Theoretical and Neurophysiological Analysis of the Functions of the Primate Hippocampus in Memory

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The aims of this paper are to consider which spatial functions are performed by the primate hippocampus, how these are related to the memory functions performed by the hippocampus, and how the hippocampus performs these functions. In addition to the evidence that is available from anatomical connections, the effects of lesions to the system, and recordings of the activity of single neurons in the system, neuronal network models of hippocampal function will also be introduced, as they have the promise of enabling one to understand what and how the hippocampus computes, and thus the functions being performed by the hippocampus. Many of the studies described have been performed with macaque monkeys to provide information as relevant as possible to understanding amnesia in humans. Effects on memory are produced by damage to the hippocampus or to some of its connections, such as the fornix, and these structures are collectively referred to below as the hippocampal system.

Damage to the Hippocampal System and Spatial Function

Damage to the hippocampus or to some of its connections, such as the fornix, in monkeys produces deficits in simple left-right-discrimination learning in which, for example, food is hidden consistently on the right or the left under one of two identical objects, and the monkey must learn whether to displace the left or the right object in order to find food (Mahut 1972). Fornix lesions also 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 (Gaffan et al. 1984; Rupniak and Gaffan 1987) (in humans, see Petrides 1985). (An example of such a conditional spatial response task is that if two objects shown are red, then the object on the left must be chosen to obtain a reward, and if the two objects shown are green, then the object on the right must be chosen to obtain a reward.) Two possible interpretations of these spatial learning impairments produced by fornix section are as follows.

First, it is possible that the learning system disrupted is only for the acquisition of map-like knowledge about the environment, such as that there is food in a certain place. This is not the case, because lesioned monkeys were impaired in learning to make a response to one side when one picture was shown and to the other side when a different picture was shown (Rupniak and Gaffan 1987), i.e., in conditional spatial response learning as described above. The spatial environment was held constant, and thus damage to the hippocampal system does not impair only the ability to acquire map-like knowledge of the environment. The experiment does show, on the other hand, that there is an impairment when monkeys must learn to make spatial responses on the basis of nonspatial stimuli.

Second, it is possible that the hippocampal learning system is only for the control of spatially directed movements, such as go left and go right. This is not the case, for fornix-sectioned monkeys are 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). Thus, the deficit is not just in learning spatial responses, for in this task the response was not spatial. The spatial aspect of this task was in the spatial position of the stimuli.

These findings suggest that fornix damage can impair learning about both the places of objects and the places of responses. Gaffan and Harrison (1989b) have analyzed further what it is that characterizes the spatial learning deficit of monkeys with damage to the hippocampal system in experiments in which the monkey was moved to different positions in a room. Impairments were found when which of two or more objects the monkey had to choose depended on the position of the monkey in the room, provided that the same parts of the room were in view from both positions of the monkey, so that the relative positions of room cues had to be remembered in order to solve the task (Gaffan and Harrison 1989b, experiment 1). This requirement is referred to as "whole scene analysis." If the parts of the room visible from the monkey's testing positions were different, then there was no impairment in learning which object to choose (Gaffan and Harrison 1989b, experiment 2). However, if the monkey had to make a spatial response to one of two identical objects which depended on different environmental cues (whether room-based or local), then fornix-sectioned monkeys displayed a learning impairment (Gaffan and Harrison, 1989b, experiments 3 and 5). These experiments suggest that fornix-sectioned monkeys can predict which of two different objects is rewarded on the basis of a conjunction of background items in the environment and the object displaced. Accordingly, they

can thus choose one of two (visually) different objects in a scene provided that the scene has different items visible in it, whether locally or distantly. However, a deficit is produced by fornix section when the monkey has to store the spatial relations of the background items and of identical objects in a scene. Accordingly, the fornix-sectioned monkeys are impaired in learning to select different objects depending on the spatial relations of items in the scene, or to make spatial responses to identical objects in a scene, as these involve storing the relative positions of places to which to respond (Gaffan and Harrison 1989b).

Another spatial task impaired by damage to the hippocampal system in monkeys (Gaffan and Saunders 1985; Parkinson et al. 1988) and humans (Smith and Milner 1981) is an object-place memory task. In this task, not only which objects have been seen before, but also where in space each object was located must be remembered. The task has been run with macaques by showing a picture in each of four positions on a screen twice (Rolls et al. 1989). The first time the monkey saw the picture in a particular position, he had to withhold a lick response (in order to avoid saline). The second time a picture appeared in a given position on the screen, the monkey could lick to obtain fruit juice. Each picture was shown in each position twice, once as novel and once as familiar for that position, and many different pictures were used in sequence. Thus, in order to perform the task, the monkey had to remember not only which pictures had been seen before, but also the position on the screen in which the picture had been seen. In humans, the object-place task was run by showing the subjects a tray containing a set of objects, and then asking later not only which objects had been seen before, but also where they were on the tray (Smith and Milner 1981). Such object-place tasks require a whole-scene or snapshot-like memory in which spatial relations in a scene must be remembered. It is not sufficient just to be able to remember the objects that have been seen before. The deficit in the object-place memory task is thus analogous to the deficit in the spatial tasks described above, in that the deficit is fully apparent when not just objects, but objects and their spatial relations to each other, must be remembered.

