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Responses of hippocampal formation neurons in the monkey related to delayed spatial response and object–place memory tasks

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The memory for where in the environment a particular visual stimulus has been seen is one of the types of memory relatively specifically impaired by hippocampal damage in primates including man. In order to investigate what processing might be performed by the hippocampus related to this type of memory, the activity of hippocampal neurons was recorded while monkeys performed an object–place memory task. In this task, the monkey was shown a sample stimulus in one position on a video screen, there was a delay of 2 s, 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 analysed 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 respond differently for stimuli shown in different positions in space, and some 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, for information about which behavioral response was required was not available until the match stimulus was shown. This is the first demonstration that some hippocampal neurons in the primate have activity related to the spatial position of stimuli. The activity of these neurons was also measured in a delayed spatial response task, in which the monkey was shown a stimulus in one position, and, after a 2 s delay when two identical stimuli were shown, had to reach to touch the stimulus which was in the position in which it had previously been seen. It was found that the majority of the neurons which responded in the object–place memory task did not respond in the delayed 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 population of hippocampal neurons had activity which was related to the preparation for or initiation of a spatial response, which can be encoded in the delayed response task as soon as the sample stimulus is seen. It is concluded (1) that there are some neurons in the primate hippocampus with activity which 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). Further, (2) some of these neurons responded to a combination of information about the object and the position in which it was seen. It is also concluded (3) there are other neurons in the hippocampus with activity which is related not to the stimulus or the memory of the stimulus, but instead to the spatial response which the monkey is preparing and remembering (as shown in the delayed spatial response task).

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INTRODUCTION

Bilateral damage to the temporal lobe in humans can cause anterograde amnesia[19,7,21]. A number of structures are damaged, and these include the hippocampus and the amygdala. Experimental investigations have been performed to determine which structures are crucial in producing the amnesia, and to analyse the neural bases of the different types of amnesia[21]. It has been shown in the monkey that the ability to remember a list of objects in a serial recognition task is impaired by combined damage to the hippocampus and amygdala[8]. In analyses of the way in which the hippocampus could contribute to a memory deficit, it has been shown that tasks which are particularly affected by hippocampal damage in the primate include tasks in which both an object, and the place in which it was seen, must be remembered[4,3,12]. It is thus of interest that the patient H.M., and humans with right temporal lobe damage, were impaired in remembering (over a 4-min delay) the positions in which objects had been placed on a board[20].

In order to analyze the functions of the hippocampus in the primate, and to advance the understanding of amnesia, we are recording the activity of single hippocampal neurons in the monkey during the performance of tasks known to be affected by hippocampal damage, and in related tasks[13]. In this paper we describe the activity of single neurons in a task in which the monkey must remember whether an object has been seen before in a particular place. The performance of object–place memory tasks has been shown to be impaired by hippocampal (but not by amygdala) damage in the monkey[3,4,12]. The object/place memory task used here required a memory for in which of two positions on a video monitor screen a given stimulus had appeared in the preceding few seconds.

It is notable there there have been very few previous investigations of hippocampal neuronal activity in primates. However, in one previous investigation Watanabe and Niki reported[22] that 14.7% of hippocampal neurons responded during the performance of a delayed spatial response task in monkeys. In a delayed spatial response task, a stimulus is shown on, for example, the left, there is then a delay period, and after this the monkey can respond, by for example touching the left stimulus position. The 6.4% of hippocampal neurons active in the delay period of such a task[22] could reflect preparation for the response to be made, or they could reflect memory of the position in which the stimulus was shown. As the type of memory to which the activity of these hippocampal neurons was not determined in this previous study[22], we investigated this by comparing the responses of the same hippocampal neurons during the performance of delayed spatial response and object–place memory tasks. In an object–place memory task, the monkey cannot prepare his response in the delay period, because it is not until the time that the match stimulus is shown that he can determine whether it is the same object in the same position, and therefore whether to make a response. Thus neurons active in the delay period of this task cannot reflect the particular response to be made in this task. Thus by recording from a hippocampal neuron with a differential response in the delay period of a delayed response task, it is possible to investigate whether it reflects memory of the stimulus position, or preparation of the response, by determining whether it responds in the delay period of the object–place memory task. If it does not, then it is likely that such a neuron reflects preparation for the spatial motor response required in the delayed response task, and that the encoding of spatial responses or spatial response memory is one aspect of hippocampal function.

