the order of 10^6 axons in the fornix and mammillo-thalamic tract. This could therefore provide an information-rich output pathway to regions such as the cingulate cortex via which some types of (e.g. spatial) behavioral response could be specified by the hippocampus. In contrast, the CA3 projections via the fimbria to the medial septum described as part of the first subcortical route are much less numerous, with indeed for example only approximately 2000 cholinergic neurons in the rat medial septum (Moore et al., 1998). Given further that this first route returns mainly to the hippocampus and connected structures, this route may be more involved in regulating hippocampal function (via cholinergic and GABAergic influences), than in directly specifying behavior (cf. Hasselmo et al., 1995).

Differential predictions of the functions mediated via the cortical versus subcortical outputs of the hippocampal system are thus as follows. Place to object recall should involve the backprojections via CA1 to the neocortex, for that is where the objects are represented. But object to place (or spatial response) tasks *might not* require CA1 and backprojections to parts of the cortex with spatial representations, in so far as the hippocampal subcortical output needs then only to affect which behavioral (spatial) response is made, which it is conceivable could be produced by fornix/fimbria efferents which indirectly reach structures such as the cingulate cortex. To test the hypothesis of potentially different output systems for different types of behavior, a new rat paradigm could be run comparing object–place versus place–object cued recall tasks. The prediction is that object–place cued recall might depend on hippocampal outputs to subcortical structures such as the mammillary bodies, etc., though cortical outputs might be an alternative route. It would at least be of interest to know whether cued object–place recall is impaired by damaging hippocampal subcortical outputs. The stronger prediction is that place–object cued recall depends on CA1 and recall to the neocortex. It is noted that in either case the hippocampus itself may be useful, because object–place and place–object associations involve places, and can not be solved by object–reward association memory, which instead depends on the orbitofrontal cortex and amygdala (Rolls, 2005).

2.2.5. Backprojections to the neocortex—a hypothesis

The need for information to be retrieved from the hippocampus to affect other brain areas was noted in the Introduction. The way in which this could be implemented via backprojections to the neocortex is now considered.

It is suggested that the modifiable connections from the CA3 neurons to the CA1 neurons allow the whole episode in CA3 to be produced in CA1. This may be assisted as described above by the direct perforant path input to CA1. This might allow details of the input key for the recall process, as well as the possibly less information-rich memory of the whole episode recalled from the CA3 network, to contribute to the firing of CA1 neurons. The CA1 neurons would then activate, via their termination in the deep layers of the entorhinal cortex, at least the pyramidal cells in the deep layers of the entorhinal cortex (see Fig. 1). These entorhinal cortex layer 5 neurons would then, by virtue of their backprojections (Lavenex and Amaral, 2000; Witter et al., 2000a) to the parts of cerebral cortex that originally provided the inputs to the hippocampus, terminate in the superficial layers (including layer 1) of those neocortical areas, where synapses would be made onto the distal parts of the dendrites of the (superficial and deep) cortical pyramidal cells (Rolls, 1989a, 1989b, 1989d). 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 from which it is thought that cortical areas such as 39 and 40 related to language developed), and also areas of unimodal association cortex (e.g. inferior temporal visual cortex). The backprojections, by recalling previous episodic events, could provide information useful to the neocortex in the building of new representations in the multimodal and unimodal association cortical areas, which by building new long-term representations can be considered as a form of memory consolidation (Rolls, 1989a, 1989b, 1989d, 1990a, 1990b), or in organizing actions.

The hypothesis of the architecture with which this would be achieved is shown in Fig. 1. The feed-forward connections from association areas of the cerebral neocortex (solid lines in Fig. 1), 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 (Rolls, 1989a, 1989b, 1989d). During the setting up of a new episodic memory, there would be strong feed-forward 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 back-projection 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, that is in the parahippocampal gyrus/perirhinal cortex stage, and in association cortical areas, as shown in Fig. 1.

The concept is that during the learning of an episodic memory, cortical pyramidal cells in at least one of the stages would be driven by forward inputs, but would simultaneously be receiving backprojected activity (indirectly) from the hippocampus which would by pattern association from the backprojecting synapses to the cortical pyramidal cells become associated with whichever cortical cells were being made to fire by the forward inputs. Then later on, during recall, a recall cue from perhaps another part of cortex might reach CA3, where the

firing during the original episode would be completed. The resulting backprojecting activity would then, as a result of the pattern association learned previously, bring back the firing in any cortical area that was present during the original episode. Thus retrieval involves reinstating the activity that was present in different cortical areas that was present during the learning of an episode. (The pattern association is also called hetero-association, to contrast it with autoassociation. The pattern association operates at multiple stages in the backprojection pathway, as made evident in Fig. 1.) If the recall cue was an object, this might result in recall of the neocortical firing that represented the place in which that object had been seen previously. As noted elsewhere in this paper and by McClelland et al. (1995), that recall might be useful to the neocortex to help it build new semantic memories, which might inherently be a slow process and is not part of the theory of recall. It is an interesting possibility that recall might involve several cycles through the recall process. After the information fed back from the first pass with a recall cue from perhaps only one cortical area, information might gradually be retrieved to other cortical areas involved in the original memory, and this would then act as a better retrieval cue for the next pass.

The timing of the backprojecting activity would be sufficiently rapid, in that for example inferior temporal cortex (ITC) neurons become activated by visual stimuli with latencies of 90–110 ms and may continue firing for several hundred ms (Rolls, 1992, 2000a); hippocampal pyramidal cells are activated in visual object-and-place and conditional spatial response tasks with latencies of 120–180 ms (Miyashita et al., 1989; Rolls et al., 1989). 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 ms period in which there would be conjunctive feed-forward activation present with simultaneous backprojected signals in the association cortex.

During recall, 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 feed-forward 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 (see Deco and Rolls, 2005b; Rolls, 1989b, 1989d).

The synapses receiving the backprojections would have to be Hebb-modifiable, as suggested by Rolls (1989b, 1989d). This would solve the de-addressing problem, which is the 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 (Rolls, 1989b, 1989d) 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 at some cortical stages at least, 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 (Rolls, 1989b, 1989d), there are NMDA receptors present especially in superficial layers of the cerebral cortex (Monaghan and Cotman, 1985), implying Hebb-like learning just where the backprojecting axons make synapses with the apical dendrites of cortical pyramidal cells. The quantitative argument that the backprojecting synapses in at least one stage have to be associatively modifiable parallels that applied to the pattern retrieval performed at the entorhinal to CA3 synapses (Treves and Rolls, 1992) and at the CA3–CA1 synapses (Schultz and Rolls, 1999), and is that the information retrieved would otherwise be very low. The performance of pattern association networks is considered in detail by Rolls and Treves (1990, 1998) and other authors (Hertz et al., 1991). It is also noted that the somewhat greater anatomical spread of the backprojection than the forward connections between two different stages in the hierarchy shown in Fig. 1 would not be a problem, for it would provide every chance for the back-projecting axons to find co-active neurons in an earlier cortical stage that are part of the representation that is relevant to the current memory being formed.

If the backprojection synapses are associatively modifiable, we may consider the duration of the period for which their synaptic modification should persist. What follows from the operation of the system described above is that there would be no point, indeed it would be disadvantageous, if the synaptic modifications lasted for longer than the memory remained in the hippocampal buffer store. What would be optimal would be to arrange for the associative modification of the backprojecting synapses to remain for as long as the memory persists in the hippocampus. This suggests that a similar mechanism for the associative modification within the hippocampus and for that of at least one stage of the backprojecting synapses would be appropriate. 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. Kirkwood et al., 1993). It is noted that it would be appropriate to have this similarity of time course (i.e. rapid learning within 1–2 s, and slow decay over perhaps weeks) 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/perirhinal cortex. 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 (Rolls, 1989b, 1989d; Rolls and Deco, 2002) mediated by the operation of neocortico-neocortical backprojecting synapses could be stable, and might not require modification during the learning of a new episodic memory (see Discussion).

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–CA1 neurons, but relatively fixed connections from there back (McClelland et al., 1995). 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.

We have noted elsewhere that backprojections, which included cortico-cortical backprojections, and backprojections originating from structures such as the hippocampus and amygdala, may have a number of different functions (Rolls, 1989a, 1989b, 1989d, 1990a, 1990b, 1992, 2005; Rolls and Deco, 2002) including implementing top-down attention by biased competition (Deco and Rolls, 2003, 2004, 2005a; Deco et al., 2005; Rolls and Deco, 2002). The particular function with which we have been concerned here is how memories stored in the hippocampus might be recalled in regions of the cerebral neocortex, and this is not at all incompatible with such theories of top-down attentional control.

2.2.6. Backprojections to the neocortex—quantitative aspects

How many backprojecting fibres does one need to synapse on 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 lines are those coming from the previous stage (closer to the hippocampus) (Treves and Rolls, 1994). (The interesting concept here is that one can treat for a capacity analysis the series of backprojection stages to the cerebral cortex which each involve a pattern association as an ''unrolled'' version of an autoassociator. Each backprojection pattern association stage would correspond to one iteration round the autoassociation system.) Implicit in this framework is the assumption that the synapses at each stage are modifiable and have been indeed modified at the time of first experiencing each episode, according to some Hebbian associative plasticity rule. A plausible requirement for a successful hippocampo-directed 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 (1991) that the maximum number of independently generated activity patterns that can be retrieved is given, essentially, by the same formula as (3) above 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 p is equal to the number of memories held in the hippocampal memory, it is limited by the retrieval capacity of the CA3 network, $p_{\max}$. Putting together the formula for the latter with that shown here, one concludes that, roughly, the requirement implies that the number of afferents of (indirect) hippocampal origin to a given neocortical stage (C^{HBP}), must be $C^{\mathrm{HBP}} = C^{\mathrm{RC}} a_{\mathrm{nc}}/a_{\mathrm{CA3}}$, where C^{RC} is the number of recurrent collaterals to any given cell in CA3, the average sparseness of a neocortical representation is a_{nc}, and a_{CA3} is the sparseness of memory representations in CA3.

The above requirement is very strong: even if representations were to remain as sparse as they are in CA3, which is unlikely, to avoid degrading the signal, C^{HBP} should be as large as C^{RC}, i.e. 12,000 in the rat. Moreover, other sources of noise not considered in the present calculation would add to the severity of the constraint, and partially compensate for the relaxation in the constraint that would result from requiring that only a fraction of the p episodes would involve any given cortical area. If then C^{HBP} has to be of the same order as C^{RC}, one is led to a very definite conclusion: a mechanism of the type envisaged here 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. C^{HBP} times the ratio between the number of neocortical and that 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 (Treves and Rolls, 1994) (cf. Fig. 1).

Although backprojections between any two adjacent areas in the cerebral cortex are approximately as numerous as forward projections, and much of the distal parts of the dendrites of cortical pyramidal cells are devoted to backprojections, the actual number of such connections onto each pyramidal cell may be on average only in the order of thousands. Further, not all might reflect backprojection signals originating from the hippocampus, for there are backprojections which might be considered to originate in the amygdala (see Amaral et al., 1992) 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. (Note that this completion would be only over the local information present within a cortical area about, e.g. visual input *or* spatial input; it provides a local "clean-up" mechanism, and could not replace the global autoassociation performed effectively over the activity of very many cortical areas which the CA3 could perform by virtue of its widespread recurrent collateral connectivity.) There are two alternative possibilities about how this would operate. First, if the recurrent collaterals showed slow and long-lasting synaptic modification, then they would be useful in completing the whole of long-term (e.g. semantic) memories. Second, if the neocortical recurrent collaterals showed rapid changes in synaptic modifiability with the same time course as that of hippocampal synaptic modification, then they would be useful in filling in parts of the information forming episodic memories which could be made available locally within an area of the cerebral neocortex.

2.2.7. Simulations of hippocampal operation

In order to test the operation of the whole system for individual parts of which an analytic theory is available (Rolls and Treves, 1998; Schultz and Rolls, 1999; Treves and Rolls, 1992, 1994), Rolls (1995) simulated a scaled down version of the part of the architecture shown in Fig. 1 from the entorhinal cortex to the hippocampus and back to the entorhinal cortex. The network included competitive learning in the dentate gyrus to form a sparse representation, using this to drive the CA3 cells by diluted non-associative mossy fibre connectivity during learning, competitive learning in CA1, and pattern association in the retrieval back to entorhinal cortex. The analytic approaches to the storage capacity of the CA3 network, the role of the mossy fibre inputs to CA3 during learning and of the perforant path inputs to CA3 during retrieval, the functions of CA1, and the operation of the backprojections in recall, were all shown to be computationally plausible in the computer simulations. In the simulation, during recall, partial keys are presented to the entorhinal cortex, completion is produced by the CA3 autoassociation network, and recall is produced in the entorhinal cortex of the original learned vector. The network, which has 1000 neurons at each stage, can recall large numbers, which approach the calculated storage capacity, of different sparse random vectors presented to the entorhinal cortex.

One of the points highlighted by the simulation is that the network operated much better if the CA3 cells operated in binary mode (either firing or not), rather than having continuously graded firing rates (Rolls, 1995). The reason for this is that given that the total amount of information that can be stored in a recurrent network such as the CA3 network is approximately constant independently of how graded the firing rates are in each pattern (Treves, 1990), then if much information is used to store the graded firing rates in the firing of CA3 cells, fewer patterns can be stored. The implication of this is that in order to store many memories in the hippocampus, and to be able to recall them at later stages of the system in for example the entorhinal cortex and beyond, it may be advantageous to utilize relatively binary firing rates in the CA3 part at least of the hippocampus. This finding has been confirmed and clarified by simulation of the CA3 autoassociative system alone, and it has been suggested that the advantage of operation with binary firing rates may be related to the low firing rates characteristic of hippocampal neurons (Rolls et al., 1997b).

Another aspect of the theory emphasized by the results of the simulation was the importance of having effectively a single network provided in the hippocampus by the CA3 recurrent collateral network, for only if this operated as a single network (given the constraint of some topography present at earlier stages), could the whole of a memory be completed from any of its parts (Rolls, 1995).

Another aspect of the theory illustrated by these simulations was the information retrieval that can occur at the CA3–CA1 (Schaeffer collateral) synapses if they are associatively modifiable, and this led to a quantitative investigation of this (Schultz and Rolls, 1999).

3. Tests of the theory

Empirical evidence that tests the theory comes from a wide range of investigation methods, including the effects of selective lesions to different subregions of the hippocampal system, the activity of single neurons in different subregions of the hippocampal system, pharmacological and genetic manipulations of different parts of the system, the detailed neuroanatomy of the system, functional neuroimaging studies and clinical neuropsychological studies in humans. Because in this analysis we are particularly interested in the contribution of different subregions of the hippocampal system, we focus here on the effects of selective lesions to different subregions of the hippocampal system, and the activity of single neurons in different subregions of the hippocampal system, together with pharmacological and genetic manipulations of different parts of the system. Having now described in Section 2 the overall theory of how different subregions of the hippocampal system contribute to its function, we now consider the effects of manipulations of different subregions of the hippocampal system, starting from the dentate gyrus, and working through to CA1.

3.1. Dentate gyrus (DG) subregion of the hippocampus

Based on the anatomy of the DG, its input and output pathways, and the development of a computational model, Rolls (1989b, 1996b) (and the present paper Section 2.2.2) has suggested that the DG can act as a competitive learning network with Hebb-like modifiability to remove redundancy from the inputs producing a more orthogonal, sparse, and categorized set of outputs. One example of this in the theory is that to the extent that some entorhinal cortex neurons represent space as a grid (Hafting et al., 2005), the correlations in this type of encoding are removed to produce a representation of place, with each place encoded differently from other places (Jung and

McNaughton, 1993). To the extent then that DG acts to produce separate representations of different places, it is predicted that the DG will be especially important when memories must be formed about similar places. We note that to form spatial representations, learned conjunctions of sensory inputs including vestibular, olfactory, visual, auditory, and somatosensory may be involved. DG may help to form orthogonal representations based on all these inputs, and could thus help to form orthogonal non-spatial as well as orthogonal spatial representations for use in CA3. In any case, the model predicts that for spatial information, the DG should play an important role in hippocampal memory functions when the spatial information is very similar, for example, when the places are close together.

3.1.1. Spatial pattern separation

To examine the contribution of the DG to spatial pattern separation, Gilbert et al. (2001) tested rats with DG lesions using a paradigm that measured one-trial short-term memory for spatial location information as a function of spatial similarity between two spatial locations (Gilbert et al., 1998).

Rats were trained to displace an object that was randomly positioned to cover a baited food well in 1 of 15 locations along a row of food wells. Following a short delay, the rats were required to choose between two objects identical to the sample phase object. One object was in the same location as the sample phase object and the second object was in a different location along the row of food wells. A rat was rewarded for displacing the object in the same position as the sample phase object (correct choice) but received no reward for displacing the foil object (incorrect choice). Five spatial separations, from 15 to 105 cm, were used to separate the correct object from the foil object on the choice phase. The results showed that rats with DG lesions were significantly impaired at short spatial separations; however, the performance of the DG lesioned rats increased as a function of increased spatial separation between the correct object and the foil on the choice phases. The performance of rats with DG lesioned matched controls at the largest spatial separation. The graded nature of the impairment and the significant linear increase in performance as a function of increased separation illustrate the deficit in pattern separation produced by DG lesions (see Fig. 8). Based on these results, it can be concluded that lesions of the DG decrease efficiency in spatial pattern separation, which resulted in impairments on trials with increased spatial proximity and hence increased spatial similarity among working memory representations. In the same study it was found that CA1 lesions do not produce a deficit in this task.