Nonspatial Aspects of the Function of the Hippocampus in Primates: Its Role in Memory

In addition to the spatial deficits described above that are produced by damage to the hippocampal system in primates, there are also deficits in nonspatial memory tasks. For example, the anterograde amnesia associated with damage to the hippocampus in humans is evident as a major deficit in learning to recognize new stimuli, and the recognition memory deficit encompasses nonspatial items (e.g., objects and people) as well as places (Scoville and Milner 1957; Milner 1972; Squire 1986; Squire and Zola-Morgan 1988). Recognition memory is also impaired in monkeys with damage to the hippocampal system (Gaffan 1974, 1977; Gaffan and Weiskrantz 1980; Owen and Butler 1981; Zola-Morgan et al. 1986), although it is possible that severe deficits in recognition memory are only found when there is also damage to the amygdala (Mishkin 1978, 1982; Murray and Mishkin 1984). In a typical recognition memory task in the monkey, a stimulus is shown to the monkey, and when it is shown again later, the monkey can choose it to obtain a reward. If no other stimuli intervene between the first and second presentations of a given stimulus, then the task is described as a match-to-sample task. If other stimuli intervene between the first (novel) and second (familiar) presentations of a stimulus, then the task is described as a serial or running recognition task. A serial recognition task is often used when analyzing the role of the hippocampus in memory, because a memory task with intervening stimuli is more difficult than a delayed match-to-sample task and may therefore be a more sensitive indicator of an effect on memory (Gaffan 1974, 1977).

It is interesting that the impairment produced by damage to the hippocampal system in recognition memory tasks as usually implemented (e.g., choose or respond to objects seen before, that is delayed match-to-sample, perhaps with intervening stimuli) is much less clear if delayed nonmatch-to-sample is used (choose the novel stimulus) (Gaffan et al. 1984). The impairment is also much less severe if the monkeys are trained initially with the long (and therefore difficult) intervals between stimuli with which they are tested later (Gaffan et al. 1984). The implication of these findings is that the deficit produced by the fornix section is not simply due to an inability to distinguish novel from familiar stimuli, but is due perhaps just as much to a difficulty these lesioned animals have in altering their instrumental response strategies, e.g., so that they respond to familiar stimuli when the natural tendency is to respond to novel stimuli, and so that they start responding at long memory intervals when they have been trained previously to respond with short memory intervals (see Gaffan et al. 1984). However, although the deficit usually found in recognition memory tasks may not strictly be due to an inability to distinguish novel from familiar stimuli, there is nevertheless a nonspatial impairment apparent in recognition memory tasks. Another nonspatial impairment produced by fornix section in monkeys is a deficit in learning the unnatural instrumental response rule "Choose the object not previously paired with reward," sometimes called the win-shift rule (Gaffan et al. 1984). (Fornix section did not impair use of the natural instrumental rule "Choose the object previously associated with reward," sometimes called the win-stay rule [Gaffan et al. 1984].) Thus, in monkeys, hippocampal function is involved not only in some types of spatial learning, but also in some aspect of nonspatial learning, even if this latter may not be pure novelty versus familiarity learning, but is instead related in some way to organizing flexibly adaptive instrumental responses.

There is also evidence from humans that the hippocampus is involved in nonspatial (as well as spatial)

memory, for e.g., in paired (word) associate learning, and in episodic memory, such as the memory of events that happened and people met on previous days (see Squire et al. 1989).

Relation between Spatial and Nonspatial Aspects of Hippocampal Function

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 set of events that describe a past episode. Furthermore, the nonspatial tasks impaired by damage to the hippocampal system may be impaired because they are tasks in which a memory of a particular episode rather than of a general rule is involved. Thus, the learning of tasks with nongeneral rules, such as choose the object not previously rewarded (i.e., win-shift, lose-stay), may be impaired because to solve them the particular pairing in the particular context (of performing with this special rule) must be remembered in order to choose the correct object later. (The natural rule, which will in the natural environment usually lead to reward, is to choose the object previously associated with reward.) Another example is that choosing familiar rather than novel objects in a recognition memory task may be particularly difficult for monkeys with damage to the hippocampal system because it involves a special rule, choose the familiar object in this task, rather than what may be a more general tendency, i.e., to choose the novel rather than the familiar object. The latter rule is what normally guides behavior, as this rule is more likely to lead to reward for objects without an explicit reward association already in the natural environment. Furthermore, recognition memory may be particularly impaired when this involves the memory of particular and arbitrary associations between parts of the image, especially when the same elements may occur in different combinations in other images. In addition, the deficit in paired associate learning in humans may be especially evident when this involves arbitrary associations between words, for example, window–lake. I suggest that the reason why the hippocampus is used for the spatial and nonspatial types of memory described above, and the reason that these two types of memory are so analogous, is that the hippocampus contains one stage, the CA3 stage, which acts as an autoassociation memory. (The structure, operation, and properties of autoassociation memories are described below.) 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 that depends on the arbitrary associations that can be made and the short temporal window that characterizes the synaptic modifiability in this system (see below and Rolls 1987, 1989a,b). The ways in which the architecture of the hippocampus appears to be specialized to perform these functions in spatial snapshot and episodic memory are described next, to lead toward a deeper understanding of hippocampal function in these types of learning.

Computational Significance of the Functional Architecture of the Hippocampus

The internal connections of the hippocampus and the learning rules implemented at its synapses are described first to delineate its functional architecture, which provides the basis for a computational theory of the hippocampus.

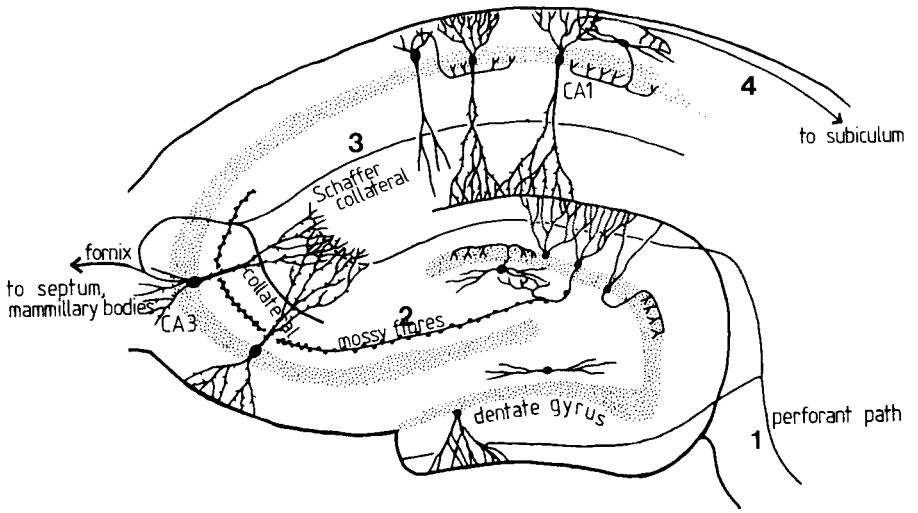

Figure 1. Representation of connections within the hippocampus. Inputs reach the hippocampus through the perforant path (1), which makes synapses with the dendrites of the dentate granule cells and also with the apical dendrites of the CA3 pyramidal cells. The dentate granule cells project via the mossy fibers (2) to the CA3 pyramidal cells. The well-developed recurrent collateral system of the CA3 cells is indicated. The CA3 pyramidal cells project via the Schaffer collaterals (3) to the CA1 pyramidal cells, which in turn have connections (4) to the subiculum.

Schematic diagrams of the connections of the hippocampus are shown in Figures 1 and 2. In primates, major input connections are from the association areas of the cerebral cortex, including the parietal cortex (which processes spatial information), the temporal lobe visual and auditory areas, and the frontal cortex. Within the hippocampus, there is a three-stage sequence of processing, consisting of the dentate granule cells (which receive from the entorhinal cortex via the perforant path), the CA3 pyramidal cells, and the CA1 pyramidal cells (see below). Outputs return from the hippocampus to the cerebral cortex via the subiculum, entorhinal cortex, and parahippocampal gyrus.

CA3 pyramidal cells. One major feature of hippocampal neuronal networks is the recurrent collateral system of the CA3 cells, formed by the output axons of the CA3 cells having a branch that returns to make synapses with the dendrites of the other CA3 cells, as shown in Figures 1 and 2. Given that the region of the CA3 cell dendrites on which the recurrent collaterals synapse is long ($\sim$ 12 mm), and that the total dendritic length is approximately 16 mm and has approximately 16,000 spines (Squire et al. 1989; Amaral et al. 1990), and that each spine receives one synapse, approximately 12,000 synapses per CA3 pyramidal cell could be devoted to recurrent collaterals, which with 304,000 CA3 neurons on each side of the brain in the (Sprague-Dawley) rat (Boss et al. 1987; Amaral et al. 1990) makes the probability of contact between the CA3 neurons 3.9%. (The quantitative values given here have been updated a little from those given by Rolls [1989a,b] in light of new estimates provided by Amaral et al. [1990].) It is remarkable that the contact probability is so high, and also that the CA3 recurrent collateral axons travel so widely in all directions that they can potentially come close to almost all other CA3 neurons (Amaral and Witter 1989; Rolls 1989a,b; Squire et al. 1989; D.G. Amaral, pers. comm.). The connectivity of these CA3 cells is even more remarkable than this, for, in addition, there is a commissural system in which CA3 neurons on one side of the brain send axons to end primarily on the dendrites of the CA3 neurons of the other side of the brain. The terminals are made on the same stretch of the CA3 dendrites as the recurrent collaterals, so that the contact probability calculated above must be reduced (with the lower limit being perhaps 2.0%, representing 12,000 synapses shared among 608,000 CA3 neurons). The remarkable effect achieved by this is that the CA3 neurons provide one interconnected network of neurons for both sides of the brain, with a reasonably high probability that any CA3 neuron will be connected to any other CA3 neuron, irrespective of the side of the brain. Although connectivity across the midline is likely to be high in the rat, the two sides of the hippocampus are probably not fully interconnected in humans, as indicated by the evidence that damage to the right temporal lobe affects spatial tasks (such as conditional spatial response learning) more than nonspatial memory tasks, whereas damage to the left temporal lobe affects nonspatial tasks such as paired word associate learning more than nonspatial tasks (Milner 1982; Kolb and Whishaw 1985).

There is evidence from studies of long-term potentiation (Bliss and Lomo 1973; Kelso et al. 1986; Wigstrom et al. 1986; P.O. Andersen 1987; Brown et al. 1990; Collingridge and Singer 1990) that the synapses in this recurrent collateral system are Hebb-modifiable, i.e., that they become stronger when there is strong conjunctive postsynaptic and presynaptic activity (Miles 1988).