Additional evidence comes from a recent study (Goodrich-Hunsaker et al., 2005) using a modified version of an exploratory paradigm developed by Poucet (1989), in which rats with CA1, CA3, DG lesions and controls were tested on tasks involving a metric spatial manipulation. In this task, a rat was allowed to explore two different visual objects that were separated by a specific distance on a cheeseboard maze. On the initial presentation of the objects, the rat explored each object. However, across subsequent presentations of the objects in their

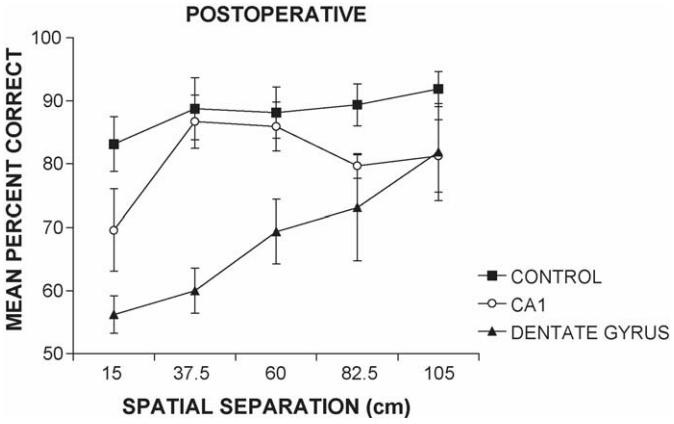

Fig. 8. Pattern separation impairment produced by dentate gyrus lesions. Mean percent correct performance as a function of spatial separation of control group, CA1 lesion group, and dentate gyrus lesion group on postoperative trials. A graded impairment was found as a function of the distance between the places only following dentate gyrus lesions (after Gilbert et al., 2001).

respective locations, the rat habituated and eventually spent less time exploring the objects. Once the rat had habituated to the objects and their locations, the metric spatial distance between the two objects was manipulated so the two objects were either closer together or further apart. The time the rat spent exploring each object was recorded. The results showed that DG lesions impaired detection of the metric distance change in that rats with DG lesions spent significantly less time exploring the two objects that were displaced. Rats with CA1 or CA3 lesions displayed re-exploration similar to controls.

The results of both experiments provide empirical validation of the role of DG in spatial pattern separation and support the prediction from the computational model presented in this paper. Also consistent are the findings that the place fields of DG cells (Mizumori et al., 1990) and specifically granular cells (Jung and McNaughton, 1993) are small and highly reliable, and this may reflect the role of DG in pattern separation.

These studies thus indicate that the DG plays an important role in spatial pattern separation in spatial memory tasks. We discuss evidence below that the CA1 but not the DG region may be involved in temporal pattern separation (Gilbert et al., 2001). Building and utilizing separate representations for other classes of stimuli engage other brain areas, including for objects the inferior temporal visual cortex (Rolls, 2000a; Rolls and Deco, 2002) and perirhinal cortex (Gilbert and Kesner, 2003), for reward value the orbitofrontal cortex (Rolls, 2005) and amygdala (Gilbert and Kesner, 2002), and for motor responses the caudate nucleus (Kesner and Gilbert, 2006).

3.1.2. Encoding versus retrieval

The theory postulates that the dentate/mossy fiber system is necessary for setting up the appropriate conditions for optimal storage of new information in the CA3 system (which could be called encoding); that (especially when an incomplete cue is provided) the retrieval of information from CA3 is optimally cued by the direct entorhinal to CA3 connections.

In addition to the study of Lassalle et al. (2000) mentioned previously that the DG input into the CA3 is essential for

encoding, but not retrieval of information, there is evidence from a study in which rats had 10 learning trials per day in a Hebb–Williams maze. Lee and Kesner (2004b) found that based on a within-day analysis DG lesions (but not lesions of the perforant path input to CA3) impaired the acquisition of this task, consistent with an encoding or learning impairment. However, when tested using a between days analysis, retrieval of what had been learned previously was not impaired by DG lesions, but was impaired by lesions of the perforant path input to CA3. This double dissociation is consistent with the hypothesis that the DG is important for optimal encoding, and the entorhinal to CA3 connections for optimal retrieval.

Further evidence for a DG mediation of spatial encoding comes from the observation that rats with DG lesions are impaired in learning the Morris water maze task when the start location varied on each trial (Nanry et al., 1989; Sutherland et al., 1983; Xavier et al., 1999). Under these conditions, spatial pattern separation may be at a premium, for different, partially overlapping, subsets of spatial cues are likely to be visible from the different starting locations.

Further evidence consistent with the hypothesis that the DG is important in spatial learning (acquisition) is that rats with DG lesions are impaired on acquisition of spatial contextual fear conditioning (Lee and Kesner, 2004a).

However, we note that in the studies described in this section (encoding versus retrieval), during acquisition of these tasks over a number of trials both the storage and the retrieval processes are likely to influence the rate of behavioral learning. Thus, even though in behavioral tasks the deficit can be described as an encoding deficit because it is apparent during initial learning, it is not easy to separate the actual underlying processes by which the DG may be important for setting up the representations for new learning in the CA3 system, and the perforant path to CA3 connections for initiating retrieval especially with a partial cue from CA3.

3.2. CA3 subregion of the hippocampus

In the model the CA3 system acts as an autoassociation system. This enables arbitrary (especially spatial in animals and probably language for humans as well) associations to be formed between whatever is represented in the hippocampus, in that for example any place could be associated with any object, and in that the object could be recalled with a spatial recall cue, or the place with an object recall cue. The same system must be capable of fast (one-trial) learning if it is to contribute to forming new episodic memories, but it could also play an important role in encoding of new information requiring multiple trials. The same system is also predicted to be important in retrieval of hippocampus-dependent information when there is an incomplete retrieval cue. The same system has the property that it can maintain firing activity because of the associative recurrent collateral connections, and for this reason is likely to be important in hippocampus-dependent delay/short-term memory tasks. The CA3 recurrent collateral system could also make a contribution to the learning of sequences if it has some temporal asymmetry in its associative synapses, as described in Section 2.2.3.7. The CA3 system might also contribute to spatial path integration, though this could be performed outside the hippocampus. Tests of these proposed functions are described next.

3.2.1. Rapid encoding of new information

The theory proposes that associative learning in the CA3 recurrent collateral connections can occur rapidly, in as little as one trial, so that it can contribute to episodic memory. Evidence for one-trial learning in the hippocampus is provided by the studies to be discussed in more detail in Section 3.2.5 (on recall) (Day et al., 2003; Rolls and Xiang, 2006; Warthen and Kesner, 2006), with the latter two studies implicating in particular the CA3 hippocampal subregion. In these studies, the one-trial learning was between objects or odors and places.

The situation is a little different in a task in which there is one-trial learning of just a spatial location. In one such task, delayed non-matching-to-place (DNMP) for a single spatial location in an 8-arm maze, Lee and Kesner (2002, 2003a) showed that blockade of CA3 NMDA receptors with AP5 or CA3 (neurotoxic) lesions did not impair one-trial learning in a familiar environment, but did impair it in an initial period in a novel environment. The implication is that a place can be remembered over a 10 s delay even without the CA3, but that learning of new spatial environments does require the CA3 subregion. Consistent with this observation is the finding that hippocampal CA3 (dorsal plus ventral) lesions disrupt learning of the standard 8-arm maze where the rats have to learn not to go back to arms previously visited (Handelmann and Olton, 1981). Rats tend to use different sequences on every trial, thus requiring new learning on every trial. When learning a new spatial environment, associations may be made between the different visual cues and their spatial locations, and this type of learning is computationally similar to that involved in object–place or odor–place association learning, providing a consistent interpretation of CA3 function.

Nakazawa et al. (2003) also reported similar findings with mice in which the function of CA3 NMDA receptors was disrupted. These mice were impaired in learning a novel platform location in a working memory water maze task, whereas they were normal in finding familiar platform locations.

Evidence that rapid learning is reflected in the responses of CA3 neurons comes from a study in which it was found that CA3 neurons alter their responses rapidly when rats encounter novel configurations of familiar cues for the first time (Lee et al., 2004a). Specifically, rats were trained to run clockwise on a ring track whose surface was composed of four different texture cues (local cues). The ring track was positioned in the center of a curtained area in which various visual landmarks were also available along the curtained walls. To produce a novel cue configuration in the environment, distal landmarks and local cues on the track were rotated in opposite directions (distal landmarks were rotated clockwise and local cues were rotated counterclockwise by equal amounts). Wilson and McNaughton (1993) demonstrated that when rats explore an environment CA1 cells within the hippocampus transmit an ensemble code for location. When the rats are then placed in a

new environment the ensemble code in CA1 for the new environment developed rapidly with exploration. They did not record from CA3 neurons making it difficult to know whether CA3 neurons would change more quickly than CA1 neurons. Jeffery et al. (2004) review evidence that CA1 cells tolerate some (metric) stretching of a spatial environment, but remap if for example the walls of the environment are switched more catastrophically, e.g. from white to black. Again it would be of interest to know how rapidly CA3 cells remap after the same environmental changes.

In sum, these results strongly suggest that rapid plastic changes in the CA3 network are essential in encoding novel information involving associations between objects and places, odors and places, or between landmark visual cues and spatial locations, and NMDA receptor-mediated plasticity mechanisms appear to play a significant role in the process.

3.2.2. The types of information associated in CA3

A prediction is that the CA3 recurrent collateral associative connections enable arbitrary associations to be formed between whatever is represented in the hippocampus, in that, for example, any place could be associated with any object. Arbitrary in this context refers to the possibility of what is provided for by non-localized connectivity within the CA3–CA3 system, in that any one representation in CA3 can potentially become associated with any other representation in CA3. The prediction is neutral with respect to what is actually represented in the CA3 system, which we note from the effects of lesions almost always includes space, at least in animals, but could include language in humans. The object representations might originate in the temporal cortical visual areas, and the spatial representations might utilize some information from the parietal cortex such as vestibular inputs related to self-motion (Rolls, 1996b) (see Section 2.1.4). Two important issues need to be clarified. First, is the hippocampus the only neural system that supports all types of stimulus-stimulus associations (Eichenbaum and Cohen, 2001)? Based on the observations that the primate orbitofrontal cortex is involved in some types of stimulus-stimulus association, including visual-to-taste and olfactory-to-taste association learning and more generally in rapid and reversible stimulus-reinforcer association learning (Rolls, 2004, 2005), there appear to be other neural systems that can learn stimulus-stimulus associations. Second, what is the nature of the information that can be associated in this arbitrary way in the CA3 recurrent collateral system? The studies described next indicate that at least the non-human hippocampus is involved in associations when one of the components is spatial.

In order to directly test the involvement of the CA3 subregion of the hippocampus in spatial paired-associate learning, rats were trained on a successive discrimination go/no-go task to examine object–place and odor–place paired associate learning. Normal rats learn these tasks in approximately 240 trials. CA3 lesions impaired the learning of these object–place and odor–place paired associations (Gilbert and Kesner, 2003). Furthermore, lesions of DG or CA1 did not produce a deficit, and the reasons for this are considered later.

In contrast, object–odor paired associate learning was not impaired by CA3 lesions (even with a delay between the object and the odor) (Kesner et al., 2005). Thus, not all types of paired associate learning require the rat hippocampus. This conclusion is supported by the fact that (large or total) hippocampal lesions do not impair the following types of association including odor–odor (Bunsey and Eichenbaum, 1996; Li et al., 1999), odor–reward (Wood et al., 2004), auditory–visual (Jarrard and Davidson, 1990), and object–object associations (Cho and Kesner, 1995; Murray et al., 1993). Thus, in rats paired associate learning appears to be impaired by CA3 lesions only when one of the associates is place. It is important to note that lesions of the parietal cortex and pre-limbic and infralimbic also disrupt the acquisition of object–place paired associate learning, suggesting that cortical regions can also associate objects with places.

3.2.3. Acquisition/encoding associated with multiple trials

The CA3 subregion also appears to be necessary in some tasks that require multiple trials to acquire the task, and a common feature of these tasks is that a new environment must be learned. For example, lesions of the CA3 (but not the CA1) subregion impair the acquisition of object–place and odor–place paired associate learning, a task that requires multiple trials to learn (Gilbert and Kesner, 2003). Another multiple trial task in which a learning set is needed that is affected by CA3, but not by CA1, lesions is acquisition of a non-match to sample one-trial spatial location task on an 8-arm maze with 10 s delays (DNMP). In this case the output from CA3 is via the fimbria, in that fimbria lesions that interrupt the CA3 hippocampal output without affecting the input also impair acquisition of this task. In another task that requires multiple trials, namely the Hebb–Williams maze, CA3, but not CA1, lesions impair within-day learning (encoding) and CA1, but not CA3, lesions impair retention retrieval across days (Jerman and Kesner, 2005; Vago and Kesner, 2005). Finally, CA3 lesioned rats are impaired in the standard water maze task which requires multiple trials (Brun et al., 2002; Florian and Roullet, 2004) (although mice that lacked NMDA receptors in CA3 do not appear to be impaired in learning the water maze (Nakazawa et al., 2002)). These findings are consistent with the hypothesis that when a new environment is learned this may involve multiple associations between different environmental cues, both with each other and with idiothetic (self-motion cues), and that this type of learning depends on new associations formed in the CA3–CA3 connections (see Section 2.2.3.2 on learning in continuous attractor networks, and Section 2.2.3.3 on learning associations between continuous and discrete representations).

It appears that in tasks that require a large number of trials to learn such as the acquisition of the delayed non-matching to place task and probably the acquisition of the spatial tasks mentioned above, the object–place learning task, and the Hebb–Williams maze task, the CA3 and fimbria output are essential, but the CA1 does not play an important role. The fimbria output would enable CA3 to influence the lateral septal area, which could in turn influence the medial septum. Any alteration of medial septum functionality would alter cholinergic input to the

hippocampus (most of which comes from the medial septum), and this would be expected to influence, probably detrimentally, LTP in the hippocampus (Hasselmo et al., 1995), and thus acquisition. Indeed, blockade of CA3 cholinergic receptors with scopolamine disrupts acquisition of the Hebb–Williams maze (Rogers and Kesner, 2003) and fear conditioning that is specific to the spatial context (Rogers and Kesner, 2004). However, it is possible that septal dysfunction disrupts the responsiveness of hippocampal neurons to environmental inputs and thereby altering attention processes which in turn could alter memory function (Vinogradova et al., 1996).

3.2.4. Pattern completion

The CA3 system is predicted to be important in the retrieval of hippocampus-dependent information when there is an incomplete retrieval cue. Support for the pattern completion process in CA3 can be found in lesion studies. Rats were tested on a cheese board with a black curtain with four extramaze cues surrounding the apparatus. (The cheese board is like a dry land water maze with 177 holes on a 119 cm diameter board.) Rats were trained to move a sample phase object covering a food well that could appear in one of five possible spatial locations. During the test phase of the task, following a 30 s delay, the animal needs to find the same food well in order to receive reinforcement with the object now removed. After reaching stable performance in terms of accuracy to find the correct location, rats received lesions in CA3. During post-surgery testing, four extramaze cues were always available during the sample phase. However, during the test phase zero, one, two, or three cues were removed in different combinations. The results indicate that controls performed well on the task regardless of the availability of one, two, three, or all cues, suggesting intact spatial pattern completion. Following the CA3 lesion, however, there was an impairment in accuracy compared to the controls especially when only one or two cues were available, suggesting impairment in spatial pattern completion in CA3-lesioned rats (Gold and Kesner, 2005) (see Fig. 9). A useful aspect of this task is that the test for the ability to remember a spatial location learned in one presentation can be tested with varying number of available cues, and many times in which the locations vary, to allow for accurate measurement of pattern completion ability when the information stored on the single presentation must be recalled.

In a different study Vazdarjanova and Guzowski (2004) placed rats in two different environments separated by ~30 min. The two environments differed greatly in that different objects were located in each room. The authors were able to monitor the time course of activations of ensembles of neurons in both CA3 and CA1, using a new immediate-early gene-based brain-imaging method (*Arc/H1a* catFISH). When the two environments were only modestly different, CA3 neurons exhibited higher overlap in their activity between the two environments compared to CA1 neurons. In another study Lee et al. (2004b) recorded from ensembles of neurons using multiple electrodes in both CA1 and CA3 in freely behaving animals. By altering cue configuration in a ring track, Lee and colleagues demonstrated that the population spatial code in

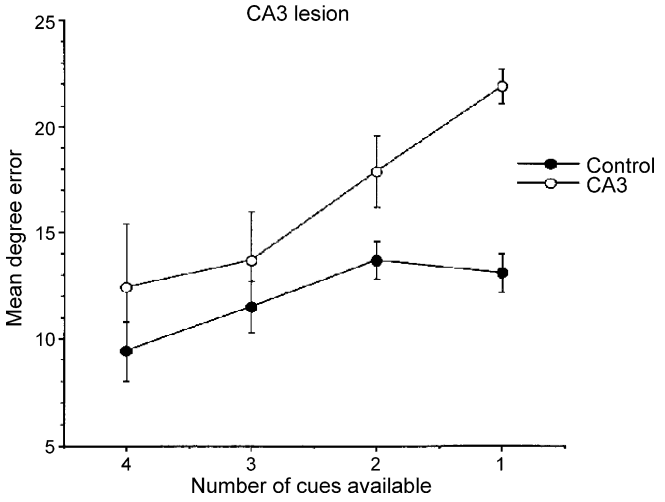

Fig. 9. Pattern completion impairment produced by CA3 lesions. The mean (and sem) degree of error in finding the correct place in the cheeseboard task when rats were tested with 1, 2, 3 or 4 of the cues available. A graded impairment in the CA3 lesion group as a function of the number of cues available was found. The task was learned in the study phase with the 4 cues present. The performance of the control group is also shown (after Gold and Kesner, 2005).

CA3 was less disrupted by modestly altered cue configurations. However, the population representation of space in CA1 was more easily disrupted by such moderately altered cue configurations. This can be considered as a pattern completion process in CA3, since the CA3 network maintained similar spatial representation of the environment (compared to the original spatial representation of the familiar cue configurations) even though the relationships among cues in the environment were altered.

In another study, Nakazawa et al. (2002) trained CA3 NMDA receptor-knockout mice in an analogous task, using the water maze. When the animals were required to perform the task in an environment where some of the familiar cues were removed, they were impaired in performing the task. The result suggests that the NMDA receptor-dependent synaptic plasticity mechanisms in CA3 are critical to perform the pattern completion process in the hippocampus.

3.2.5. Recall

A prediction of the theory is that the CA3 recurrent collateral associative connections enable arbitrary associations to be formed between whatever is represented in the hippocampus, in that for example any place could be associated with any object, and in that the object could be recalled with a spatial recall cue, or the place with an object recall cue.

In one test of this, Day et al. (2003) trained rats in a study phase to learn in one trial an association between two flavors of food and two spatial locations. During a recall test phase they were presented with a flavor which served as a cue for the selection of the correct location. They found that injections of an NMDA blocker (AP5) or AMPA blocker (CNQX) to the dorsal hippocampus prior to the study phase impaired encoding, but injections of AP5 prior to the test phase did not impair the place recall, whereas injections of CNQX did

impair the place recall. The interpretation is that somewhere in the hippocampus NMDA receptors are necessary for forming one-trial odor–place associations, and that recall can be performed without further involvement of NMDA receptors.