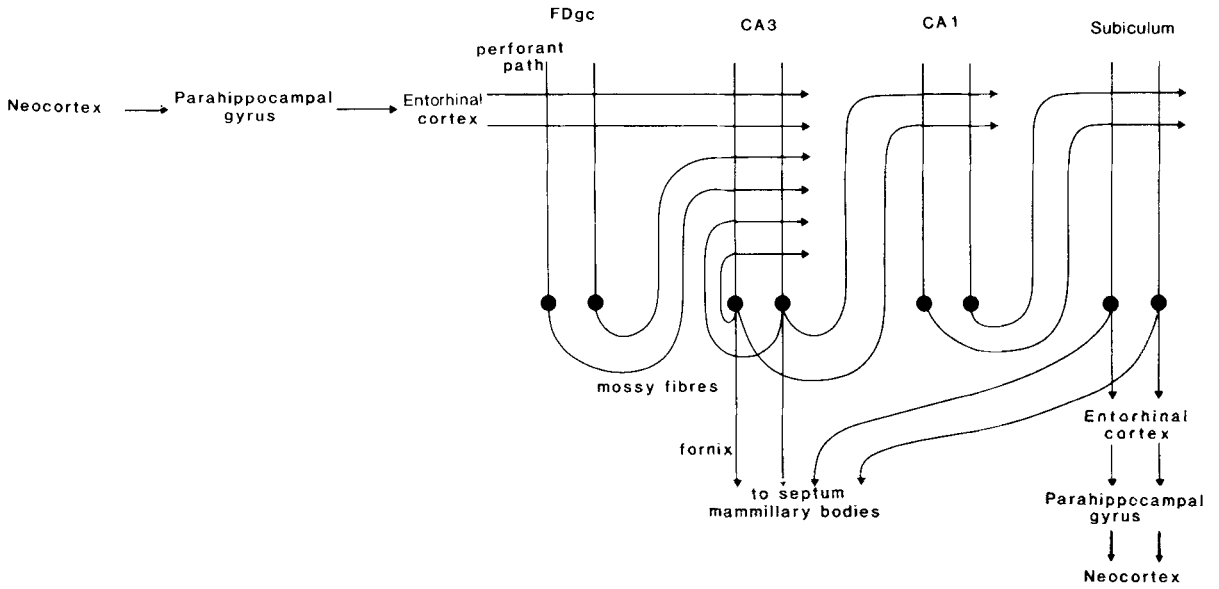

Figure 2. Schematic representation of the connections of the hippocampus, showing also that the cerebral cortex (neocortex) is connected to the hippocampus via the parahippocampal gyrus and entorhinal cortex, and that the hippocampus projects back to the neocortex via the subiculum, entorhinal cortex, and parahippocampal gyrus. (FDgc) Dentate granule cells.

Autoassociation memory implemented by the CA3 recurrent collateral system. This functional anatomy of the CA3 pyramidal cells immediately suggests that this is an autoassociation (or autocorrelation) matrix memory. The autoassociation arises because the outputs of the CA3 cells are fed back by the recurrent collateral axons to make Hebb-modifiable synapses with the dendrites of the other CA3 neurons. The result of implementation of the Hebb rule in this architecture is that any strongly activated cell or set of cells becomes linked by strengthened synapses with any other conjunctively strongly activated cell or set of cells. During learning, the matrix of synaptic weights that link the cells together (see Fig. 3) comes to reflect the correlations between the activities of the CA3 cells. Because the matrix of synaptic weights stores the correlations between the activities of the cells of the memory, this type of memory is called an autocorrelation or autoassociation matrix memory. During recall, presentation of even a part of the original pattern of activity of the CA3 cells, which might represent one part of or key to the memory, elicits the firing of the whole set of cells that were originally conjunctively activated. This important property of this type of memory is termed completion and is fundamental to any biological memory system. During recall, if a pattern similar to one learned by the system is presented, then insofar as some of the neurons active in the key stimulus were also part of a pattern stored previously in the memory, the previously stored pattern is recalled. This property, which is also fundamental to biological memory, is termed generalization. Another property of this type of memory is that it continues to function moderately well if it is partially damaged, or if, for example, not every synapse in the matrix is present, either because of limitations of fan-in of individual neurons or because of limitations of the precision of development. This property is also important for a biological memory system and is termed graceful degradation or fault tolerance. More extensive descriptions of the properties of autoassociation matrix memories are given by Kohonen et al. (1981), Kohonen (1984), and Rolls (1987). The suggestion made here is that the output of the CA3 pyramidal cells is fed back along the horizontally running recurrent collateral axons that make Hebb-modifiable synapses with other CA3 dendrites so that the pattern of activity in the CA3 pyramidal cells is associated with itself.

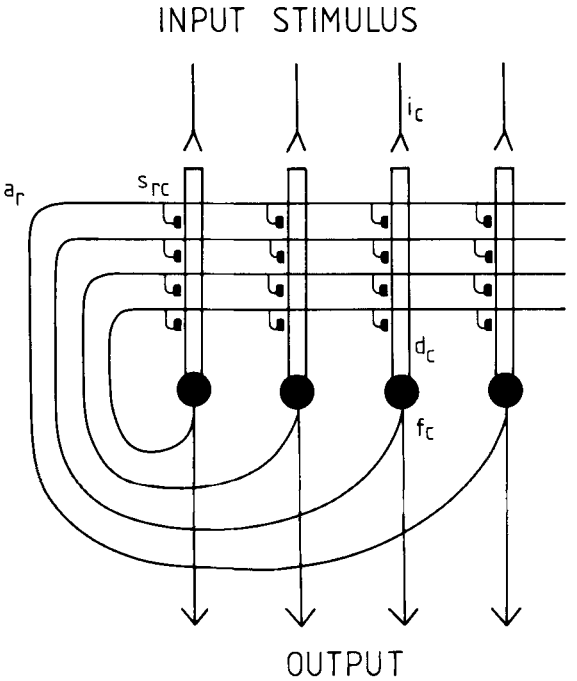

Figure 3. An autoassociation matrix memory. The dendrites, d_c, have recurrent collateral axons, a_r, which make Hebb-modifiable synapses, s_{rc}, with the other neurons in the population.

For this autoassociation to work correctly, it is important that a depolarization produced by synaptic input on one part of the dendrite is effective on other parts of the dendrite, so that even distant active synapses experience the postsynaptic term required for the Hebb rule to be implemented. This condition does appear to be met, as shown by the short electrical length of the dendrites and by the cooperation which occurs between inputs that synapse on different parts of the dendrite in setting up the postsynaptic depolarization required for long-term potentiation (McNaughton 1984; P.O. Andersen 1987). This cooperativity between active synapses made at different positions along the postsynaptic membrane, so that active synapses onto a neuron alter their strength only when other synapses are active on the same dendrite and produce postsynaptic activation, enables associations to be formed on the basis of temporal conjunctions that occur between any set of conjunctively active afferents. In a sense, the large number of synapses of these CA3 cells devoted to the recurrent collaterals allows correlations of firing across a large information space to be detected. Consistent with this suggestion about the computational role of the CA3 system of the hippocampus, it is known that the probability of contact of the neurons in an autoassociation matrix memory must not be very low if it is to operate usefully (see Marr 1971; Gardner-Medwin 1976). The synaptic modifiability implemented in the CA3 recurrent collateral system may utilize NMDA receptors, which allow synaptic modifiability only when the postsynaptic membrane is strongly activated. This interesting nonlinearity of the learning rule means that only correlations between strongly activated CA3 pyramidal cells are stored, which may help to maximize the storage capacity of the system and to minimize interference.

It is suggested below that the systems level function of this autoassociation memory is to enable events occurring conjunctively in quite different parts of the association areas of the cerebral cortex to be associated together to form a memory that could well be described as episodic. Each episode would be defined by a conjunction of a set of events, and each episodic memory would consist of the association of one set of events (such as where, with whom, and what one ate at lunch on the preceding day). It is suggested that the "snapshot, whole-scene" spatial memory in which the hip-

pocampus is implicated, as shown above, is what the hippocampus can achieve for spatial information processing by allowing all the parts of a whole scene to be associated together to provide a memory of the whole scene. The importance of the hippocampus in episodic memory and "whole-scene" memory may arise from the fact that in one part of it, the CA3 region, there is one autoassociation matrix memory with a relatively high contact probability that receives information originating in many different areas of the cerebral cortex, and from both sides of the brain. It is suggested that this ability to link information originating from different brain regions in a single autoassociation matrix in the CA3 regions is a key feature of hippocampal architecture, which is unlikely to be implemented in input regions such as the entorhinal cortex and dentate granule cells, which not only do not have the required system of recurrent collaterals over the whole population of cells, but also appear to maintain some segregation of inputs originating from different parts of the cerebral cortex (Insausti et al. 1987). One reason why there may not be more cells in the CA3 region is that it is important that the connectivity be kept relatively high so that any event represented by the firing of a sparse set of CA3 cells can be associated with any other event represented by a different set of CA3 cells firing. Because each CA3 pyramidal cell has a limited fan-in or number of synapses (perhaps 16,000, see above), the total number of cells in the autoassociation memory cannot be increased beyond the limit set by the fan-in and the connectivity. The advantages of sparse encoding and a well interconnected matrix are that a large number of different (episodic) memories can be stored in the CA3 system and that the advantageous emergent properties of a matrix memory, such as completion, generalization, and graceful degradation (see Kohonen et al. 1977, 1981; Kohonen 1984; Rolls 1987), are produced efficiently. Completion may operate particularly effectively here with a sparse representation, because it is under these conditions that the simple autocorrelation effect can reconstruct the whole of one pattern without interference, which would arise if too high a proportion of the input neurons was active.

Dentate granule cells and the CA1 pyramidal cells. The theory is developed elsewhere that the dentate granule cell stage of hippocampal processing that precedes the CA3 stage acts in two ways to produce the sparse yet efficient (i.e., nonredundant) representation in CA3 neurons that is required for the autoassociation to perform well (Rolls 1989a,b). 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 matrix to remove redundancy from the inputs, producing a more orthogonal and categorized set of outputs. The second way arises because there is a very low (0.008% in the rat) contact probability in the mossy fiber/CA3 connections, which achieves by pattern separation relatively orthogonal representations (compared to those on the dentate granule cells, and within the limits set by the relative numbers of dentate granule and CA3 cells; see Rolls 1989a), which are required if the autoassociation matrix memory formed by the CA3 cells is to operate with usefully large memory capacity and with minimal interference (see Kohonen et al. 1977, 1981; Rolls 1987). As the neurons have positive continuous firing rates, the only way in which relatively orthogonal representations can be formed is by making the number of neurons active for any one input stimulus relatively low (see, e.g., Jordan 1986), and this sparse representation is exactly what can be achieved by the low contact probability pattern separation effect of the mossy fibers (Rolls 1989a,b). The pattern separation effect refers to the point that input patterns which are correlated produce output patterns which are less correlated with each other.

The function of the CA1 stage that follows the CA3 cells (see Figs. 1 and 2) is also considered to be related to the CA3 autoassociation effect in which 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 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. 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 a relatively few neurons to represent each episodic memory. The episodic memory would thus consist in the CA3 region of ensembles of active cells, each ensemble representing one of the subcomponents of the episodic memory (including context), whereas the whole episodic memory would be represented not by its parts, but as a single collection of active cells at the CA1 stage. It is suggested below that one role these economical (in terms of the number of activated fibers) and relatively orthogonal signals in the CA1 cells have is to guide information storage or consolidation in the cerebral cortex. To understand how the hippocampus may perform this function for the cerebral cortex, it is necessary to turn to a systems level analysis to show how the computations performed by the hippocampus fit into overall brain function. It may be noted that by forming associations of events derived from different parts of the cerebral cortex (the CA3 stage) and by building new economical (i.e., less redundant) representations of the conjunctions detected (the CA1 stage), the hippocampus provides an output that is suitable for directing the long-term storage of information.

Synaptic modification occurs with presynaptic firing rates in the physiological range in the hippocampus. The ideas introduced above on the operation of neuronal networks in the hippocampus during learning

include the postulate that synapses in the hippocampus modify according to rules analyzed in studies of long-term potentiation. In studies of long-term potentiation, the presynaptic neurons are typically induced to fire synchronously at a high frequency by electrical stimulation. In a recent series of experiments (Cahusac and Rolls 1989), we investigated whether pairing of the normal firing of presynaptic neurons (i.e., at physiologically occurring firing rates and without the synchronous firing induced by electrical stimulation) could be effective when paired with postsynaptic activation in leading to synaptic enhancement.

Recordings were made extracellularly of action potentials from hippocampal neurons while macaques performed a task in which hippocampal neurons were known to be activated by visual stimuli (Miyashita et al. 1989). The task was a visual discrimination task in which the monkey could make lick or arm-reach responses when one visual stimulus was shown and had to avoid such responses when the other visual stimulus was shown in order to avoid the taste of saline. When a neuron was found that had some response to one or both of the visual stimuli, one of the stimuli was temporally paired with the ionophoretic application of L-glutamate (25–190 nA), which was switched on to cause firing for 350–950 msec while that stimulus was displayed. The visual stimuli were presented in random sequence until 30–50 pairings of one of the visual stimuli with firing of the postsynaptic neuron induced by glutamate had occurred.