In a hippocampus subregion test of this, rats in a study phase are shown one object in one location, and then a second object in another location. (There are 50 possible objects, and 48 locations.) In the test phase, the rat is shown one object in the start box, and then after a 10 s delay must go to the correct location (choosing between two marked locations). After training in the task, CA3 lesions produced chance performance on this one-trial object–place recall task (Warthen and Kesner, 2006). A control fixed visual conditional to place task with the same delay was not impaired, showing that it is recall after one-trial (or rapid) learning that is impaired. In the context of arbitrary associations between whatever is represented in CA3, the theory also predicts that cued place–object recall tasks and cued place–odor recall tasks should be impaired by CA3 lesions.

Evidence that the CA3 is not necessarily required during recall in a reference memory spatial task, such as the water maze spatial navigation for a single spatial location task, is that CA3 lesioned rats are not impaired during recall of a previously learned water maze task (Brun et al., 2002; Florian and Roullet, 2004). However, if completion from an incomplete cue is needed, then CA3 NMDA receptors are necessary (presumably to ensure satisfactory CA3–CA3 learning) even in a reference memory task (Nakazawa et al., 2002). Thus, the CA3 system appears to be especially needed in rapid, one-trial object–place recall, and when completion from an incomplete cue is needed.

In a neurophysiological investigation of one-trial object–place learning followed by recall of the spatial position in which to respond when shown the object, Rolls and Xiang (2006) showed that some primate hippocampal (including CA3) neurons respond to an object cue with the spatial position in which the object had been shown earlier in the trial. Thus, some hippocampal neurons appear to reflect spatial recall given an object recall cue.

3.2.6. Mossy fiber versus direct perforant path input into CA3

The computational model (see Sections 2.2.2 and 2.2.3) suggests that the dentate granule cell/mossy fiber pathway to CA3 may be important during the learning of new associations in the CA3 network, and that part of the way in which it is important is that it helps by pattern separation to produce relatively sparse and orthogonal representations in CA3. In contrast, the theory predicts that the direct perforant path input to CA3 is important in initiating retrieval from the CA3 autoassociation network, especially with an incomplete retrieval cue.

Support for this hypothesis comes from the findings that Lee and Kesner (2004b) and Jerman and Kesner (2005) have shown that lesions of the DG or CA3 (or a crossed lesion) disrupt within-day learning on the Hebb–Williams maze, but that retrieval of information at the start of the following day is not impaired. In contrast, lesions of the perforant path input to CA3 from entorhinal cortex disrupt retrieval (i.e. initial performance on the following day), but not learning within a day (Lee and Kesner, 2004b).

The perforant path can be divided into a medial and lateral component. It has been suggested that the medial component processes spatial information and that the lateral component processes non-spatial (e.g. objects, odors) information (Hargreaves et al., 2005; Witter et al., 1989a). In one study Ferbinteanu et al. (1999) showed that lesions of the medial perforant path disrupted water maze learning, whereas lateral perforant path lesions had no effect. As predicted by the theory, there is associative LTP between the medial or lateral perforant path and the intrinsic commissural/associational—CA3 synapses) (Martinez et al., 2002). Either place or object recall cues could thus be introduced by the associative MPP and LPP connections to CA3 cells. This is consistent with the finding that disruption of the perforant path input impairs the multiple trial acquisition of an object–place paired associate task (perhaps because retrieval of what has been previously learned is impaired) (Lee and Kesner, 2006).

In addition, Martinez et al. (2002) demonstrated associative (cooperative) LTP between the medial and lateral perforant path inputs to the CA3 neurons. This could provide a mechanism for object (LPP)—place (MPP) associative learning, with either the object or the place during recall activating a CA3 neuron. However, this LPP to MPP cooperative LTP onto a CA3 neuron would be a low capacity memory system, in that there are only 3300 PP inputs to a CA3 cell, compared to 12,000 recurrent collaterals in the CA3–CA3 connections, and these numbers are the leading term in the memory capacity of pattern association and autoassociation memory systems (Rolls and Deco, 2002; Rolls and Treves, 1998).

We note that disruption of DG and mossy fiber input into CA3 do not produce a disruption in the acquisition of the object–place paired associate task (Gilbert and Kesner, 2003) unless the stimuli are close together, implying that the DG contribution is important particularly when pattern separation is needed. The implication is that sufficient input for object–place learning can be introduced into the CA3 system (which is required for this object–place learning) by the perforant path inputs provided that spatial pattern separation is not at a premium (or perhaps the storage of large numbers of different object–place associations is not at a premium, as this is the other condition for which the computational theory indicates that the DG is needed to help produce sparse and orthogonal representations in the CA3 system).

3.2.7. Pattern separation

The CA3 subregion may have more distinct representations of different environments than CA1. This may be consistent with the computational point that if CA3 is an autoassociator, the pattern representations in it should be as orthogonal as possible to maximize memory capacity and minimize interference. The actual pattern separation may be performed the theory holds as a result of the operation of the dentate granule cells as a competitive net, and the nature of the mossy fiber connections to CA3 cells. Some of the empirical evidence is as follows.

Tanila (1999) showed that CA3 place cells were able to maintain distinct representations of two visually identical environments, and selectively reactivate either one of the representation patterns depending on the experience of the rat. Also, Leutgeb et al. (2004) recently showed that when rats experienced a completely different environment, CA3 place cells developed orthogonal representations of those different environments by changing their firing rates between the two environments, whereas CA1 place cells maintained similar responses**.** In a different study Vazdarjanova and Guzowski (2004) placed rats in two different environments separated by ∼30 min. The two environments differed greatly in that different objects were located in each room. The authors were able to monitor the time course of activations of ensembles of neurons in both CA3 and CA1, using a new immediate-early gene-based brain-imaging method (*Arc*/*H1a* catFISH). When the two environments were significantly different, CA3 neurons exhibited lower overlap in their activity between the two environments compared to CA1 neurons. Thus CA3 may represent different environments relatively orthogonally. In the computational account, each environment would be a separate chart, and the number of charts that could be stored in CA3 would be high if the representations in each chart are relatively orthogonal to those in other charts (see Section 2.2.3.4 and Battaglia and Treves, 1998a), and further, the charts could operate independently (Stringer et al., 2004). Any one chart of one spatial environment can be understood as a continuous attractor network, with place cells with Gaussian shaped place fields, which overlap continuously with each other. In different charts (different spatial environments) the neurons may represent very different parts of space, and neurons representing close places in one environment may represent distant places in another environment (chart).

3.2.8. Short-term memory, and path integration

The CA3 recurrent collateral associative connections suggest that the CA3 system can operate as an attractor network which can be useful in some types of working memory. Support for this idea comes from a variety of studies analyzed by Kesner and Rolls (2001), including a study where in the short-term (30 s delay) memory for spatial location task to measure spatial pattern separation, it was shown that CA3 lesioned rats were impaired for all pattern separations, consistent with the hypothesis that the rats could not remember the correct spatial location (Gilbert and Kesner, 2006). Furthermore, in the short-term memory based delayed non-matching to sample place task mentioned above (Lee and Kesner, 2003b), lesions of CA3 impaired the acquisition of this task with 10 s delays. Also single neuron activity has been recorded in CA3 during the delay period in rats in a spatial position short-term memory task (Hampson et al., 2000) and in monkeys in an object–place and a location-scene association short-term memory task (Rolls et al., 1989; Wirth et al., 2003). Also, firing of spatial view neurons recorded in the CA cells of the primate hippocampus can be maintained in the dark (Robertson et al., 1998). An important property of an attractor network is that it can maintain firing in a delay interval in the absence of the input stimulus, and all the observations just cited are consistent with this short-term memory functionality of CA3. The finding that neuronal representations in the hippocampus switch abruptly from representing a square versus a circular environment on which rats have been trained when the environment changes incrementally between the two has also been suggested as evidence that the hippocampus implements attractor dynamics (Wills et al., 2005).

In a task in which rats were required to remember multiple places, CA3 and CA1 lesions produced a deficit. In the task, during the study phase rats were presented with four different places within sections that were sequentially visited on a newly devised maze (i.e., *Tulum* maze). Each place was cued by a unique object that was specifically associated with each location within the section during the study phase. Following a 15-s delay and during the test phase in the absence of the cued object, rats were required to recall and revisit the place within one section of the maze that had been previously visited. Both CA1 and CA3 lesions disrupted accurate relocation of a previously visited place (Lee et al., 2005). Thus, short-term memory for multiple places in a one-trial multiple place task depends on both CA3 and CA1. As an attractor network can in general hold only one item active in a delay period by maintained firing, this type of multiple item short-term memory is computationally predicted to require synaptic modification to store each item, and both CA3 and CA1 appear to contribute to this.

As described in Section 2.2.3.5, to the extent that path integration of place or spatial view representations is performed within the hippocampus itself, then the CA3 system is the most likely subregion of the hippocampus to be involved in this, because it has the appropriate recurrent collateral connections. Consistent with this, Whishaw and colleagues (Maaswinkel et al., 1999; Wallace and Whishaw, 2003; Whishaw et al., 2001) and Save et al. (2001) have shown that path integration is impaired by hippocampal lesions. Path integration of head direction is reflected in the firing of neurons in the presubiculum, and mechanisms outside the hippocampus probably implement path integration for head direction (Sharp, 2002). Place cells are also updated idiothetically in the dark (Mizumori et al., 1999), as are CA3 and CA1 primate spatial view cells (Robertson et al., 1998).

3.3. CA1 subregion of the hippocampus

The CA1 subregion of the hippocampus receives inputs from two major sources: the Schaffer collateral inputs from CA3, and the perforant path inputs from the entorhinal cortex (see Fig. 1). CA1 outputs are directed towards the subiculum, entorhinal cortex, prefrontal cortex and many other neural regions including the lateral septum, anterior thalamus and the mammillary bodies (Amaral and Witter, 1995). The anatomical and physiological characteristics suggest that the CA1 can operate as a competitive network and have triggered the development of computational models of CA1 in which for example the CA1 system is involved in the recall process by which backprojections to the cerebral neocortex allow neuronal

activity during recall to reflect that present during the original learning (see Section 2.2.5). In this terminology, cortico-cortical backprojections originate from deep (layer 5) pyramidal cells, and terminate on the apical dendrites of pyramidal cells in layer one of the preceding cortical area (see Fig. 1). In contrast, cortico-cortical forward projections originate from superficial (layers 2 and 3) pyramidal cells, and terminate in the deep layers of the hierarchically next cortical area (see Fig. 1 and Rolls and Deco, 2002; Rolls and Treves, 1998). Within this context, the projections from the entorhinal cortex to DG, CA3 and CA1 can be thought of as forward projections; and from CA1 to entorhinal cortex, subiculum etc. as the start of the back-projection system (see Fig. 1).

The evidence reviewed next of the effects of selective damage to CA1 indicates that it makes a special contribution to temporal aspects of memory including associations over a delay period, and sequence memory. There is also evidence relating it to intermediate memory as well as consolidation. We note that the effects of damage to the CA1 may not be identical to the effects of damage to CA3, because CA1 has some inputs that bypass CA3 (e.g. the direct entorhinal/perforant path input); and CA3 has some outputs that bypass CA1. In particular, the CA3 output through the fimbria projects directly to the lateral septum and then to the medial septum or directly to the medial septum (Amaral and Witter, 1995; Gaykema et al., 1991; Risold and Swanson, 1997). The medial septum, in turn, provides cholinergic and GABAergic inputs to the hippocampus (Amaral and Witter, 1995).

3.3.1. Sequence memory

In Section 2.2.3.7, we described how a sequence memory could be implemented in a recurrent collateral network such as CA3 with some temporal asymmetry in the associative synaptic modification learning rule. One behavioral test in which this type of memory may be needed is in complex maze learning, which is impaired by hippocampal including dorsal hippocampal and CA3 lesions (Jerman and Kesner, 2005). Maze learning could be implemented by pairwise associations between spatial views, or between responses if the task has become habit-based. However, it could also be implemented by associations between views and body responses (e.g. turns), and there might not be an explicitly sequential association involved in this case, as each body action would lead to the next view. Further, in the cases where complex maze learning is impaired by hippocampal lesions, it would remain to be shown that the deficit is due to sequence learning impairments rather than only to spatial learning deficits.

In another paradigm in which a fixed sequence is learned over multiple trials, it appears that pairwise sequential learning and not just temporal decay is required to account for the findings. In a sequential spatial location list learning paradigm, rats are trained by correction to visit the arms of an 8-arm maze in a particular sequence, with food obtained in each arm if a correct choice (made by orienting) is made. Even though lesions of the hippocampus impair the acquisition of this task (learned by control rats in 80 trials), there are no deficits when hippocampus lesions are made after reaching 90–100% correct performance (DeCoteau and Kesner, 2000). Thus the hippocampus may be necessary for learning new spatial sequences, but once learned, it appears that other brain systems can implement the behavior, perhaps using other egocentric or habit strategies.

The implications of these empirical results for the computations underlying sequence learning, and the contributions of the hippocampus to this, are now considered. The hypothesis that temporally asymmetric associations between the successive pairs of items in a sequence implemented in CA3 by some temporally asymmetric synaptic modifiability (see Section 2.2.3.7) is consistent with the evidence that the learning of the fixed spatial sequence task is impaired by hippocampal lesions (DeCoteau and Kesner, 2000). The CA1 network in this situation could help to separate out the representation of the next item in the list from the currently processed item, as illustrated in Fig. 7b, but in any case as shown by the subregion lesion analysis, is on the output route from CA3. The CA3 attractor network could enable a preceding item in the sequence to be kept active until the next item arrives, and this is incorporated into the simulation illustrated in Fig. 7a.

3.3.2. Associations across time

There is evidence implicating the hippocampus in mediating associations across time (Kesner, 1998; Rawlins, 1985). The subregion analyses described next show that CA1 lesions impair this. Computationally, a strong hypothesis would be that the CA3 system could provide the working memory necessary for hippocampus-dependent associations across time, and that the CA3 then influences the CA1 for this function to be implemented. The actual learning could involve holding one item active in CA3 but continuing firing in an attractor state until the next item in the sequence arrives, when it could be associated with the preceding item by temporally asymmetric synaptic associativity, as described in the model of Rolls and Stringer illustrated in Fig. 7. The computational suggestion thus is that associations across time could be implemented in the hippocampus by using the same functionality that may be used for sequence memory.

The CA1 subregion of the hippocampus may play a role in influencing the formation of associations whenever a time component (requiring a memory trace) is introduced between any two stimuli that need to be associated. Support for this idea comes from studies based on a classical conditioning paradigm. Lesions of the hippocampus in rabbits or rats disrupt the acquisition of eye-blink trace conditioning. In trace conditioning a short delay intervenes between the conditioned stimulus (CS) and the unconditioned stimulus (UCS). When, however, a UCS and CS overlap in time (delay conditioning), rabbits with hippocampal damage typically perform as well as normals (Moyer et al., 1990; Weiss et al., 1999). Based on a subregional analysis, it has now been shown that ventral, but not dorsal, CA1 lesions impair at least the retention (tested after 48 h) of trace fear conditioning (Rogers et al., in press). Similar learning deficits in trace fear conditioning (but not in conditioning without a delay between the CS and UCS), were observed for mice that lacked NMDA receptors in both dorsal and ventral

CA1 subregions of the hippocampus (Huerta et al., 2000). In an interesting study, McEchron et al. (2003) recorded from single cells in the CA1 region of the hippocampus during and after trace heart rate (fear) conditioning using either a 10 or 20 s trace interval. They reported that a significant number of cells showed maximal firing on CS-alone retention trials timed to the 10 or 20 s trace after CS offset. This could reflect the transition from an attractor state implemented in CA3 with its recurrent collaterals that represents the CS to an attractor state that represents the conditioned response (CR) (Deco and Rolls, 2003, 2005a; Rolls and Deco, 2002).

Based on a previous finding that the acquisition of an object–odor association is not dependent on the hippocampus, would adding a temporal component to an object–odor association task recruit the hippocampus and more specifically the CA1 region? To test this idea rats were given dorsal CA1, CA3, or control lesions prior to learning an object-trace-odor task. The task was run in a 115 cm linear box in which the rat was presented with an object for 10 s after which it was removed, followed by a 10 s trace period, and by the presentation of an odor 50 cm away. If the odor and the object were paired, the rat was to dig in the odor cup for a reward. If unpaired, the rat was to refrain from digging. Animals that had dorsal CA1 lesions were unable to make the association and never performed above chance (Kesner et al., 2005). These results support the idea that the CA1 region is at least on the route for forming arbitrary associations across time even when there is no spatial component.

3.3.3. Order memory

There are also data on order memory, which does not necessarily imply that a particular sequence has been learned, and could be recalled. Estes (1986) summarized data demonstrating that in human memory there are fewer errors for distinguishing items (by specifying the order in which they occurred) that are far apart in a sequence than those that are temporally adjacent. Other studies have also shown that order judgments improve as the number of items in a sequence between the test items increases (Banks, 1978; Chiba et al., 1994; Madsen and Kesner, 1995). This phenomenon is referred to as a temporal distance effect (sometimes referred to as a temporal pattern separation effect). It is assumed to occur because there is more interference for temporally proximal events than temporally distant events. Based on these findings, Gilbert et al. (2001) tested memory for the temporal order of items in a one-trial sequence learning paradigm. In the task, each rat was given one daily trial consisting of a sample phase followed by a choice phase. During the sample phase, the animal visited each arm of an 8-arm radial maze once in a randomly predetermined order and was given a reward at the end of each arm. The choice phase began immediately following the presentation of the final arm in the sequence. In the choice phase, two arms were opened simultaneously and the animal was allowed to choose between the two arms. To obtain a food reward, the animal had to enter the arm that occurred earliest in the sequence that it had just followed. Temporal separations of 0, 2, 4, and 6 were randomly selected for each choice phase. These values represented the number of arms in the sample phase that intervened between the two arms that were to be used in the test phase. After reaching criterion rats received CA1 lesions. Following surgery, control rats matched their preoperative performance across all temporal separations. In contrast, rats with CA1 lesions performed at chance across 0, 2, or 4 temporal separations and a little better than chance in the case of a six separation. The results suggest that the CA1 subregion is involved in memory for spatial location as a function of temporal separation of spatial locations and that lesions of the CA1 decrease efficiency in temporal pattern separation. CA1 lesioned rats cannot separate events across time, perhaps due to an inability to inhibit interference that may be associated with sequentially occurring events. The increase in temporal interference impairs the rat's ability to remember the order of specific events.