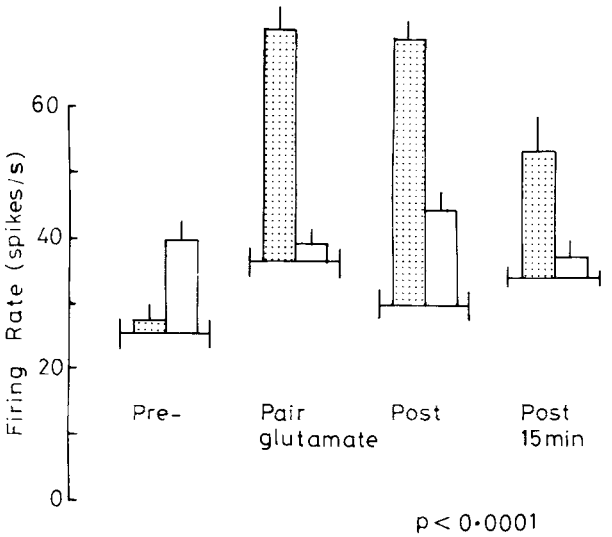

Figure 4. Evidence on synaptic modification in the primate hippocampus when the presynaptic firing is that induced by natural inputs to the hippocampus. (Pre-) The responses of the single neuron to two visual stimuli (dotted and open bars) in a visual discrimination task are shown (means ± S.E.M. shown above the spontaneous firing rate of the neuron). (Pair glutamate) One of the visual stimuli (dotted bars) was paired with ionophoretic application of glutamate, which produced fast firing of the neuron during the presentation of that stimulus. This pairing was repeated for many trials. (Post) After pairing with glutamate, the neuron responded more to the visual stimulus previously paired with glutamate. (Post 15 min) This effect lasted for at least 15 min.

Of 28 neurons studied, 6 showed potentiation of responses to the visual stimulus paired with the ionophoretic application of glutamate (as indicated by $p < 0.001$ in each case in an ANOVA) (see, e.g., Fig. 4). There was no potentiation to the unpaired visual stimulus. The modifications of responses lasted for at least 8–18 minutes. These experiments provide evidence that pairing of naturally induced firing of presynaptic neurons with postsynaptic activation in the primate hippocampus can lead to modifications of the neuronal responses elicited by the input paired with the postsynaptic activation. In terms of the network models described above, these experiments provide additional evidence that synaptic modification rules of the type incorporated in the models do operate in the hippocampus (for further details, see Rolls 1989c).

Systems Level Analysis of Hippocampal Function, Including Neuronal Activity in the Primate Hippocampus

We have just utilized the functional architecture (internal anatomy and physiology) of the hippocampus to suggest a computational theory of how it operates. To understand how these computations are used and how they contribute to the information processing being performed by other parts of the brain, we now turn to a systems level analysis in which we consider the connections of the hippocampus with the rest of the brain, and the activity of single neurons in the hippocampus when it is performing its normal function, as assessed by the effects of selective damage to the hippocampus as described above.

Systems level anatomy. The primate hippocampus receives inputs via the entorhinal cortex (area 28) and the parahippocampal gyrus from many areas of the cerebral association cortex, including the parietal cortex, which is concerned with spatial functions, the visual and auditory temporal association cortical areas, and the frontal cortex (Van Hoesen 1982; Amaral 1987; Rolls 1989a,b). In addition, the entorhinal cortex receives inputs from the amygdala. There are also subcortical inputs from, for example, the amygdala and septum. The hippocampus in turn projects back via the subiculum, entorhinal cortex, and parahippocampal gyrus (area TF-TH), to the cerebral cortical areas from which it receives inputs (Van Hoesen 1982), as well as to subcortical areas such as the mammillary bodies (see Figs. 1 and 2).

Systems level neurophysiology. The information processing being performed by the primate hippocampus while it is performing the functions for which lesion studies have shown it is needed has been investigated in studies in which the activity of single hippocampal neurons has been analyzed during the performance and learning of these (and related) spatial tasks. Watanabe and Niki (1985) analyzed hippocampal neuronal activity while monkeys performed a delayed spatial response task. In a delayed spatial response task, a stimulus is shown, for example, on the left; there is then a delay

period, and after this the monkey can respond by touching the left stimulus position. They reported that 6.4% of hippocampal neurons responded differently while the monkey was remembering left as compared to right. The responses of these neurons could reflect preparation for the spatial response to be made, or they could reflect memory of the spatial position in which the stimulus was shown. To provide evidence on which was important, Cahusac et al. (1989) analyzed hippocampal activity in this task, and in an object-place memory task. In the object-place memory task, the monkey was shown a sample stimulus in one position on a video screen; there was a delay of two seconds, and then the same or a different stimulus was shown in the same or in a different position. The monkey remembered the sample and its position, and if both matched the delayed stimulus, he licked to obtain fruit juice. Of the 600 neurons analyzed in this task, 3.8% responded differently for the different spatial positions, with some of these responding differentially during the sample presentation, some in the delay period, and some in the match period. Thus, some hippocampal neurons (those differentially active in the sample or match periods) respond differently for stimuli shown in different positions in space, and some (those differentially active in the delay period) respond differently when the monkey is remembering different positions in space. In addition, some of the neurons responded to a combination of object and place information, in that they responded only to a novel object in a particular place. These neuronal responses were not due to any response being made or prepared by the monkey, because information about which behavioral response was required was not available until the match stimulus was shown. Cahusac et al. (1989) also found that the majority of the neurons that responded in the object-place memory task did not respond in the delayed spatial response task. Instead, a different population of neurons (5.7% of the total) responded in the delayed spatial response task, with differential left-right responses in the sample, delay, or match periods. Thus, this latter population of hippocampal neurons had activity that was related to the preparation for or initiation of a spatial response, which in the delayed response task could be encoded as soon as the sample stimulus was seen. These recordings showed that there are some neurons in the primate hippocampus with activity that is related to the spatial position of stimuli or to the memory of the spatial position of stimuli (as shown in the object-place memory task) and that there are other neurons in the hippocampus with activity that is related not to the stimulus or the memory of the stimulus, but instead to the spatial response that the monkey is preparing and remembering (as shown in the delayed spatial response task).

The responses of hippocampal neurons in primates with activity related to the place in which a stimulus is shown were further investigated using a serial multiple object-place memory task. The task required a memory for the position on a video monitor in which a given object had appeared previously (Rolls et al. 1989). This task was designed to allow a wider area of space to be tested than in the previous study and was chosen also because memory of where objects had been seen previously in space was known to be disrupted by hippocampal damage (Gaffan and Saunders 1985; Gaffan 1987). In the task, a visual image appeared in one of four or nine positions on a screen. If the stimulus had been seen in that position before, the monkey could lick to obtain fruit juice, but if the image had not appeared in that position before, the monkey had not to lick in order to avoid the taste of saline. Each image appeared in each position on the screen only twice, once as novel and once as familiar. The task thus required memory not only of which visual stimuli had been seen before, but of the positions in which they had been seen, and is an object-place memory task. It was found that 9% of neurons recorded in the hippocampus and parahippocampal gyrus had spatial fields in this and related tasks, in that they responded whenever there was a stimulus in some but not in other positions on the screen. Of the neurons, 2.4% responded to a combination of spatial information and information about the object seen, in that they responded more the first time a particular image was seen in any position. Six of these neurons were found that showed this combination even more clearly, because they, for example, responded only to some positions and only if it was the first time a particular stimulus had appeared there. Thus, not only is spatial information processed by the primate hippocampus, but it also can be combined, as shown by the responses of single neurons, with information about which stimuli have been seen before (Rolls et al. 1989).

The ability of the hippocampus to form such arbitrary associations of information probably originating from the parietal cortex about position in space with information originating from the temporal lobe about objects may be important for its role in memory. Moreover, these findings provide neurophysiological support for the computational theory described above, according to which such arbitrary associations should be formed onto single neurons in the hippocampus.

These "space" neurons (Cahusac et al. 1989; Rolls et al. 1989) may be compared with "place" cells recorded in the rat hippocampus (see McNaughton et al. 1983; O'Keefe 1984). The "place" cells described in the rat respond when the rat is in a particular place in the environment as specified by extra-maze cues, whereas the cells described here respond to particular positions in space, or at least when stimuli are shown in particular positions in space (for further details, see Feigenbaum and Rolls 1990).

These studies showed that some hippocampal neurons in primates have spatial fields. To investigate how space is represented in the hippocampus, Feigenbaum et al. (1987) and Feigenbaum and Rolls (1990) investigated whether the spatial fields use egocentric or some form of allocentric coordinates. This was investigated by finding a neuron with a space field and then moving the monitor screen and the monkey relative to each

other and to different positions in the laboratory. For 10% of the spatial neurons, the responses remained in the same position relative to the monkey's body axis when the screen was moved or the monkey was rotated or moved to a different position in the laboratory. These neurons thus represented space in egocentric coordinates. For 46% of the spatial neurons analyzed, the responses remained in the same position on the screen or in the room when the monkey was rotated or moved to a different position in the laboratory. These neurons thus represented space in allocentric coordinates. Evidence for two types of allocentric encoding was found. In the first type, the field was defined by its position on the monitor screen independently of the position of the monitor relative to the monkey's body axis and independently of the position of the monkey and the screen in the laboratory. These neurons were called "frame of reference" allocentric, since their fields were defined by the local frame provided by the monitor screen. The majority of the allocentric neurons responded in this way. In the second type of allocentric encoding, the field was defined by its position in the room and was relatively independent of position relative to the monkey's body axis or to position on the monitor screen face. These neurons were called "absolute" allocentric, since their fields were defined by position in the room. These results provide evidence that in addition to neurons with egocentric spatial fields, which have also been found in other parts of the brain (Sakata 1985; R.A. Andersen 1987), there are neurons in the primate hippocampal formation that encode space in allocentric coordinates.

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, i.e., to acquire associations between visual stimuli and spatial responses, 14% of hippocampal neurons responded to particular combinations of stimuli and 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, it was found that during such conditional spatial response learning, 22% of this type of neuron analyzed 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 (Rolls et al. 1990b). These changes occurred for different neurons just before, at, or just after the time when the monkey learned the correct response to the stimuli. In addition to these neurons, which had differential responses that were sustained for as long as the recordings continued, another population of neurons (45% of this type of neuron analyzed) developed differential activity to the two stimuli, yet showed such differential responses transiently for only a small number of trials at about the time when the monkey learned. These findings are consistent with the hypothesis that some synapses on hippocampal neurons modify during this type of learning so that some neurons come to respond to particular stimulus/spatial response associations that are being learned. Furthermore, the finding that many hippocampal neurons started to reflect the new learning, but then stopped responding differentially (the transient neurons), is consistent with the hypothesis that the hippocampal neurons with large sustained changes in their activity inhibited the transient neurons, which then underwent reverse learning, thus providing a competitive mechanism by which not all neurons are allocated to any one learned association or event. These transient modifications are consistent with the computational theory outlined above and elsewhere (Rolls 1989a,b), since the return of the neuronal activity to nondifferential responsiveness is consistent with an implementation of competitive networks using reverse learning when the postsynaptic neuron is inhibited conjunctively with active afferents (see Rolls 1989c).