Even though CA1 lesions produced a deficit in temporal pattern separation, some computational models (Levy, 1996; Lisman, 1999; Wallenstein and Hasselmo, 1997) and the model described above in Section 2.2.3.7 have suggested that the CA3 region is an appropriate part of the hippocampus to form a sequence memory, for example by utilizing synaptic associativity in the CA3–CA3 recurrent collaterals that has a temporally asymmetric component (Section 2.2.3.7). It was thus of interest to use the temporal order task to determine whether the CA3 region plays an important role in sequence memory. The CA3 lesions impaired the same sequence learning task described above that was also impaired by lesions of the CA1 region (Gilbert and Kesner, 2006). However, this is likely to be the case only for spatial information.

The hippocampus is known to process spatial and temporal information independently (Kesner, 1998; O'Keefe and Nadel, 1978). In the previous experiments sequence learning and temporal pattern separation was assessed using spatial cues. Therefore, one possibility is that the CA1 and CA3 deficits were due to the processing of spatial rather than non-spatial temporal information. To determine if the hippocampus is critical for processing all domains of temporal information, it is necessary to use a task that does not depend on spatial information. Since the hippocampus does not mediate short-term (delayed match to sample) memory for odors (Dudchenko et al., 2000; Otto and Eichenbaum, 1992), it is possible to test whether the hippocampus plays a role in memory for the temporal sequence of odors (i.e. temporal separation effect). Memory for the temporal order for a sequence of odors was assessed in rats based on a varied sequence of five odors, using a similar paradigm described for sequences of spatial locations. Rats with hippocampal lesions were impaired relative to control animals for memory for all temporal distances for the odors, yet the rats were able to discriminate between the odors (Kesner et al., 2002). Fortin et al. (2002) reported similar results. In a further subregional analysis, rats with dorsal CA1 lesions show a mild impairment, but rats with ventral CA1 lesions show a severe impairment in memory for the temporal distance for odors (Kesner, 2006). Thus, the CA1 appears to be involved in separating events in time for spatial and non-spatial information, so that one event can be remembered distinct from another

event, but the dorsal CA1 might play a more important role than the ventral CA1 for spatial information (Chiba et al., 1992), and conversely ventral CA1 might play a more important role than the dorsal CA1 for odor information. In a more recent experiment using a paradigm described by Hannesson et al. (2004), it can be shown that temporal order information for visual objects is impaired only for CA1, but not CA3 lesions (Hoge and Kesner, 2006). Thus, with respect to sequence learning or memory for order information one hypothesis that would be consistent with the data is that the CA1 is the critical substrate for sequence learning and temporal order or temporal pattern separation. This would be consistent with CA1 deficits in sequence completion of a spatial task and CA1 deficits in temporal order for spatial locations, odor and visual objects. Dorsal CA3 contributes to this temporal order or sequence process whenever spatial location is also important. When visual objects are used the CA3 region does not play a role. It is not known yet whether for odors the ventral CA3 plays an important role. It is predicted that it will not be involved.

We note that in these order tasks the animals are not required to recall the sequence (for example by retracing their steps). Instead, the animals are asked which of two items occurred earlier in the list. To implement this type of memory, some temporally decaying memory trace or temporally increasing memory trace via a consolidation process might provide a model (Marshuetz, 2005), and in such a model, temporally adjacent items would have memory traces of more similar strength and would be harder to discriminate than the strengths of the memory traces of more temporally distant items. (We assume that the animal could learn the rule of responding to the stronger or weaker trace.)

3.3.4. Intermediate memory

The following evidence suggests that the CA1 region is especially involved in an intermediate term memory. Rats with CA3, but not CA1 lesions were impaired in the acquisition of a delayed non-match to place task (in an 8-arm maze) with a 10 s delay. Also, when transferred to a new maze in a different room and using a 10 s delay, there was a deficit for CA3, but not CA1 lesioned rats. Deficits for CA1 emerged when rats were transferred to a 5 min delay. Comparable deficits at a 5 min delay were also found for CA3 lesioned rats. It should be noted that similar results as described for the lesion data were obtained following AP5 injections, which impaired transfer to the new environment when made into CA3 but not CA1. At 5 min delays AP5 injections into CA1 produced a sustained deficit in performance, whereas AP5 injections to CA3 did not produce a sustained deficit (Lee and Kesner, 2002, 2003a).

Although the CA3 system is involved even at short delays in acquiring this spatial short-term memory task, it is not apparently involved in the task once it has been acquired (Lee and Kesner, 2003a). The implication is that (after acquisition) the CA3 system is not required to operate as a short-term attractor working memory to hold on line in the 10 s delay the place that has just been shown, although it could contribute to acquisition by operating in this way. The CA3 could also help in acquisition by providing a good spatial representation for the task, and in particular would enable the spatial cues in the environment to be learned. The suggestion therefore is that at the 5 min delay, the system must operate by associative connections from entorhinal cortex to CA1, which enable the sample place in the 8-arm maze to be remembered until the non-match part of the trial 5 min later, and the AP5 impairment after injection into CA1 is consistent with this.

Another implication is that the CA3 contribution to this task can be implemented partly independently of CA1. Consistent with this, lesions of the fimbria impair the acquisition of the delayed match to place task at a 10 s delay. With longer delays, the task may no longer be implemented by an attractor process in CA3, but may involve LTP to set up an episodic-like memory which appears in this case to depend especially on CA1. Thus, this evidence suggests two types of short-term memory implementations in the hippocampus. One is a very short term (10 s) memory (typically involving space) that may be implemented in CA3. The other is an intermediate term (5 min) memory that appears to be a more episodic-like memory involving LTP in CA1. Also, it is likely that the direct entorhinal to CA1 connections may be of importance in that the CA1 lesion effect on the delayed non-match to place task at 5 min delays can also be produced by injections of apomorphine into CA1 which influence the entorhinal to CA1 connections (Vago et al., 2003).

Further evidence for some dissociation of an intermediate-term from a short-term memory in the hippocampus is that in the Hebb–Williams maze, learning/encoding measured within a day is impaired by CA3 and DG, but not by CA1 lesions. In contrast, retention/retrieval measured between days is impaired by CA1 but not by CA3 lesions. Thus, there may be an acquisition versus retention dissociation with CA3 versus CA1 lesions. Interestingly, the CA1 lesion effect on this task can also be produced by injections of apomorphine into CA1 which influence the entorhinal to CA1 connections, suggesting that on the following day when retrieval is at a premium, the direct entorhinal to CA1 connections may play an important role (Vago and Kesner, 2005).

In addition to the processing of temporal information, the CA1 subregion appears to have cellular processes that match it to longer term types of memory than CA3. To test the idea that the CA1 region might be involved in retrieval after long (e.g. 5 min, 24 h) time delays, rats with CA1 lesions were tested in a modified Hebb–Williams maze. The results indicate that CA1 lesioned rats are impaired in retrieval with a 24 h delay (across-day tests), but have no difficulty in encoding new information (i.e. within-day tests) (Jerman and Kesner, 2005; Vago and Kesner, 2005). Using a spatial contextual fear conditioning paradigm, rats with dorsal CA1 lesions are relative to controls impaired in retention (intermediate-term memory) of conditioning when tested 24 h following acquisition (Lee and Kesner, 2004a). Using the same paradigm Hall et al. (2000) have demonstrated a relationship between contextual fear memory and the expression of LTP-related immediate early genes (i.e., *BDNF* and *zif268*) in the CA1 30 min after the exposure to a contextual fear-conditioning situation. Hall et al. (2001) also demonstrated that 30 min following a test for

contextual retrieval administered 24 h after fear conditioning resulted in an increase in *zif 268* detected in CA1. Strekalova et al. (2003) showed that following a single footshock, a test for contextual retrieval 48 h later revealed 90 min later an induction of c-Fos and JunB early genes in dorsal CA1. No changes were observed in the absence of a test of contextual retrieval. In addition, Gall et al. (1998) demonstrated that *c-fos* gene expression was elevated selectively more in CA1 compared to CA3 only after overtraining in an olfactory discrimination task, whereas the same gene expression in CA3 compared to that in CA1 was selectively enhanced after the initial acquisition of the olfactory discrimination task (see also Hess et al., 1995a, 1995b). In another study Bertaina-Anglade et al. (2000) showed that learning of an appetitive operant conditioning task in mice resulted in increased c-Fos expression in CA1 primarily as a function of improvement in performance between day 1 and day 2. As these early genes containing the cAMP response element (CRE) are essential for gene transcription and protein synthesis after induction of LTP, the enhanced expression of *BDNF* and *zif268*, c-Fos, and JunB also suggests that CA1 is a key subregion for the establishment of intermediate-term memory using cellular consolidation processes.

Support for assigning the above mentioned results to the processing of intermediate memory within CA1 comes from the observation that early gene changes in CA1 while observed on day 1 are not observed with longer term retention test at 5 days (Hall et al., 2001) or 28 days (Bertaina-Anglade et al., 2000).

In addition, it has been shown in a water maze study that post-training lesions of the CA1 24 h after learning disrupted subsequent recall, whereas the same lesion made 3 weeks later did not produce a disruptive effect (Remondes and Schuman, 2004). In another study injections of propranolol into CA1 to block beta adrenergic receptors 5 min after contextual fear conditioning disrupted subsequent retention, whereas the same injections had no effect when administered 6 h later (Ji et al., 2003).

How could memories become hippocampal-independent after long time delays? One possibility is that there is active recall to the neocortex which can then use episodic information to build new semantic memories, as described in Section 2.1.2 (McClelland et al., 1995; Rolls, 1989b, 1989d, 1990a; Treves and Rolls, 1994). In this case, the hippocampus could be said to play a role in the consolidation of memories in the neocortex. We note that in another sense a consolidation process is required in the neocortex during the original learning of the episodic memory, in that we hypothesize that associative connections between hippocampal backprojections and neocortical neurons activated by forward inputs are formed (and presumably consolidated) during the original learning, so that later a hippocampal signal can recall neocortical representations. Another possibility is that there are more passive effects of what has been learned in the hippocampus on the neocortex, occurring for example during sleep (Wilson, 2002; Wilson and McNaughton, 1994). Indeed, given that the hippocampus is massively connected to the neocortex by backprojections as described above, it is very likely that any alteration of the functional connectivity within the hippocampus, for example the coactivity of place neurons representing nearby places in an environment which has just been learned, will have an influence on the correlations found between neocortical neurons also representing the places of events (Wilson, 2002; Wilson and McNaughton, 1994). In this case, there could be synaptic modification in the neocortex between newly correlated neuronal activity, and this would effectively produce a form of new learning (''consolidation'') in the neocortex. Another sense in which consolidation might be used is to refer to the findings considered in this section that there is a time-dependency of the learning in CA1 that seems special, enabling CA1 to contribute to the formation of memories (''consolidation'') with long time delays, and also, perhaps with a different time course, to their subsequent forgetting or reconsolidation. The term ''consolidation'' could thus be used to refer to many different types of computational process, which should be distinguished.

3.4. CA1 and CA3: interactions and dissociations

The dominant view of the relationship among the three major subregions is that they operate as a feed-forward sequential processing system. The more recent data, however, suggest that for certain tasks there are dissociations between the involvement of the CA3 versus CA1 subregions and for other tasks there are dissociations for the CA1 versus CA3 subregions. Yet for a different set of tasks both the CA1 and CA3 interact in processing of critical information. In this section we explore in more detail the nature of these dissociations and interactions.

First, one can observe a deficit following dysfunction of the CA3 subregion, but no deficit following dysfunction of the CA1 subregion. Examples follow:

(A) Lesions of the CA3, but not the CA1, subregion impair the acquisition of object–place and odor–place paired associate learning (Gilbert and Kesner, 2003). In these tests, the recall of for example an object in neocortex by a place retrieval cue is not required, and hence the backprojection system started by CA1 may not be required. The CA3 recurrent collateral system could be important for building the object–place association, and then the hippocampus may be able to influence performance via, for example, the CA3 output via the fimbria indirectly to the lateral septum and thus to the medial septum or directly to the medial septum (which in turn may influence the mammillary bodies, hippocampus, subiculum and entorhinal cortex).

(B) Another task affected by CA3 but not by CA1 lesions is acquisition of a non-match to sample one-trial spatial location task on an 8-arm maze with 10 s delays, and in this case the output from CA3 is via the fimbria, in that fimbria lesions that interrupt the CA3 hippocampal output without affecting the input also impair acquisition of this task. The CA3 could provide a spatial attractor short-term memory for the 10 s delays in the task, and synaptic modification may be needed to set up the attractors required for this task

but not to use the attractors later, in that after acquisition NMDA receptor blockade in CA3 with AP5 does not impair performance of the 10 s DNMP task (Kesner and Rolls, 2001; Lee and Kesner, 2002).

(C) CA3 but not CA1 lesions impair transfer to a novel environment (a new maze) of short-term (10 s) memory in a nonmatching-to-place task (Lee and Kesner, 2003a). In this case the CA3 output can be mediated by either the fimbria/septum or CA1 route, in that a combined fimbria and CA1 lesion (but not either alone) impair this task.

(D) CA3 lesions impair within-day learning in a Hebb–Williams maze, and CA1 lesions impair retention across days (Jerman and Kesner, 2005). It appears that in tasks that require a large number of trials to learn such as the spatial task mentioned above, the object–place learning task and the Hebb–Williams maze task, that the CA3 and fimbria output is essential and that the CA1 does not play an important role. However, for rapid acquisition and intermediate memory the CA3–CA1 pathway is essential and the fimbria output pathway is not important.

In the cases where a fimbria cut can induce an acquisition deficit, a possible mechanism is the influence that the medial septum cholinergic projections have on the hippocampus. It is assumed that the fimbria output to the medial septum is excitatory, so that a cut in the fimbria output would result in reduced activation of cholinergic fiber projections especially to CA3. The consequence of a reduction in the cholinergic influence on the hippocampus could be an increase in the effective strength of the CA3–CA3 connections, which would impair new learning because existing associations in the CA3–CA3 network would tend to dominate the CA3 cell firing (Hasselmo et al., 1995). In this sense, low acetylcholine is appropriate for recall but not for new learning, and with low acetylcholine, memories already in CA3 may interfere with setting up new representations in CA3 to be learned. In addition, low acetylcholine after a fimbria cut could impair new learning because long-term potentiation in the CA3–CA3 synapses is reduced (Hasselmo et al., 1995). These acquisition deficits may be especially evident when the task is difficult to learn and requires multiple trials, and thus this interference in encoding of new spatial information becomes more pronounced. Consistent with these hypotheses are observations of Rogers and Kesner (2003, 2004) where they examined the effects of scopolamine injections into dorsal CA3 on the acquisition of the Hebb–Williams maze as well as the acquisition of contextual delay fear conditioning. Scopolamine acted to inhibit or reduce acquisition (referred to by the authors as encoding in the context of the experiments) over multiple trials, but had no real effect on retrieval. The same encoding/retrieval effect was observed for spatial contextual fear conditioning. These data also fit with evidence that the medial septum cholinergic input is stronger to the CA3 than CA1, as this may help to emphasize the role of CA3 in encoding.

There is some neurophysiological evidence that also suggests differences between CA3 and CA1. For example, when the rats encountered the changed cue configurations for the first time in the Lee et al. (2004a) experiment, the CA3 place fields shifted their locations on the first day only, whereas CA1 place fields started to shift from day 2. This double dissociation in the time course of plasticity between CA1 and CA3 place fields suggests that CA3 reacts first to any changed components in the environment presumably to incorporate the novel components into an existing system or build a new representation of the environment if changes are significant. CA1 neurons retain their spatial firing in the dark more than do CA3 neurons in primates (Robertson et al., 1998) and rats (Mizumori et al., 1999), and this it is suggested is due to some information completion in the CA3 recurrent collateral system, with further information recovery at the CA3–CA1 synapses, which are associative (Rolls, 1995; Schultz and Rolls, 1999).

Second, one can observe a deficit following dysfunction of the CA1 subregion, but no deficit following dysfunction of the CA3 subregion. For example, (A) intermediate-term memory in a delayed (5 min) nonmatching-to-sample for a spatial location task is disrupted by APV injections into the CA1, but not into the CA3 subregion (Lee and Kesner, 2002); (B) retrieval of information acquired in a Hebb–Williams maze is disrupted following CA1 lesions, but not following CA3 lesions (Jerman and Kesner, 2005; Vago and Kesner, 2005); (C) retention of contextual fear conditioning is disrupted by CA1, but not CA3 lesions (Lee and Kesner, 2004a). In all these cases when there is a deficit following CA1 lesions, but not CA3 lesions, the possibility exists that the deficit is due to a faulty input from the direct perforant pathway to CA1, since the Schaffer collateral input is intact. Based on the idea that in vitro dopamine injections into the CA1 region inhibit the direct perforant path projection to the CA1 region without affecting the Schaffer collateral projection into the CA1 region (Otmakhova and Lisman, 1998, 1999), rats were injected with apomorphine (a dopamine agonist) or vehicle control in the CA1 region in the delayed (5 min) nonmatching-to-sample for a spatial location task, in the Hebb–Williams maze task, and the contextual fear conditioning task. The results show that apomorphine injections into the CA1 disrupt performance in all these tasks. Furthermore, apomorphine injections into CA1 do not disrupt encoding in the Hebb–Williams maze and transfer of short-term memory for a spatial location in a nonmatching-to-sample task to a novel environment (a new maze) which are processes that are not dependent on the CA1 region (Vago et al., 2003). Apomorphine injections into the CA1 subregion produce the same pattern of deficits as are produced by CA1 but not CA3 lesions. This result implies that in situations where there is a CA1, but no CA3, lesion effect then the direct perforant path input into the CA1 region represents the main input for the integrity of intact performance perhaps based on intermediate-term memory processing.

Third, one can observe a deficit following dysfunction of either the CA3 or CA1 subregions. For example, for the tasks in which the order of presented items must be used (see Section 3.3.3 on one-trial sequence learning, and referred to as temporal pattern separation tasks), there are deficits following CA1 or CA3 lesions (Gilbert and Kesner, 2006; Gilbert et al., 2001). Thus for certain types of temporal processing there is an

implication that both regions are working cooperatively and that CA1 is likely to benefit from a feed-forward Schaffer collateral connection from CA3, but CA1 could also be receiving critical information from the direct perforant path. However, the main prediction of the computational theory with respect to this issue is that the CA3–CA1 connections will be especially important when recall of information is required back to the neocortex using backprojections. One such task might be place–object recall, for when an object must be recalled, it is likely that the object can only be represented in high order visual cortical areas in the temporal lobe. Unfortunately there is little evidence as yet on the effects of selective subregion lesions on recall. In terms of neurophysiology, it has been shown that both CA3 and CA1 neurons in the primate respond to the recalled place in an object–place recall task (Rolls and Xiang, 2006). Although we know that CA3 lesions impair object–place recall in the rat (Warthen and Kesner, 2006), we do not yet know whether CA1 lesions do the same. In any case, the strong prediction from the computational theory is that either CA3 or CA1 lesions will affect place–object recall.

4. Comparison with other theories of hippocampal function

The model described here is quantitative, and supported by both formal analyses and quantitative simulations. Many of the points made, such as on the number of memories that can be stored in autoassociative networks, the utility of sparse representations, and the dynamics of the operation of networks with recurrent connections, are quite general, and will apply to networks in a number of different brain areas. With respect to the hippocampus, the theory specifies the maximum number of memories that could be stored in it, and this has implications for how it could be used biologically. It indicates that if this number is approached, it will be useful to have a mechanism for recalling information from the hippocampus for incorporation into memories elsewhere. With respect to recall, the theory provides a quantitative account for why there are as many backprojections as forward projections in the cerebral cortex. Overall, the theory provides an explanation for *how* this part of the brain could work, and even if this theory needs to be revised, it is suggested that a fully quantitative theory along the lines proposed which is based on the evidence available from a wide range of techniques will be essential before we can say that we understand *how* a part of the brain operates.

Hypotheses have been described about how a number of different parts of hippocampal and related circuitry might operate. Although these hypotheses are consistent with a theory of how the hippocampus operates, some of these hypotheses could be incorporated into other views or theories. In order to highlight the differences between alternative theories, and in order to lead to constructive analyses that can test them, the theory described above is compared with other theories of hippocampal function in the following section. Although the differences between the theories are highlighted in this section, the overall view described here is close in different respects to those of a number of other investigators (Brown and Zador, 1990; Eichenbaum et al., 1992; Gaffan, 1992; Marr, 1971; McNaughton and Nadel, 1990; Moscovitch et al., 2005; Squire, 1992) and of course priority is not claimed on all the propositions put forward here.

Some theories postulate that the hippocampus performs spatial computation. The theory of O'Keefe and Nadel (1978), that the hippocampus implements a cognitive map, placed great emphasis on spatial function. It supposed that the hippocampus at least holds information about allocentric space in a form which enables rats to find their way in an environment even when novel trajectories are necessary, that is it permits an animal to ''go from one place to another independent of particular inputs (cues) or outputs (responses), and to link together conceptually parts of the environment which have never been experienced at the same time''. O'Keefe (1990) extended this analysis and produced a computational theory of the hippocampus as a cognitive map, in which the hippocampus performs geometric spatial computations. Key aspects of the theory are that the hippocampus stores the centroid and slope of the distribution of landmarks in an environment, and stores the relationships between the centroid and the individual landmarks. The hippocampus then receives as inputs information about where the rat currently is, and where the rat's target location is, and computes geometrically the body turns and movements necessary to reach the target location. In this sense, the hippocampus is taken to be a spatial computer, which produces an output which is very different from its inputs. This is in contrast to the present theory, in which the hippocampus is a memory device, which is able to recall what was stored in it, using as input a partial cue. A prototypical example in Rolls' theory is the learning of object–place association memory and the recall of the whole memory from a part, which can be used as a model of event or episodic memory. The theory of O'Keefe postulates that the hippocampus actually performs a spatial computation. A later theory (Burgess et al., 2000, 1994) also makes the same postulate, but now the firing of place cells is determined by the distance and approximate bearing to landmarks, and the navigation is performed by increasing the strength of connections from place cells to ''goal cells'', and then performing gradient-ascent style search for the goal using the network.

McNaughton et al. (1991) have also proposed that the hippocampus is involved in spatial computation. They propose a ''compass'' solution to the problem of spatial navigation along novel trajectories in known environments, postulating that distances and bearings (i.e. vector quantities) from landmarks are stored, and that computation of a new trajectory involves vector subtraction by the hippocampus. They postulate that a linear associative mapping is performed, using as inputs a ''cross-feature'' (combination) representation of (head) angular velocity and (its time integral) head direction, to produce as output the future value of the integral (head direction) after some specified time interval. The system can be reset by learned associations between local views of the environment and head direction, so that when later a local view is seen, it can lead to an output from the network which is a (corrected) head direction. They suggest that some of the key signals in the computational system can be identified with the firing of hippocampal cells (e.g. local view

cells) and subicular cells (head direction cells). It should be noted that this theory requires a (linear) associative mapping with an output (head direction) different in form from the inputs (head angular velocity over a time period, or local view). This is pattern association (with the conditioned stimulus local view, and the unconditioned stimulus head direction), not autoassociation, and it has been postulated that this pattern association can be performed by the hippocampus (cf. McNaughton and Morris, 1987). This theory is again in contrast to the present theory, in which the hippocampus operates as a memory to store events that occur at the same time, and can recall the whole memory *from any part* of what was stored. (A pattern associator uses a conditioned stimulus to map an input to a pattern of firing in an output set of neurons which is like that produced in the output neurons by the unconditioned stimulus. A description of pattern associations and autoassociators in a neurobiological context is provided by Rolls (1996a) and Rolls and Treves (1998).) The present theory is fully consistent with the presence of ''spatial view'' cells and whole body motion cells in the primate hippocampus (Rolls, 1999; Rolls and O'Mara, 1993; Rolls and Xiang, 2006) (or place or local view cells in the rat hippocampus, and head direction cells in the presubiculum), for it is often important to store and later recall where one has been (views of the environment, body turns made, etc.), and indeed such (episodic) memories are required for navigation by ''dead reckoning'' in small environments.

The present theory thus holds that the hippocampus is used for the formation of episodic memories using autoassociation. This function is often necessary for successful spatial computation, but is not itself spatial computation. Instead, we believe that spatial computation is more likely to be performed in the neocortex (utilising information if necessary recalled from the hippocampus). Consistent with this view, hippocampal damage impairs the ability to learn new environments but not to perform spatial computations such as finding one's way to a place in a familiar environment, whereas damage to the parietal cortex and parahippocampal cortex can lead to problems such as topographical and other spatial agnosias, in humans (see Grusser and Landis, 1991; Kolb and Whishaw, 2003). This is consistent with spatial computations normally being performed in the neocortex. (In monkeys, there is evidence for a role of the parietal cortex in allocentric spatial computation. For example, monkeys with parietal cortex lesions are impaired at performing a landmark task, in which the object to be chosen is signified by the proximity to it of a ''landmark'' (another object) (Ungerleider and Mishkin, 1982).)

A theory closely related to the present theory of how the hippocampus operates has been developed by McClelland et al. (1995). It is very similar to the theory we have developed (Rolls, 1987, 1989a, 1989b, 1989d; Treves and Rolls, 1992, 1994) at the systems level, except that it takes a stronger position on the gradient of retrograde amnesia, emphasises that recall from the hippocampus of episodic information is used to help build semantic representations in the neocortex, and holds that the last set of synapses that are modified rapidly during the learning of each episode are those between the CA3 and the CA1 pyramidal cells (see Fig. 1). It also emphasizes the important point that the hippocampal and neocortical memory systems may be quite different, with the hippocampus specialized for the rapid learning of single events or episodes, and the neocortex for the slower learning of semantic representations which may necessarily benefit from the many exemplars needed to shape the semantic representation. In the formulation by McClelland et al. (1995), the entorhinal cortex connections via the perforant path onto the CA1 cells are non-modifiable (in the short term), and allow a representation of neocortical long-term memories to activate the CA1 cells. The new information learned in an episode by the CA3 system is then linked to existing long-term memories by the CA3–CA1 rapidly modifiable synapses. All the connections from the CA1 back via the subiculum, entorhinal cortex, parahippocampal cortex, etc., to the association neocortex are held to be unmodifiable in the short term, during the formation of an episodic memory. The formal argument that leads us to suggest that the backprojecting synapses are associatively modifiable during the learning of an episodic memory is similar to that which we have used to show that for efficient recall, the synapses which initiate recall in the CA3 system (identified above with the perforant path projection to CA3) must be associatively modifiable if recall is to operate efficiently (see Treves and Rolls, 1992). The present theory holds that it is possible that for several stages back into neocortical processing, the backprojecting synapses should be associatively modifiable, with a similar time course to the time it takes to learn a new episodic memory. It may well be that at earlier stages of cortical processing, for example from inferior temporal visual cortex to V4, and from V4 to V2, the backprojections are relatively more fixed, being formed (still associatively) during early developmental plasticity or during the formation of new long-term semantic memory structures. Having such relatively fixed synaptic strengths in these earlier cortical backprojection systems could ensure that whatever is recalled in higher cortical areas, such as objects, will in turn recall relatively fixed and stable representations of parts of objects or features. Given that the functions of backprojections may include many top–down processing operations, including attention (Deco and Rolls, 2005a) and priming, it may be useful to ensure that there is consistency in how higher cortical areas affect activity in earlier ''front-end'' or preprocessing cortical areas. Indeed, the current theory shows that at least one backprojection stage the hippocampo-cortical connections must be associatively modifiable during the learning of an episodic memory, but does not require the associative backprojection learning to occur at all backprojection stages during the learning of the episodic memory. Crucial stages might include CA1 to subiculum or to entorhinal cortex (see Fig. 1), or entorhinal cortex to parahippocampal gyrus and perirhinal cortex. It would be interesting to test this using local inactivation of NMDA receptors at different stages of the backprojection system to determine where this impairs the learning of for example place–object recall, i.e. a task that is likely to utilize the hippocampo-cortical backprojection pathways.

If a model of the hippocampal/neocortical memory system could store only a small number of patterns, it would not be a

good model of the real hippocampal/neocortical memory system in the brain. Indeed, this appears to be a major limitation of another model presented recently by Alvarez and Squire (1994). The model specifies that the hippocampus helps the operation of a neocortical multimodal memory system in which all memories are stored by associative recurrent collaterals between the neocortical neurons. Although the idea worked in the model with twenty neurons and two patterns to be learned (Alvarez and Squire, 1994), the whole idea is computationally not feasible, because the number of memories that can be stored in a single autoassociative network of the type described is limited by the number of inputs per neuron from other neurons, not by the number of neurons in the network (Treves and Rolls, 1991, 1994). This would render the capacity of the whole neocortical multimodal (or amodal) memory store very low (in the order of the number of inputs per neuron from the other neurons, that is in the order of 5000–10,000) (cf. O'Kane and Treves, 1992). This example makes it clear that it is important to take into account analytic and quantitative approaches when investigating memory systems. The current work is an attempt to do this.

The theory of Lisman and colleagues (2005) of the memory for sequences has been described and evaluated in Section 2.2.3.7. This theory of sequential recall within the hippocampus is inextricably linked to the internal timing within the hippocampus imposed he believes by the theta and gamma oscillations, and this makes it difficult to recall each item in the sequence as it is needed. It is not specified how one would read out the sequence information, given that the items are only 12 ms apart. The Jensen and Lisman (1996) model requires short time constant NMDA channels, and is therefore unlikely to be implemented in the hippocampus. Hasselmo and Eichenbaum (2005) have taken up some of these sequence ideas and incorporated them into their model, which has its origins in the Rolls and Treves model (Rolls, 1989b; Treves and Rolls, 1992, 1994), but proposes for example that sequences are stored in entorhinal cortex layer III. The proposal that acetylcholine could be important during encoding by facilitating CA3–CA3 LTP, and should be lower during retrieval (Hasselmo et al., 1995), is a useful concept.

Another type of sequence memory uses synaptic adaptation to effectively encode the order of the items in a sequence (Deco and Rolls, 2005c). This could be implemented in recurrent networks such as the CA3 or the prefrontal cortex.

The aim of this comparison of the present theory with other theories has been to highlight differences between the theories, to assist in the future assessment of the utility and the further development of each of the theories.

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References

Abbott, L.F., Blum, K.I., 1996. Functional significance of long-term potentiation for sequence learning and prediction. Cereb. Cortex 6, 406–416.

Abbott, L.F., Nelson, S.B., 2000. Synaptic plasticity: taming the beast. Nat. Neurosci. 3, 1178–1183.

Alvarez, P., Squire, L.R., 1994. Memory consolidation and the medial temporal lobe: a simple network model. Proc. Natl. Acad. Sci. U.S.A. 91, 7041–7045.

Amaral, D.G., 1986. Amygdalohippocampal and amygdalocortical projections in the primate brain. In: Schwarz, R., Ben-Ari, Y. (Eds.), Excitatory Amino Acids and Epilepsy. Plenum, New York, pp. 3–17.

Amaral, D.G., 1987. Memory: anatomical organization of candidate brain regions. In: Moutcastle, V.B. (Ed.), Handbook of Physiology. Section 1, The Nervous System, vol. V, Higher Functions of the Brain. American Physiological Society, Washington, DC, pp. 211–294.

Amaral, D.G., 1993. Emerging principles of intrinsic hippocampal organisation. Curr. Opin. Neurobiol. 3, 225–229.

Amaral, D.G., Ishizuka, N., Claiborne, B., 1990. Neurons, numbers and the hippocampal network. Prog. Brain Res. 83, 1–11.

Amaral, D.G., Price, J.L., Pitkanen, A., Carmichael, S.T., 1992. Anatomical organization of the primate amygdaloid complex. In: Aggleton, J.P. (Ed.), The Amygdala. Wiley–Liss, New York, pp. 1–66.

Amaral, D.G., Witter, M.P., 1989. The three-dimensional organization of the hippocampal formation: a review of anatomical data. Neuroscience 31, 571–591.

Amaral, D.G., Witter, M.P., 1995. The hippocampal formation. In: Paxinos, G. (Ed.), The Rat Nervous System. Academic Press, San Diego, pp. 443–493.

Amari, S., 1977. Dynamics of pattern formation in lateral-inhibition type neural fields. Biol. Cybern. 27, 77–87.

Amit, D.J., 1989. Modeling Brain Function. Cambridge University Press, Cambridge.

Banks, W.P., 1978. Encoding and processing of symbolic information in comparative judgements. In: Bower, G.H. (Ed.), The Psychology of Learning and Motivation: Advances in Theory and Research. Academic Press, New York, pp. 101–159.

Battaglia, F.P., Treves, A., 1998a. Attractor neural networks storing multiple space representations: a model for hippocampal place fields. Phys. Rev. E 58, 7738–7753.

Battaglia, F.P., Treves, A., 1998b. Stable and rapid recurrent processing in realistic auto-associative memories. Neural Comput. 10, 431–450.

Baylis, G.C., Rolls, E.T., 1987. Responses of neurons in the inferior temporal cortex in short term and serial recognition memory tasks. Exp. Brain Res. 65, 614–622.

Bertaina-Anglade, V., Tramu, G., Destrade, C., 2000. Differential learning-stage dependent patterns of c-Fos protein expression in brain regions during the acquisition and memory consolidation of an operant task in mice. Eur. J. Neurosci. 12, 3803–3812.

Brown, M.W., Aggleton, J.P., 2001. Recognition memory: what are the roles of the perirhinal cortex and hippocampus? Nat. Rev. Neurosci. 2, 51–61.

Brown, M.W., Xiang, J.Z., 1998. Recognition memory: neuronal substrates of the judgement of prior occurrence. Prog. Neurobiol. 55, 149–189.

Brown, T.H., Ganong, A.H., Kairiss, E.W., Keenan, C.L., Kelso, S.R. (Eds.), 1989. Long-term Potentiation in Two Synaptic Systems of the Hippocampal Brain Slice. Academic Press, San Diego.

Brown, T.H., Kairiss, E.W., Keenan, C.L., 1990. Hebbian synapses: biophysical mechanisms and algorithms. Annu. Rev. Neurosci. 13, 475–511.

Brown, T.H., Zador, A., 1990. The hippocampus. In: Shepherd, G. (Ed.), The Synaptic Organisation of the Brain. Oxford University Press, New York, pp. 346–388.

Brun, V.H., Otnass, M.K., Molden, S., Steffenach, H.A., Witter, M.P., Moser, M.B., Moser, E.I., 2002. Place cells and place recognition maintained by direct entorhinal–hippocampal circuitry. Science 296, 2243–2246.

Buckley, M.J., Gaffan, D., 2000. The hippocampus, perirhinal cortex, and memory in the monkey. In: Bolhuis, J.J. (Ed.), Brain, Perception, and Memory: Advances in Cognitive Neuroscience. Oxford University Press, Oxford, pp. 279–298.

Buhl, E.H., Halasy, K., Somogyi, P., 1994. Diverse sources of hippocampal unitary inhibitory postsynaptic potentials and the number of synaptic release sites. Nature 368, 823–828.

Bunsey, M., Eichenbaum, H., 1996. Conservation of hippocampal memory function in rats and humans. Nature 379, 255–257.

Burgess, N., Jackson, A., Hartley, T., O'Keefe, J., 2000. Predictions derived from modelling the hippocampal role in navigation. Biol. Cybern. 83, 301–312.

Burgess, N., Maguire, E.A., O'Keefe, J., 2002. The human hippocampus and spatial and episodic memory. Neuron 35, 625–641.

Burgess, N., Recce, M., O'Keefe, J., 1994. A model of hippocampal function. Neural Netw. 7, 1065–1081.

Burwell, R.D., Witter, M.P., Amaral, D.G., 1995. Perirhinal and postrhinal cortices of the rat: a review of the neuroanatomical literature and comparison with findings from the monkey brain. Hippocampus 5, 390–408.

Cahusac, P.M.B., Rolls, E.T., Miyashita, Y., Niki, H., 1993. Modification of the responses of hippocampal neurons in the monkey during the learning of a conditional spatial response task. Hippocampus 3, 29–42.

Carmichael, S.T., Price, J.L., 1995. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. J. Comp. Neurol. 346, 403–434.

Cassaday, H.J., Rawlins, J.N., 1997. The hippocampus, objects, and their contexts. Behav. Neurosci. 111, 1228–1244.

Chiba, A.A., Johnson, D.L., Kesner, R.P., 1992. The effects of lesions of the dorsal hippocampus or the ventral hippocampus on performance of a spatial location order recognition task. Soc. Neurosci. Abstr. 18, 1422.

Chiba, A.A., Kesner, R.P., Reynolds, A.M., 1994. Memory for spatial location as a function of temporal lag in rats: role of hippocampus and medial prefrontal cortex. Behav. Neural. Biol. 61, 123–131.

Cho, Y.H., Kesner, R.P., 1995. Relational object association learning in rats with hippocampal lesions. Behav. Brain Res. 67, 91–98.