The activity of hippocampal neurons in nonhuman primates has also been analyzed during the performance of nonspatial tasks for which the hippocampus is needed, such as recognition memory tasks (Rolls et al. 1985, 1990a). It has been found that in the macaque hippocampus, some neurons do respond differently to novel and familiar stimuli in a serial recognition memory task, with those that did respond differentially typically responding more to novel than to familiar visual stimuli. It was notable that the proportion of hippocampal neurons that responded in this way was small, 2.3%, but that this is not inconsistent with the hypothesis that the hippocampus is involved in episodic memory. It might be of interest in future studies of recognition memory and hippocampal function to investigate whether there are hippocampal neurons tuned to respond to only rather few of a set of stimuli being remembered and whether the representation found is sparse, as would be useful if the CA3 neurons are to store many different stimuli using an autoassociation network. Brown et al. (1987) have also found context sensitivity of hippocampal neurons recorded during a delayed match-to-sample memory task (consistent with a role in episodic memory, in which context is important), but the task also included a conditional response component that may have contributed to the neuronal responses found.

Systems level theory. The effects of damage to the hippocampus indicate that the very long term storage of information is not in the hippocampus, at least in

humans, because the retrograde amnesia produced by damage to the hippocampal system in humans is not always severe and because very old memories (e.g., for events which occurred 30 years previously) are not destroyed (Squire 1986; Squire and Zola-Morgan 1988). On the other hand, the hippocampus does appear to be necessary for the storage of certain types of information (characterized by the description declarative, or knowing that, as contrasted with procedural, or knowing how, which is spared in amnesia). Declarative memory includes what can be declared or brought to mind as a proposition or an image. Declarative memory includes episodic memory, i.e., memory for particular episodes, and semantic memory, i.e., memory for facts (Squire and Zola-Morgan 1988; Squire et al. 1989).

These computational and systems level analyses suggest that the hippocampus is specialized to detect the best way in which to store information, and then by the return paths to the cerebral cortex to direct memory storage there. The hypothesis is that the CA3 autoassociation system is ideal for remembering particular episodes, for perhaps uniquely in the brain it provides a single autoassociation matrix that receives from many different areas of the cerebral association cortex. It is thus able to make almost any arbitrary association, including incorporation by association of the context in which a set of events occurred. This autoassociation type of memory is also required for paired-associate learning, in which arbitrary associations must be made between words, and an impairment of which is almost a defining test of anterograde amnesia. Impairment of this ability to remember episodes by using the CA3 autoassociation matrix memory may also underlie many of the memory deficits produced by damage to the hippocampal system. For example, conditional spatial response learning (see Miyashita et al. 1989) may be impaired by hippocampal damage because a monkey or human cannot make use of the memory of the episode of events on each particular trial (e.g., that a particular stimulus and a particular response were made, and reward was received). Similarly, object-place memory tasks, also impaired by hippocampal damage, require associations to be made between particular locations and particular objects—again a natural function for an autoassociation memory. Furthermore, the difficulty with memory for places produced by hippocampal damage (see Barnes 1988) may be because a place is normally defined by a conjunction of a number of features or environmental cues or stimuli, and this type of conjunction is normally made by the autoassociation memory capability of the hippocampus (see further, Rolls et al. 1989). Clearly, the hippocampus, with its large number of synapses on each neuron, its potentiation type of learning, and its CA3 autoassociation system, is able to detect when there is conjunctive activation of arbitrary sets of its input fibers and is able, as indicated both theoretically and by recordings made in the behaving monkey, to allocate neurons economically (i.e., with relatively few neurons active) to code for each complex input event (by the output or CA1 stage). Such output neurons could then represent an efficient way in which to store information, since complex memories with little redundancy would have been generated. It should be noted that this theory is not inconsistent with the possibility that the hippocampus provides a working memory, since in the present theory, the hippocampus sets up a representation using Hebbian learning, which is useful in determining how information can best be stored in the neocortex, and this representation could provide a useful working memory. Perhaps by understanding the operations performed by the hippocampus at the neuronal network level, it can be seen how the hippocampus could contribute to several functions that are not necessarily inconsistent.

The question of how the hippocampal output is used by the neocortex (i.e., cerebral cortex) is considered next. Given that the hippocampal output returns to the neocortex, a theory of back projections in the neocortex will be needed. This is developed elsewhere (Rolls 1989a,b). By way of introduction, it may be noted that which particular hippocampal neurons happen to represent a complex input event is not determined by any teacher or forcing (unconditioned) stimulus. Thus, the neocortex must be able to utilize the signal rather cleverly. One possibility is that any neocortical neuron with a number of afferents active at the same time as hippocampal return fibers in its vicinity are active modifies its responses so that it comes to respond better to those afferents the next time they occur. This learning by the cortex would involve a Hebb-like learning mechanism. It may be noted that one function served by what are thus in effect back projections from the hippocampus is some guidance for or supervision of neocortical learning. Unsupervised learning systems can detect local conjunctions efficiently, but these are not necessarily those of most use to the whole system. It is exactly this problem which it is proposed the hippocampus helps to solve by detecting useful conjunctions globally (i.e., over the whole of information space) and then directing storage locally at earlier stages of processing so that filters are built locally and provide representations of input stimuli useful for later processing. It is also suggested (Rolls 1989a,b) that the back projections are used for recall, for dynamic adjustment of the processing of earlier stages to facilitate the optimal satisfaction of multiple constraints, and for attention.

CONCLUSION

A computational theory of the hippocampus that has as a key feature the ability to implement an autoassociation memory using the CA3 pyramidal cells has been proposed. It is proposed that the hippocampus is involved in both spatial and episodic memory as a result of its ability to form arbitrary associations between input stimuli, so that whole spatial scenes or all the events that comprise a single episodic memory can be associated together. Recordings from single neurons in

the primate hippocampus are consistent with the theory that inputs to the hippocampus originating from different parts of the cerebral cortex are brought together onto single neurons within the hippocampus and that synaptic modifications within the hippocampus implement the associations, although further work is needed to test the detailed predictions of the theory.

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