Crane, J., Milner, B., 2005. What went where? Impaired object-location learning in patients with right hippocampal lesions. Hippocampus 15, 216–231.

Day, M., Langston, R., Morris, R.G., 2003. Glutamate-receptor-mediated encoding and retrieval of paired-associate learning. Nature 424, 205–209.

de Araujo, I.E.T., Rolls, E.T., Stringer, S.M., 2001. A view model which accounts for the spatial fields of hippocampal primate spatial view cells and rat place cells. Hippocampus 11, 699–706.

Debiec, J., LeDoux, J.E., Nader, K., 2002. Cellular and systems reconsolidation in the hippocampus. Neuron 36, 527–538.

Deco, G., Rolls, E.T., 2003. Attention and working memory: a dynamical model of neuronal activity in the prefrontal cortex. Eur. J. Neurosci. 18, 2374–2390.

Deco, G., Rolls, E.T., 2004. A neurodynamical cortical model of visual attention and invariant object recognition. Vis. Res. 44, 621–644.

Deco, G., Rolls, E.T., 2005a. Attention, short-term memory, and action selection: a unifying theory. Prog. Neurobiol. 76, 236–256.

Deco, G., Rolls, E.T., 2005b. Neurodynamics of biased competition and cooperation for attention: a model with spiking neurons. J. Neurophysiol. 94, 295–313.

Deco, G., Rolls, E.T., 2005c. Sequential memory: a putative neural and synaptic dynamical mechanism. J. Cogn. Neurosci. 17, 294–307.

Deco, G., Rolls, E.T., Zihl, J., 2005. A neurodynamical model of visual attention. In: Itti, L., Rees, G., Tsotos, J. (Eds.), Neurobiology of Attention. Elsevier, San Diego, CA, (Chapter 597), pp. 593–599.

DeCoteau, W.E., Kesner, R.P., 2000. A double dissociation between the rat hippocampus and medial caudoputamen in processing two forms of knowledge. Behav. Neurosci. 114, 1096–1108.

Delatour, B., Witter, M.P., 2002. Projections from the parahippocampal region to the prefrontal cortex in the rat: evidence of multiple pathways. Eur. J. Neurosci. 15, 1400–1407.

Dudchenko, P.A., Wood, E.R., Eichenbaum, H., 2000. Neurotoxic hippocampal lesions have no effect on odor span and little effect on odor recognition memory but produce significant impairments on spatial span, recognition, and alternation. J. Neurosci. 20, 2964–2977.

Eichenbaum, H., 1997. Declarative memory: insights from cognitive neurobiology. Annu. Rev. Psychol. 48, 547–572.

Eichenbaum, H., Cohen, N.J., 2001. From Conditioning to Conscious Recollection: Memory Systems of the Brain. Oxford University Press, New York.

Eichenbaum, H., Otto, T., Cohen, N.J., 1992. The hippocampus—what does it do? Behav. Neural. Biol. 57, 2–36.

Ekstrom, A.D., Kahana, M.J., Caplan, J.B., Fields, T.A., Isham, E.A., Newman, E.L., Fried, I., 2003. Cellular networks underlying human spatial navigation. Nature 425, 184–188.

Erreger, K., Chen, P.E., Wyllie, D.J., Traynelis, S.F., 2004. Glutamate receptor gating. Crit. Rev. Neurobiol. 16, 187–224.

Estes, W.K., 1986. Memory for temporal information. In: Michon, J.A., Jackson, J.L. (Eds.), Time, Mind and Behavior. Springer-Verlag, New York, pp. 151–168.

Fazeli, M.S., Collingridge, G.L. (Eds.), 1996. Cortical Plasticity: LTP and LTD. Bios, Oxford.

Feigenbaum, J.D., Rolls, E.T., 1991. Allocentric and egocentric spatial information processing in the hippocampal formation of the behaving primate. Psychobiology 19, 21–40.

Ferbinteanu, J., Holsinger, R.M., McDonald, R.J., 1999. Lesions of the medial or lateral perforant path have different effects on hippocampal contributions to place learning and on fear conditioning to context. Behav. Brain Res. 101, 65–84.

Florian, C., Roullet, P., 2004. Hippocampal CA3-region is crucial for acquisition and memory consolidation in Morris water maze task in mice. Behav. Brain Res. 154, 365–374.

Fortin, N.J., Agster, K.L., Eichenbaum, H.B., 2002. Critical role of the hippocampus in memory for sequences of events. Nat. Neurosci. 5, 458–462.

Foster, T.C., Castro, C.A., McNaughton, B.L., 1989. Spatial selectivity of rat hippocampal neurons: dependence on preparedness for movement. Science 244, 1580–1582.

Franco, L., Rolls, E.T., Aggelopoulos, N.C., Jerez, J.M., 2006. Neuronal selectivity, population sparseness, and ergodicity in the inferior temporal visual cortex.

Fried, I., MacDonald, K.A., Wilson, C.L., 1997. Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. Neuron 18, 753–765.

Fyhn, M., Molden, S., Witter, M.P., Moser, E.I., Moser, M.B., 2004. Spatial representation in the entorhinal cortex. Science 305, 1258–1264.

Gaffan, D., 1992. The role of hippocampo–fornix–mammillary system in episodic memory. In: Squire, L.R., Butters, N. (Eds.), Neuropsychology of Memory. Guilford, New York, pp. 336–346.

Gaffan, D., 1993. Additive effects of forgetting and fornix transection in the temporal gradient of retrograde amnesia. Neuropsychology 31, 1055–1066.

Gaffan, D., 1994. Scene-specific memory for objects: a model of episodic memory impairment in monkeys with fornix transection. J. Cogn. Neurosci. 6, 305–320.

Gaffan, D., Harrison, S., 1989a. A comparison of the effects of fornix section and sulcus principalis ablation upon spatial learning by monkeys. Behav. Brain Res. 31, 207–220.

Gaffan, D., Harrison, S., 1989b. Place memory and scene memory: effects of fornix transection in the monkey. Exp. Brain Res. 74, 202–212.

Gaffan, D., Saunders, R.C., 1985. Running recognition of configural stimuli by fornix transected monkeys. Quart. J. Exp. Psychol. 37B, 61–71.

Gaffan, D., Saunders, R.C., Gaffan, E.A., Harrison, S., Shields, C., Owen, M.J., 1984. Effects of fornix transection upon associative memory in monkeys: role of the hippocampus in learned action. Q. J. Exp. Psychol. B 36, 173–221.

Gall, C.M., Hess, U.S., Lynch, G., 1998. Mapping brain networks engaged by, and changed by, learning. Neurobiol. Learn. Mem. 70, 14–36.

Gardner-Medwin, A.R., 1976. The recall of events through the learning of associations between their parts. Proc. R. Soc. Lond. B 194, 375–402.

Gaykema, R.P., van der Kuil, J., Hersh, L.B., Luiten, P.G., 1991. Patterns of direct projections from the hippocampus to the medial septum-diagonal band complex: anterograde tracing with Phaseolus vulgaris leucoagglutinin combined with immunohistochemistry of choline acetyltransferase. Neuroscience 43, 349–360.

Georges-François, P., Rolls, E.T., Robertson, R.G., 1999. Spatial view cells in the primate hippocampus: allocentric view not head direction or eye position or place. Cereb. Cortex 9, 197–212.

Gilbert, P.E., Kesner, R.P., 2002. The amygdala but not the hippocampus is involved in pattern separation based on reward value. Neurobiol. Learn. Mem. 77, 338–353.

Gilbert, P.E., Kesner, R.P., 2003. Localization of function within the dorsal hippocampus: the role of the CA3 subregion in paired-associate learning. Behav. Neurosci. 117, 1385–1394.

Gilbert, P.E., Kesner, P.E., 2006. The role of dorsal CA3 hippocampal subregion in spatial working memory and pattern separation. Beh. Brain Res. 169, 142–149.

Gilbert, P.E., Kesner, R.P., DeCoteau, W.E., 1998. Memory for spatial location: role of the hippocampus in mediating spatial pattern separation. J. Neurosci. 18, 804–810.

Gilbert, P.E., Kesner, R.P., Lee, I., 2001. Dissociating hippocampal subregions: double dissociation between dentate gyrus and CA1. Hippocampus 11, 626–636.

Gold, A.E., Kesner, R.P., 2005. The role of the CA3 subregion of the dorsal hippocampus in spatial pattern completion in the rat. Hippocampus 15, 808–814.

Goodrich-Hunsaker, N.J., Hunsaker, M.R., Kesner, R.P., 2005. Effects of hippocampus sub-regional lesions for metric and topological spatial information processing. Soc. Neurosci. Abstr., in press

Grusser, O.-J., Landis, T., 1991. Visual Agnosias. Macmillan, London.

Gulyas, A.I., Miles, R., Hajos, N., Freund, T.F., 1993. Precision and variability in postsynaptic target selection of inhibitory cells in the hippocampal CA3 region. Eur. J. Neurosci. 5, 1729–1751.

Hafting, T., Fyhn, M., Molden, S., Moser, M.B., Moser, E.I., 2005. Microstructure of a spatial map in the entorhinal cortex. Nature 436, 801–806.

Hall, J., Thomas, K.L., Everitt, B.J., 2000. Rapid and selective induction of BDNF expression in the hippocampus during contextual learning. Nat. Neurosci. 3, 533–535.

Hall, J., Thomas, K.L., Everitt, B.J., 2001. Cellular imaging of zif268 expression in the hippocampus and amygdala during contextual and cued fear memory retrieval: selective activation of hippocampal CA1 neurons during the recall of contextual memories. J. Neurosci. 21, 2186–2193.

Hampson, R.E., Hedberg, T., Deadwyler, S.A., 2000. Differential information processing by hippocampal and subicular neurons. Ann. N Y Acad. Sci. 911, 151–165.

Handelmann, G.E., Olton, D.S., 1981. Spatial memory following damage to hippocampal CA3 pyramidal cells with kainic acid: impairment and recovery with preoperative training. Brain Res. 217, 41–58.

Hannesson, D.K., Howland, G.J., Phillips, A.G., 2004. Interaction between perirhinal and medial prefrontal cortex is required for temporal order but not recognition memory for objects in rats. J. Neurosci. 24, 4596–4604.

Hargreaves, E.L., Rao, G., Lee, I., Knierim, J.J., 2005. Major dissociation between medial and lateral entorhinal input to dorsal hippocampus. Science 308, 1792–1794.

Hasselmo, M.E., Eichenbaum, H.B., 2005. Hippocampal mechanisms for the context-dependent retrieval of episodes. Neurl. Netwk. 18, 1172–1190.

Hasselmo, M.E., Schnell, E., Barkai, E., 1995. Dynamics of learning and recall at excitatory recurrent synapses and cholinergic modulation in rat hippocampal region CA3. J. Neurosci. 15, 5249–5262.

Hasselmo, M.E., Wyble, B.P., 1997. Free recall and recognition in a network model of the hippocampus: simulating effects of scopolamine on human memory function. Behav. Brain Res. 89, 1–34.

Hertz, J., Krogh, A., Palmer, R.G., 1991. An Introduction to the Theory of Neural Computation. Addison-Wesley, Wokingham.

Hess, U.S., Lynch, G., Gall, C.M., 1995a. Changes in c-fos mRNA expression in rat brain during odor discrimination learning: differential involvement of hippocampal subfields CA1 and CA3. J. Neurosci. 15, 4786–4795.

Hess, U.S., Lynch, G., Gall, C.M., 1995b. Regional patterns of c-fos mRNA expression in rat hippocampus following exploration of a novel environment versus performance of a well-learned discrimination. J. Neurosci. 15, 7796–7809.

Hoge, J., Kesner, R.P., 2006. Role of CA3 and CA1 subregions of the dorsal hippocampus on temporal processing of objects, in preparation.

Hölscher, C., Jacob, W., Mallot, H.A., 2003a. Reward modulates neuronal activity in the hippocampus of the rat. Behav. Brain Res. 142, 181–191.

Hölscher, C., Rolls, E.T., 2002. Perirhinal cortex neuronal activity is actively related to working memory in the macaque. Neural Plasticity 9, 41–51.

Hölscher, C., Rolls, E.T., Xiang, J.-Z., 2003b. Perirhinal cortex neuronal activity related to long-term familiarity memory in the macaque. Eur. J. Neurosci. 18, 2037–2046.

Hopfield, J.J., 1982. Neural networks and physical systems with emergent collective computational abilities. Proc. Natl. Acad. Sci. U.S.A. 79, 2554–2558.

Huerta, P.T., Sun, L.D., Wilson, M.A., Tonegawa, S., 2000. Formation of temporal memory requires NMDA receptors within CA1 pyramidal neurons. Neuron 25, 473–480.

Ishizuka, N., Weber, J., Amaral, D.G., 1990. Organization of intrahippocampal projections originating from CA3 pyramidal cells in the rat. J. Comp. Neurol. 295, 580–623.

Jakab, R.L., Leranth, C., 1995. Septum. In: Paxinos, G. (Ed.), The Rat Nervous System. Academic Press, San Diego.

Jarrard, E.L., 1993. On the role of the hippocampus in learning and memory in the rat. Behav. Neural Biol. 60, 9–26.

Jarrard, L.E., Davidson, T.L., 1990. Acquisition of concurrent conditional discriminations in rats with ibotenate lesions of hippocampus and subiculum. Psychobiology 18, 68–73.

Jay, T.M., Witter, M.P., 1991. Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of *Phaseolus vulgaris*-leucoagglutinin. J. Comp. Neurol. 313, 574–586.

Jeffery, K.J., Anderson, M.I., Hayman, R., Chakraborty, S., 2004. A proposed architecture for the neural representation of spatial context. Neurosci. Biobehav. Rev. 28, 201–218.

Jeffery, K.J., Hayman, R., 2004. Plasticity of the hippocampal place cell representation. Rev. Neurosci. 15, 309–331.

Jensen, O., Idiart, M.A., Lisman, J.E., 1996. Physiologically realistic formation of autoassociative memory in networks with theta/gamma oscillations: role of fast NMDA channels. Learn. Mem. 3, 243–256.

Jensen, O., Lisman, J.E., 1996. Theta/gamma networks with slow NMDA channels learn sequences and encode episodic memory: role of NMDA channels in recall. Learn. Mem. 3, 264–278.

Jensen, O., Lisman, J.E., 2005. Hippocampal sequence-encoding driven by a cortical multi-item working memory buffer. Trends Neurosci. 28, 67–72.

Jerman, T., Kesner, R.P., 2005. Disconnection analysis of CA3 and DG in mediating encoding but not retrieval in a spatial maze learning task. Soc. Neurosci. Abstr., in press.

Ji, J.Z., Wang, X.M., Li, B.M., 2003. Deficit in long-term contextual fear memory induced by blockade of beta-adrenoceptors in hippocampal CA1 region. Eur. J. Neurosci. 17, 1947–1952.

Jung, M.W., McNaughton, B.L., 1993. Spatial selectivity of unit activity in the hippocampal granular layer. Hippocampus 3, 165–182.

Kesner, R.P., 1998. Neural mediation of memory for time: role of hippocampus and medial prefrontal cortex. Psychol. Bull. Rev. 5, 585–596.

Kesner, R.P., 2006. Ventral but not dorsal CA1 disrupts temporal pattern separation of odors, in preparation.

Kesner, R.P., Gilbert, P.E., 2006. The role of the medial caudate nucleus, but not the hippocampus, in a delayed-matching-to sample task for motor response. Eur. J. Neurosci. 23, 1888–1894.

Kesner, R.P., Gilbert, P.E., Barua, L.A., 2002. The role of the hippocampus in memory for the temporal order of a sequence of odors. Behav. Neurosci. 116, 286–290.

Kesner, R.P., Hunsaker, M.R., Gilbert, P.E., 2005. The role of CA1 in the acquisition of an object-trace-odor paired associate task. Behav. Neurosci. 119, 781–786.

Kesner, R.P., Lee, I., Gilbert, P., 2004. A behavioral assessment of hippocampal function based on a subregional analysis. Rev. Neurosci. 15, 333–351.

Kesner, R.P., Rolls, E.T., 2001. Role of long term synaptic modification in short term memory. Hippocampus 11, 240–250.

Kirkwood, A., Dudek, S.M., Gold, J.T., Aizenman, C.D., Bear, M.F., 1993. Common forms of synaptic plasticity in the hippocampus and neocortex in vitro. Science 260, 1518–1521.

Kleinfeld, D., 1986. Sequential state generation by model neural networks. Proc. Natl. Acad. Sci. U.S.A. 83, 9469–9473.

Kohonen, T., 1977. Associative Memory: A System Theoretical Approach. Springer, New York.

Kohonen, T., Oja, E., Lehtio, P., 1981. Storage and processing of information in distributed memory systems. In: Hinton, G.E., Anderson, J.A. (Eds.), Parallel Models of Associative Memory. Lawrence Erlbaum, Hillsdale, pp. 129–167.

Kolb, B., Whishaw, I.Q., 2003. Fundamentals of Human Neuropsychology. Worth, New York.

Kreiman, G., Koch, C., Fried, I., 2000. Category-specific visual responses of single neurons in the human medial temporal lobe. Nat. Neurosci. 3, 946–953.

Lassalle, J.M., Bataille, T., Halley, H., 2000. Reversible inactivation of the hippocampal mossy fiber synapses in mice impairs spatial learning, but neither consolidation nor memory retrieval, in the Morris navigation task. Neurobiol. Learn. Mem. 73, 243–257.

Lavenex, P., Amaral, D.G., 2000. Hippocampal–neocortical interaction: a hierarchy of associativity. Hippocampus 10, 420–430.

Lavenex, P., Suzuki, W.A., Amaral, D.G., 2004. Perirhinal and parahippocampal cortices of the macaque monkey: Intrinsic projections and interconnections. J. Comp. Neurol. 472, 371–394.

Lee, I., Jerman, T.S., Kesner, R.P., 2005. Disruption of delayed memory for a sequence of spatial locations following CA1- or CA3-lesions of the dorsal hippocampus. Neurobiol. Learn. Mem. 84, 138–147.

Lee, I., Kesner, R.P., 2002. Differential contribution of NMDA receptors in hippocampal subregions to spatial working memory. Nat. Neurosci. 5, 162–168.

Lee, I., Kesner, R.P., 2003a. Differential roles of dorsal hippocampal subregions in spatial working memory with short versus intermediate delay. Behav. Neurosci. 117, 1044–1053.

Lee, I., Kesner, R.P., 2003b. Time-dependent relationship between the dorsal hippocampus and the prefrontal cortex in spatial memory. J. Neurosci. 23, 1517–1523.

Lee, I., Kesner, R.P., 2004a. Differential contributions of dorsal hippocampal subregions to memory acquisition and retrieval in contextual fear-conditioning. Hippocampus 14, 301–310.

Lee, I., Kesner, R.P., 2004b. Encoding versus retrieval of spatial memory: double dissociation between the dentate gyrus and the perforant path inputs into CA3 in the dorsal hippocampus. Hippocampus 14, 66–76.

Lee, I., Kesner, R.P., 2006. Perforant path to CA3 lesions disrupt object–place paired associate learning, in preparation.

Lee, I., Rao, G., Knierim, J.J., 2004a. A double dissociation between hippocampal subfields: differential time course of CA3 and CA1 place cells for processing changed environments. Neuron 42, 803–815.

Lee, I., Yoganarasimha, D., Rao, G., Knierim, J.J., 2004b. Comparison of population coherence of place cells in hippocampal subfields CA1 and CA3. Nature 430, 456–459.

Lester, R.A., Clements, J.D., Westbrook, G.L., Jahr, C.E., 1990. Channel kinetics determine the time course of NMDA receptor-mediated synaptic currents. Nature 346, 565–567.

Lester, R.A., Jahr, C.E., 1992. NMDA channel behavior depends on agonist affinity. J. Neurosci. 12, 635–643.

Leutgeb, S., Leutgeb, J.K., Treves, A., Moser, M.B., Moser, E.I., 2004. Distinct ensemble codes in hippocampal areas CA3 and CA1. Science 305, 1295–1298.

Levy, W.B., 1989. A computational approach to hippocampal function. In: Hawkins, R.D., Bower, G.H. (Eds.), Computational Models of Learning in Simple Neural Systems. Academic Press, San Diego, pp. 243–305.

Levy, W.B., 1996. A sequence predicting CA3 is a flexible associator that learns and uses context to solve hippocampal-like tasks. Hippocampus 6, 579–590.

Levy, W.B., Colbert, C.M., Desmond, N.L., 1990. Elemental adaptive processes of neurons and synapses: a statistical/computational perspective. In: Gluck, M.A., Rumelhart, D.E. (Eds.), Neuroscience and Connectionist Theory. Erlbaum, Hillsdale, NJ, pp. 187–235.

Levy, W.B., Desmond, N.L., 1985. The rules of elemental synaptic plasticity. In: Levy, W.B., Anderson, J.A., Lehmkuhle, S. (Eds.), Synaptic Modification, Neuron Selectivity, and Nervous System Organization. Erlbaum, Hillsdale, NJ, pp. 105–121.

Levy, W.B., Wu, X., Baxter, R.A., 1995. Unification of hippocampal function via computational/encoding considerations. Int. J. Neural. Syst. 6, 71–80.

Li, H., Matsumoto, K., Watanabe, H., 1999. Different effects of unilateral and bilateral hippocampal lesions in rats on the performance of radial maze and odor-paired associate tasks. Brain Res. Bull. 48, 113–119.

Lisman, J.E., 1999. Relating hippocampal circuitry to function: recall of memory sequences by reciprocal dentate-CA3 interactions. Neuron 22, 233–242.

Lisman, J.E., Idiart, M.A., 1995. Storage of 7 ± 2 short-term memories in oscillatory subcycles. Science 267, 1512–1515.

Lisman, J.E., Talamini, L.M., Raffone, A., 2005. Recall of memory sequences by interaction of the dentate and CA3: a revised model of the phase precession. Neurl. Netwk. 18, 1191–1201.

Lynch, M.A., 2004. Long-term potentiation and memory. Physiol. Rev. 84, 87–136.

Maaswinkel, H., Jarrard, L.E., Whishaw, I.Q., 1999. Hippocampectomized rats are impaired in homing by path integration. Hippocampus 9, 553–561.

Madsen, J., Kesner, R.P., 1995. The temporal-distance effect in subjects with dementia of the Alzheimer type. Alzheimer Dis. Assoc. Disord. 9, 94–100.

Malkova, L., Bachevalier, J., Mishkin, M., Saunders, R.C., 2001. Neurotoxic lesions of perirhinal cortex impair visual recognition memory in rhesus monkeys. Neuroreport 12, 1913–1917.

Malkova, L., Mishkin, M., 2003. One-trial memory for object–place associations after separate lesions of hippocampus and posterior parahippocampal region in the monkey. J. Neurosci. 23, 1956–1965.

Markram, H., Pikus, D., Gupta, A., Tsodyks, M.V., 1998. Information processing with frequency-dependent synaptic connections. Neuropharmacology 37, 489–500.

Markus, E.J., Qin, Y.L., Leonard, B., Skaggs, W., McNaughton, B.L., Barnes, C.A., 1995. Interactions between location and task affect the spatial and directional firing of hippocampal neurons. J. Neurosci. 15, 7079–7094.

Marr, D., 1971. Simple memory: a theory for archicortex. Phil. Trans. R. Soc., London B 262, 23–81.

Marshuetz, C., 2005. Order information in working memory: an integrative review of evidence from brain and behavior. Psychol. Bull. 131, 323–339.

Martin, S.J., Grimwood, P.D., Morris, R.G., 2000. Synaptic plasticity and memory: an evaluation of the hypothesis. Annu. Rev. Neurosci. 23, 649–711.

Martinez, C.O., Do, V.H., Martinez Jr., J.L., Derrick, B.E., 2002. Associative long-term potentiation (LTP) among extrinsic afferents of the hippocampal CA3 region in vivo. Brain Res. 940, 86–94.

Matsumura, N., Nishijo, H., Tamura, R., Eifuku, S., Endo, S., Ono, T., 1999. Spatial- and task-dependent neuronal responses during real and virtual translocation in the monkey hippocampal formation. J. Neurosci. 19, 2318–2393.

McClelland, J.L., McNaughton, B.L., O'Reilly, R.C., 1995. Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. Psych. Rev. 102, 419–457.

McEchron, M.D., Tseng, W., Disterhoft, J.F., 2003. Single neurons in CA1 hippocampus encode trace interval duration during trace heart rate (fear) conditioning in rabbit. J. Neurosci. 23, 1535–1547.

McGaugh, J.L., 2000. Memory—a century of consolidation. Science 287, 248–251.

McNaughton, B.L., 1991. Associative pattern completion in hippocampal circuits: new evidence and new questions. Brain Res. Rev. 16, 193–220.

McNaughton, B.L., Barnes, C.A., O'Keefe, J., 1983. The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. Exp. Brain Res. 52, 41–49.

McNaughton, B.L., Chen, L.L., Markus, E.J., 1991. Dead reckoning, landmark learning, and the sense of direction: a neurophysiological and computational hypothesis. J. Cogn. Neurosci. 3, 190–202.

McNaughton, B.L., Morris, R.G.M., 1987. Hippocampal synaptic enhancement and information storage within a distributed memory system. Trends Neurosci. 10, 408–415.

McNaughton, B.L., Nadel, L., 1990. Hebb–Marr networks and the neurobiological representation of action in space. In: Gluck, M.A., Rumelhart, D.E. (Eds.), Neuroscience and Connectionist Theory. Erlbaum, Hillsdale, NJ.

Miller, E.K., Li, L., Desimone, R., 1998. Activity of neurons in anterior inferior temporal cortex during a short-term memory task. J. Neurosci. 13, 1460–1478.

Minai, A.A., Levy, W.B., 1993. Sequence learning in a single trial. Int. Neural Netw. Soc. World Congr. Neural Netw. 2, 505–508.

Miyashita, Y., Kameyama, M., Hasegawa, I., Fukushima, T., 1998. Consolidation of visual associative long-term memory in the temporal cortex of primates. Neurobiol. Learn. Mem. 1, 197–211.

Miyashita, Y., Okuno, H., Tokuyama, W., Ihara, T., Nakajima, K., 1996. Feedback signal from medial temporal lobe mediates visual associative mnemonic codes of inferotemporal neurons. Cogn. Brain Res. 5, 81–86.

Miyashita, Y., Rolls, E.T., Cahusac, P.M., Niki, H., Feigenbaum, J.D., 1989. Activity of hippocampal formation neurons in the monkey related to a conditional spatial response task. J. Neurophysiol. 61, 669–678.

Mizumori, S.J., Perez, G.M., Alvarado, M.C., Barnes, C.A., McNaughton, B.L., 1990. Reversible inactivation of the medial septum differentially affects two forms of learning in rats. Brain Res. 528, 12–20.

Mizumori, S.J., Ragozzino, K.E., Cooper, B.G., Leutgeb, S., 1999. Hippocampal representational organization and spatial context. Hippocampus 9, 444–451.

Monaghan, D.T., Cotman, C.W., 1985. Distribution of *N*-methyl-D-aspartate-sensitive L-[3H]glutamate-binding sites in the rat brain. J. Neurosci. 5, 2909–2919.

Moore, D.B., Lee, P., Paiva, M., Walker, D.W., Heaton, M.B., 1998. Effects of neonatal ethanol exposure on cholinergic neurons of the rat medial septum. Alcohol 15, 219–226.

Morris, R.G., 2003. Long-term potentiation and memory. Philos. Trans. R. Soc., London B. Biol. Sci. 358, 643–647.

Morris, R.G., Moser, E.I., Riedel, G., Martin, S.J., Sandin, J., Day, M., O'Carroll, C., 2003. Elements of a neurobiological theory of the hippocampus: the role of activity-dependent synaptic plasticity in memory. Philos. Trans. R. Soc., London B. Biol. Sci. 358, 773–786.

Morris, R.G.M., 1989. Does synaptic plasticity play a role in information storage in the vertebrate brain? In: Morris, R.G.M. (Ed.), Parallel Distributed Processing: Implications for Psychology and Neurobiology. Oxford University Press, Oxford, pp. 248–285.

Moscovitch, M., Rosenbaum, R.S., Gilboa, A., Addis, D.R., Westmacott, R., Grady, C., McAndrews, M.P., Levine, B., Black, S., Winocur, G., Nadel, L., 2005. Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. J. Anat. 207, 35–66.

Moser, E.I., 2004. Hippocampal place cells demand attention. Neuron 42, 183–185.

Moser, M.B., Moser, E.I., 1998. Functional differentiation in the hippocampus. Hippocampus 8, 608–619.

Moyer Jr., J.R., Deyo, R.A., Disterhoft, J.F., 1990. Hippocampectomy disrupts trace eye-blink conditioning in rabbits. Behav. Neurosci. 104, 243–252.

Muller, R.U., Kubie, J.L., Bostock, E.M., Taube, J.S., Quirk, G.J., 1991. Spatial firing correlates of neurons in the hippocampal formation of freely moving rats. In: Paillard, J. (Ed.), Brain and Space. Oxford University Press, Oxford, pp. 296–333.

Muller, R.U., Ranck Jr., J.B., Taube, J.S., 1996. Head direction cells: properties and functional significance. Curr. Opin. Neurobiol. 6, 196–206.

Murray, E.A., Baxter, M.G., Gaffan, D., 1998. Monkeys with rhinal cortex damage or neurotoxic hippocampal lesions are impaired on spatial scene learning and object reversals. Behav. Neurosci. 112, 1291–1303.

Murray, E.A., Gaffan, D., Mishkin, M., 1993. Neural substrates of visual stimulus–stimulus association in rhesus monkeys. J. Neurosci. 13, 4549–4561.

Naber, P.A., Lopes da Silva, F.H., Witter, M.P., 2001. Reciprocal connections between the entorhinal cortex and hippocampal fields CA1 and the subiculum are in register with the projections from CA1 to the subiculum. Hippocampus 11, 99–104.

Nakazawa, K., Quirk, M.C., Chitwood, R.A., Watanabe, M., Yeckel, M.F., Sun, L.D., Kato, A., Carr, C.A., Johnston, D., Wilson, M.A., Tonegawa, S., 2002. Requirement for hippocampal CA3 NMDA receptors in associative memory recall. Science 297, 211–218.

Nakazawa, K., Sun, L.D., Quirk, M.C., Rondi-Reig, L., Wilson, M.A., Tonegawa, S., 2003. Hippocampal CA3 NMDA receptors are crucial for memory acquisition of one-time experience. Neuron 38, 305–315.

Nanry, K.P., Mundy, W.R., Tilson, H.A., 1989. Colchicine-induced alterations of reference memory in rats: role of spatial versus non-spatial task components. Behav. Brain Res. 35, 45–53.

Oja, E., 1982. A simplified neuron model as a principal component analyser. J. Math. Biol. 15, 267–273.

O'Kane, D., Treves, A., 1992. Why the simplest notion of neocortex as an autoassociative memory would not work. Network 3, 379–384.

O'Keefe, J., 1984. Spatial memory within and without the hippocampal system. In: Seifert, W. (Ed.), Neurobiology of the Hippocampus. Academic Press, London, pp. 375–403.

O'Keefe, J., 1990. A computational theory of the hippocampal cognitive map. Prog. Brain Res. 83, 301–312.

O'Keefe, J., Dostrovsky, J., 1971. The hippocampus as a spatial map: preliminary evidence from unit activity in the freely moving rat. Brain Res. 34, 171–175.

O'Keefe, J., Nadel, L., 1978. The Hippocampus as a Cognitive Map. Clarendon Press, Oxford.

Ono, T., Nakamura, K., Nishijo, H., Eifuku, S., 1993. Monkey hippocampal neurons related to spatial and nonspatial functions. J. Neurophysiol. 70, 1516–1529.

O'Reilly, R.C., Rudy, J.W., 2001. Conjunctive representations in learning and memory: principles of cortical and hippocampal function. Psychol. Rev. 108, 311–345.

Otmakhova, N.A., Lisman, J.E., 1998. D1/D5 dopamine receptors inhibit depotentiation at CA1 synapses via cAMP-dependent mechanism. J. Neurosci. 18, 1270–1279.

Otmakhova, N.A., Lisman, J.E., 1999. Dopamine selectively inhibits the direct cortical pathway to the CA1 hippocampal region. J. Neurosci. 19, 1437–1445.

Otto, T., Eichenbaum, H., 1992. Complementary roles of the orbital prefrontal cortex and the perirhinal-entorhinal cortices in an odor-guided delayed-nonmatching-to-sample task. Behav. Neurosci. 106, 762–775.

Panzeri, S., Rolls, E.T., Battaglia, F., Lavis, R., 2001. Speed of information retrieval in multilayer networks of integrate-and-fire neurons. Network: Comput. Neural Syst. 12, 423–440.

Parkinson, J.K., Murray, E.A., Mishkin, M., 1988. A selective mnemonic role for the hippocampus in monkeys: memory for the location of objects. J. Neurosci. 8, 4059–4167.

Petrides, M., 1985. Deficits on conditional associative-learning tasks after frontal- and temporal-lobe lesions in man. Neuropsychology 23, 601–614.

Pitkanen, A., Kelly, J.L., Amaral, D.G., 2002. Projections from the lateral, basal, and accessory basal nuclei of the amygdala to the entorhinal cortex in the macaque monkey. Hippocampus 12, 186–205.

Poucet, B., 1989. Object exploration, habituation, and response to a spatial change in rats following septal or medial frontal cortical damage. Behav. Neurosci. 103, 1009–1016.

Ranck, J.B.J., 1985. Head direction cells in the deep cell layer of dorsolateral presubiculum in freely moving rats. In: Buzsaki, G., Vanderwolf, C.H. (Eds.), Electrical Activity of the Archicortex. Akademiai Kiado, Budapest.

Rawlins, J.N.P., 1985. Associations across time: the hippocampus as a temporary memory store. Behav. Brain Sci. 8, 479–496.

Remondes, M., Schuman, E.M., 2004. Role for a cortical input to hippocampal area CA1 in the consolidation of a long-term memory. Nature 431, 699–703.

Renart, A., Moreno, R., de la Rocha, J., Parga, N., Rolls, E.T., 2001. A model of the IT-PF network in object working memory which includes balanced persistent activity and tuned inhibition. Neurocomputing 38–40, 1525–1531.

Risold, P.Y., Swanson, L.W., 1997. Connections of the rat lateral septal complex. Brain Res. Brain Res. Rev. 24, 115–195.

Robertson, R.G., Rolls, E.T., Georges-François, P., 1998. Spatial view cells in the primate hippocampus: Effects of removal of view details. J. Neurophysiol. 79, 1145–1156.

Robertson, R.G., Rolls, E.T., Georges-François, P., Panzeri, S., 1999. Head direction cells in the primate pre-subiculum. Hippocampus 9, 206–219.

Rogers, J.L., Hunsaker, M.R., Kesner, R.P., in press. Effects of ventral and dorsal CA1 subregional lesions on trace fear conditioning. Neurobiol. Learn. Mem.

Rogers, J.L., Kesner, R.P., 2003. Cholinergic modulation of the hippocampus during encoding and retrieval. Neurobiol. Learn. Mem. 80, 332–342.

Rogers, J.L., Kesner, R.P., 2004. Cholinergic modulation of the hippocampus during encoding and retrieval of tone/shock-induced fear conditioning. Learn. Mem. 11, 102–107.

Rolls, E.T., 1987. Information representation, processing and storage in the brain: analysis at the single neuron level. In: Changeux, J.-P., Konishi, M. (Eds.), The Neural and Molecular Bases of Learning. Wiley, Chichester, pp. 503–540.

Rolls, E.T., 1989a. Functions of neuronal networks in the hippocampus and cerebral cortex in memory. In: Cotterill, R.M.J. (Ed.), Models of Brain Function. Cambridge University Press, Cambridge, pp. 15–33.

Rolls, E.T., 1989b. Functions of neuronal networks in the hippocampus and neocortex in memory. In: Byrne, J.H., Berry, W.O. (Eds.), Neural Models of Plasticity: Experimental and Theoretical Approaches. Academic Press, San Diego, pp. 240–265.

Rolls, E.T., 1989c. Parallel distributed processing in the brain: Implications of the functional architecture of neuronal networks in the hippocampus. In: Morris, R.G.M. (Ed.), Parallel Distributed Processing: Implications for Psychology and Neurobiology. Oxford University Press, Oxford, pp. 286–308.

Rolls, E.T., 1989d. The representation and storage of information in neuronal networks in the primate cerebral cortex and hippocampus. In: Durbin, R., Miall, C., Mitchison, G. (Eds.), The Computing Neuron. Addison-Wesley, Wokingham, England, pp. 125–159.

Rolls, E.T., 1990a. Functions of the primate hippocampus in spatial processing and memory. In: Olton, D.S., Kesner, R.P. (Eds.), Neurobiology of Comparative Cognition. L. Erlbaum, Hillsdale, NJ, pp. 339–362.

Rolls, E.T., 1990b. Theoretical and neurophysiological analysis of the functions of the primate hippocampus in memory. Cold Spring Harbor Symposia in Quant. Biol. 55, 995–1006.

Rolls, E.T., 1991. Functions of the primate hippocampus in spatial and non-spatial memory. Hippocampus 1, 258–261.

Rolls, E.T., 1992. Neurophysiological mechanisms underlying face processing within and beyond the temporal cortical visual areas. Phil. Trans. R. Soc., London B 335, 11–21.

Rolls, E.T., 1994. Neurophysiological and neuronal network analysis of how the primate hippocampus functions in memory. In: Delacour, J. (Ed.), The Memory System of the Brain. World Scientific, London, pp. 713–744.

Rolls, E.T., 1995. A model of the operation of the hippocampus and entorhinal cortex in memory. Int. J. Neural Syst. 6, 51–70.

Rolls, E.T., 1996a. Roles of long term potentiation and long term depression in neuronal network operations in the brain. In: Fazeli, M.S., Collingridge, G.L. (Eds.), Cortical Plasticity. Bios, Oxford, pp. 223–250.

Rolls, E.T., 1996b. A theory of hippocampal function in memory. Hippocampus 6, 601–620.

Rolls, E.T., 1999. Spatial view cells and the representation of place in the primate hippocampus. Hippocampus 9, 467–480.

Rolls, E.T., 2000a. Functions of the primate temporal lobe cortical visual areas in invariant visual object and face recognition. Neuron 27, 205–218.

Rolls, E.T., 2000b. Memory systems in the brain. Annu. Rev. Psychol. 51, 599–630.

Rolls, E.T., 2003. Consciousness absent and present: a neurophysiological exploration. Progr. Brain Res. 144, 95–106.

Rolls, E.T., 2004. The functions of the orbitofrontal cortex. Brain Cogn. 55, 11–29.

Rolls, E.T., 2005. Emotion Explained. Oxford University Press, Oxford.

Rolls, E.T., Deco, G., 2002. Computational Neuroscience of Vision. Oxford University Press, Oxford.

Rolls, E.T., Franco, L., Stringer, S.M., 2005a. The perirhinal cortex and long-term familiarity memory. Quart. J. Exp. Psychol. B 58, 234–245.

Rolls, E.T., Miyashita, Y., Cahusac, P.M.B., Kesner, R.P., Niki, H., Feigenbaum, J., Bach, L., 1989. Hippocampal neurons in the monkey with activity related to the place in which a stimulus is shown. J. Neurosci. 9, 1835–1845.

Rolls, E.T., O'Mara, S., 1993. Neurophysiological and theoretical analysis of how the primate hippocampus functions in memory. In: Ono, T., Squire, L.R., Raichle, M.E., Perrett, D.I., Fukuda, M. (Eds.), Brain Mechanisms of Perception and Memory: from Neuron to Behavior. Oxford University Press, New York, pp. 276–300.

Rolls, E.T., O'Mara, S.M., 1995. View-responsive neurons in the primate hippocampal complex. Hippocampus 5, 409–424.

Rolls, E.T., Robertson, R.G., Georges-François, P., 1997a. Spatial view cells in the primate hippocampus. Eur. J. Neurosci. 9, 1789–1794.

Rolls, E.T., Stringer, S.M., 2005. Spatial view cells in the hippocampus, and their idiothetic update based on place and head direction. Neural Netw. 18, 1229–1241.

Rolls, E.T., Stringer, S.M., Elliot, T., 2006. Entorhinal cortex grid cells can map to hippocampal place cells by competitive learning.

Rolls, E.T., Stringer, S.M., Trappenberg, T.P., 2002. A unified model of spatial and episodic memory. Proc. R. Soc., London B 269, 1087–1093.

Rolls, E.T., Treves, A., 1990. The relative advantages of sparse versus distributed encoding for associative neuronal networks in the brain. Network 1, 407–421.

Rolls, E.T., Treves, A., 1998. Neural Networks and Brain Function. Oxford University Press, Oxford.

Rolls, E.T., Treves, A., Foster, D., Perez-Vicente, C., 1997b. Simulation studies of the CA3 hippocampal subfield modelled as an attractor neural network. Neural Netw. 10, 1559–1569.

Rolls, E.T., Treves, A., Robertson, R.G., Georges-François, P., Panzeri, S., 1998. Information about spatial view in an ensemble of primate hippocampal cells. J. Neurophysiol. 79, 1797–1813.

Rolls, E.T., Xiang, J.-Z., 2005. Reward-spatial view representations and learning in the hippocampus. J. Neurosci. 25, 6167–6174.

Rolls, E.T., Xiang, J.-Z., 2006. Spatial view cells in the primate hippocampus, and memory recall. Reviews in the Neurosciences 17, 175–200.

Rolls, E.T., Xiang, J.-Z., Franco, L., 2005b. Object, space and object–space representations in the primate hippocampus. J. Neurophysiol. 94, 833–844.

Rupniak, N.M.J., Gaffan, D., 1987. Monkey hippocampus and learning about spatially directed movements. J. Neurosci. 7, 2331–2337.

Samsonovich, A., McNaughton, B.L., 1997. Path integration and cognitive mapping in a continuous attractor neural network model. J. Neurosci. 17, 5900–5920.

Saper, C.B., Swanson, L.W., Cowan, W.M., 1979. An autoradiographic study of the efferent connections of the lateral hypothalamic area in the rat. J. Comp. Neurol. 183, 689–706.

Save, E., Guazzelli, A., Poucet, B., 2001. Dissociation of the effects of bilateral lesions of the dorsal hippocampus and parietal cortex on path integration in the rat. Behav. Neurosci. 115, 1212–1223.

Schultz, S., Rolls, E.T., 1999. Analysis of information transmission in the Schaffer collaterals. Hippocampus 9, 582–598.

Sharp, P.E. (Ed.), 2002. The Neural Basis of Navigation: Evidence From Single Cell Recording. Kluwer, Boston.

Simmen, M.W., Rolls, E.T., Treves, A., 1996a. On the dynamics of a network of spiking neurons. In: Eekman, F.H., Bower, J.M. (Eds.), Computations and Neuronal Systems: Proceedings of CNS95. Kluwer, Boston.

Simmen, M.W., Treves, A., Rolls, E.T., 1996b. Pattern retrieval in threshold-linear associative nets. Network 7, 109–122.

Skaggs, W.E., Knierim, J.J., Kudrimoti, H.S., McNaughton, B.L., 1995. A model of the neural basis of the rat's sense of direction. In: Tesauro, G., Touretzky, D.S., Leen, T.K. (Eds.), Advances in Neural Information Processing Systems, vol. 7. MIT Press, Cambridge, MA, pp. 173–180.

Smith, M.L., Milner, B., 1981. The role of the right hippocampus in the recall of spatial location. Neuropsychology 19, 781–793.

Sompolinsky, H., Kanter, I.I., 1986. Temporal association in asymmetric neural networks. Phys. Rev. Lett. 57, 2861–2864.

Squire, L.R., 1992. Memory and the hippocampus: a synthesis from findings with rats, monkeys and humans. Psych. Rev. 99, 195–231.

Stefanacci, L., Suzuki, W.A., Amaral, D.G., 1996. Organization of connections between the amygdaloid complex and the perirhinal and parahippocampal cortices in macaque monkeys. J. Comp. Neurol. 375, 552–582.

Storm-Mathiesen, J., Zimmer, J., Ottersen, O.P. (Eds.), 1990. Understanding the Brain through the Hippocampus, vol. 83. Elsevier, Oxford.

Strekalova, T., Zorner, B., Zacher, C., Sadovska, G., Herdegen, T., Gass, P., 2003. Memory retrieval after contextual fear conditioning induces c-Fos and JunB expression in CA1 hippocampus. Genes Brain Behav. 2, 3–10.

Stringer, S.M., Rolls, E.T., 2002. Invariant object recognition in the visual system with novel views of 3D objects. Neural Comput. 14, 2585–2596.

Stringer, S.M., Rolls, E.T., Trappenberg, T.P., 2004. Self-organising continuous attractor networks with multiple activity packets, and the representation of space. Neural Netw. 17, 5–27.

Stringer, S.M., Rolls, E.T., Trappenberg, T.P., 2005. Self-organizing continuous attractor network models of hippocampal spatial view cells. Neurobiol. Learn. Mem. 83, 79–92.

Stringer, S.M., Rolls, E.T., Trappenberg, T.P., Araujo, I.E.T., 2002a. Self-organizing continuous attractor networks and path integration. Two-dimensional models of place cells. Network: Comput. Neural Syst. 13, 429–446.

Stringer, S.M., Trappenberg, T.P., Rolls, E.T., Araujo, I.E.T., 2002b. Self-organizing continuous attractor networks and path integration: one-dimensional models of head direction cells. Network: Comput. Neural Syst. 13, 217–242.

Sutherland, R.J., Rudy, J.W., 1991. Exceptions to the rule of space. Hippocampus 1, 250–252.

Sutherland, R.J., Whishaw, I.Q., Kolb, B., 1983. A behavioural analysis of spatial localization following electrolytic, kainate- or colchicine-induced damage to the hippocampal formation in the rat. Behav. Brain Res. 7, 133–153.

Suzuki, W.A., Amaral, D.G., 1994a. Perirhinal and parahippocampal cortices of the macaque monkey—cortical afferents. J. Comp. Neurol. 350, 497–533.

Suzuki, W.A., Amaral, D.G., 1994b. Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. J. Neurosci. 14, 1856–1877.

Swanson, L.W., Cowan, W.M., 1977. An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. J. Comp. Neurol. 172, 49–84.

Tabuchi, E., Mulder, A.B., Wiener, S.I., 2003. Reward value invariant place responses and reward site associated activity in hippocampal neurons of behaving rats. Hippocampus 13, 117–132.

Tanila, H., 1999. Hippocampal place cells can develop distinct representations of two visually identical environments. Hippocampus 9, 235–246.

Taube, J.S., Goodridge, J.P., Golob, E.J., Dudchenko, P.A., Stackman, R.W., 1996. Processing the head direction signal: a review and commentary. Brain Res. Bull. 40, 477–486.

Taube, J.S., Muller, R.U., Ranck, J.B.J., 1990. Head-direction cells recorded from the postsubiculum in freely moving rats 1: description and quantitative analysis. J. Neurosci. 10, 420–435.

Taylor, J.G., 1999. Neural ''bubble'' dynamics in two dimensions: foundations. Biol. Cybern. 80, 393–409.

Treves, A., 1990. Graded-response neurons and information encodings in autoassociative memories. Phys. Rev. A 42, 2418–2430.

Treves, A., 1993. Mean-field analysis of neuronal spike dynamics. Network 4, 259–284.

Treves, A., 1995. Quantitative estimate of the information relayed by Schaffer collaterals. J. Comput. Neurosci. 2, 259–272.

Treves, A., Rolls, E.T., 1991. What determines the capacity of autoassociative memories in the brain? Network 2, 371–397.

Treves, A., Rolls, E.T., 1992. Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. Hippocampus 2, 189–199.

Treves, A., Rolls, E.T., 1994. A computational analysis of the role of the hippocampus in memory. Hippocampus 4, 374–391.

Ungerleider, L.G., Mishkin, M., 1982. Two cortical visual systems. In: Ingle, D.J., Goodale, M.A., Mansfield, R.J.W. (Eds.), Analysis of Visual Behavior. MIT Press, Cambridge, MA, pp. 549–586.

Vago, D., Kesner, R.P., 2005. An electrophysiological and behavioral characterization of the temporoammonic pathway: disruption produces deficits in retrieval and spatial mismatch. Soc. Neurosci. Abstr., in press.

Vago, D.R., Calder, A.J., Kesner, R.P., 2003. Functional characterisation of the direct perforant path into the hippocampus. Soc. Neurosci. Abstr.

van Haeften, T., Baks-te-Bulte, L., Goede, P.H., Wouterlood, F.G., Witter, M.P., 2003. Morphological and numerical analysis of synaptic interactions between neurons in deep and superficial layers of the entorhinal cortex of the rat. Hippocampus 13, 943–952.

Van Hoesen, G.W., 1982. The parahippocampal gyrus. New observations regarding its cortical connections in the monkey. Trends Neurosci. 5, 345–350.

Vann, S.D., Aggleton, J.P., 2004. The mammillary bodies: two memory systems in one? Nat. Rev. Neurosci. 5, 35–44.

Vazdarjanova, A., Guzowski, J.F., 2004. Differences in hippocampal neuronal population responses to modifications of an environmental context: evidence for distinct, yet complementary, functions of CA3 and CA1 ensembles. J. Neurosci. 24, 6489–6496.

Vinogradova, O.S., Brazhnik, E.S., Kichigina, V.F., Stafekhina, V.S., 1996. Modulation of the reaction of hippocampal neurons to sensory stimuli by cholinergic substances. Neurosci. Behav. Physiol. 26, 113–124.

Wallace, D.G., Whishaw, I.Q., 2003. NMDA lesions of Ammon's horn and the dentate gyrus disrupt the direct and temporally paced homing displayed by rats exploring a novel environment: evidence for a role of the hippocampus in dead reckoning. Eur. J. Neurosci. 18, 513–523.

Wallenstein, G.V., Hasselmo, M.E., 1997. GABAergic modulation of hippocampal population activity: sequence learning, place field development, and the phase precession effect. J. Neurophysiol. 78, 393–408.

Warthen, M.W., Kesner, R.P., 2006. CA3 involvement in one-trial short-term memory for cued recall object–place associations, in preparation.

Weiss, C., Bouwmeester, H., Power, J.M., Disterhoft, J.F., 1999. Hippocampal lesions prevent trace eyeblink conditioning in the freely moving rat. Behav. Brain Res. 99, 123–132.

Whishaw, I.Q., Hines, D.J., Wallace, D.G., 2001. Dead reckoning (path integration) requires the hippocampal formation: evidence from spontaneous exploration and spatial learning tasks in light (allothetic) and dark (idiothetic) tests. Behav. Brain Res. 127, 49–69.

Wills, T.J., Lever, C., Cacucci, F., Burgess, N., O'Keefe, J., 2005. Attractor dynamics in the hippocampal representation of the local environment. Science 308, 873–876.

Willshaw, D.J., 1981. Holography, associative memory, and inductive generalization. In: Hinton, G.E., Anderson, J.A. (Eds.), Parallel Models of Associative Memory. Lawrence Erlbaum, Hillsdale, pp. 103–124.

Willshaw, D.J., Buckingham, J.T., 1990. An assessment of Marr's theory of the hippocampus as a temporary memory store. Phil. Trans. R. Soc., London B 329, 205–215.

Wilson, F.A.W., Riches, I.P., Brown, M.W., 1990. Hippocampus and medial temporal cortex: neuronal responses related to behavioural responses during the performance of memory tasks by primates. Behav. Brain Res. 40, 7–28.

Wilson, M.A., 2002. Hippocampal memory formation, plasticity, and the role of sleep. Neurobiol. Learn. Mem. 78, 565–569.

Wilson, M.A., McNaughton, B.L., 1993. Dynamics of the hippocampal ensemble code for space. Science 261, 1055–1058.

Wilson, M.A., McNaughton, B.L., 1994. Reactivation of hippocampal ensemble memories during sleep. Science 265, 676–679.

Winters, B.D., Bussey, T.J., 2005. Transient inactivation of perirhinal cortex disrupts encoding, retrieval, and consolidation of object recognition memory. J. Neurosci. 25, 52–61.

Wirth, S., Yanike, M., Frank, L.M., Smith, A.C., Brown, E.N., Suzuki, W.A., 2003. Single neurons in the monkeys hippocampus and learning of new associations. Science 300, 1578–1581.

Witter, M.P., 1993. Organization of the entorhinal-hippocampal system: a review of current anatomical data. Hippocampus 3, 33–44.

Witter, M.P., Groenewegen, H.J., Lopes da Silva, F.H., Lohman, A.H., 1989a. Functional organization of the extrinsic and intrinsic circuitry of the parahippocampal region. Prog. Neurobiol. 33, 161–253.

Witter, M.P., Naber, P.A., van Haeften, T., Machielsen, W.C., Rombouts, S.A., Barkhof, F., Scheltens, P., Lopes da Silva, F.H., 2000a. Cortico-hippocampal

communication by way of parallel parahippocampal-subicular pathways. Hippocampus 10, 398–410.

Witter, M.P., Van Hoesen, G.W., Amaral, D.G., 1989b. Topographical organisation of the entorhinal projection to the dentate gyrus of the monkey. J. Neurosci. 9, 216–228.

Witter, M.P., Wouterlood, F.G., Naber, P.A., Van Haeften, T., 2000b. Anatomical organization of the parahippocampal-hippocampal network. Ann. N.Y. Acad. Sci. 911, 1–24.

Wood, E.R., Agster, K.M., Eichenbaum, H., 2004. One-trial odor-reward association: a form of event memory not dependent on hippocampal function. Behav. Neurosci. 118, 526–539.

Wood, E.R., Dudchenko, P.A., Eichenbaum, H., 1999. The global record of memory in hippocampal neuronal activity. Nature 397, 613–616.

Wu, X., Baxter, R.A., Levy, W.B., 1996. Context codes and the effect of noisy learning on a simplified hippocampal CA3 model. Biol. Cybern. 74, 159–165.

Xavier, G.F., Oliveira-Filho, F.J., Santos, A.M., 1999. Dentate gyrus-selective colchicine lesion and disruption of performance in spatial tasks: difficulties in ''place strategy'' because of a lack of flexibility in the use of environmental cues? Hippocampus 9, 668–681.

Xiang, J.-Z., Brown, M.W., 1998. Differential neuronal encoding of novelty, familiarity and recency in regions of the anterior tempral lobe. Neuropharmacology 37, 657–676.

Zhang, K., 1996. Representation of spatial orientation by the intrinsic dynamics of the head-direction cell ensemble: a theory. J. Neurosci. 16, 2112–2126.

Zola-Morgan, S., Squire, L.R., Amaral, D.G., Suzuki, W.A., 1989. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. J. Neurosci. 9, 4355–4370.

Zola-Morgan, S., Squire, L.R., Ramus, S.J., 1994. Severity of memory impairment in monkeys as a function of locus and extent of damage within the medial temporal lobe memory system. Hippocampus 4, 483–494.