MATERIALS AND METHODS

The object–place memory task

In the object–place delayed-match-to-sample memory task, the monkey had to remember the position in which he had seen a sample stimulus. On each trial, following a 0.5-s tone to enable the monkey to fixate a video monitor, a sample stimulus was shown in one of two positions, left or right, on the video monitor. There was then a delay period, which was usually 2 s. If the same stimulus was shown in the same position in the match part of the stimulus trial, then the monkey

could lick a tube in front of his mouth to obtain fruit juice. If a different stimulus was shown in either position, or the same stimulus was shown in the different position, then the monkey had to withold licking the tube, otherwise he obtained a taste of aversive saline. A new stimulus was used for the sample for each trial. The computer sequenced the trials randomly, with the probability of reward set to 0.5, and the probability of the different types of non-match trials set equal to each other. The task was completely computer-controlled, to ensure that no influence by the experimenters on the monkey's behavior or on the neuronal activity was possible. The computer switched the stimuli on and off for each trial, and synchronized its data collection so that the stimulus was turned on at the start of the 21st bin of a 100-bin peristimulus time histogram. The stimuli were displayed 30 cm from the monkey on a color video monitor which subtended 12 degrees at the retina, and were positioned either 3 degrees to the left or 3 degrees to the right of the center of the screen. The stimuli were squares divided into quadrants, with each quadrant having a randomly allocated color for each new stimulus. The resolution of these images was 256 pixels wide by 256 pixels high with 256 colors. The stimuli were created on a PDP11 computer and loaded into the AED512 video framestore. The task was thus a delayed-match-to-sample object–place memory task with trial unique stimuli and asymmetrical reinforcement. It should be noted that two-dimensional stimuli displayed on a memory screen were always used (although the generic name used for this task is 'object–place' because in some earlier studies in the literature real objects rather than stimuli presented on a monitor were used).

The delayed spatial response task

This was a delayed response task with trial unique stimuli. The stimuli were of the same type as those used in the object–place memory task. The monkey had to press a central key in order to start a trial. This turned on a 0.5-s tone, during which the monkey was able to start fixating the monitor, and then the sample stimulus was switched on on one side for 1 s. After the sample stimulus, there was a delay period of 2 s. The monkey had to keep depressing the central (observing response) key throughout the sample and delay periods, otherwise the trial was aborted with a warning sound, and the onset of the next trial was delayed for 5 s beyond the normal 5–10 s intertrial interval. After the end of the delay period, the same stimulus reappeared in both left and right positions on the screen, and the monkey could stop depressing the central key and press the key on the side on which the sample stimulus had been seen previously. The 3 response keys were situated immediately below the video monitor. If the monkey pressed the key on the side on which the sample had been shown, then for each press he received fruit juice through the lick tube. There was sufficient time for approximately 3 rewards to be obtained if the monkey was already looking at the video monitor when the match stimuli appeared. (This procedure ensured that the monkey regularly maintained fixation of the monitor screen [see Rolls et al.[18]]. Trials with poor fixation as shown by recordings of the electro-oculogram [EOG] were discarded from the analysis.) If he pressed the key on the incorrect side, then he obtained the taste of saline. It should be noted that the sample stimulus and delay parts of this task were identical (apart from the observing response) to those of the object–place memory task, enabling the activity of the neuron to be directly compared in the sample and delay periods of these tasks.

Other tasks

The monkeys were also trained to perform a visual discrimination task, which was run as a control to ensure that any results obtained were not due to obtaining reinforcement, licking for fruit juice, etc. If a circle – the positive discriminative stimulus (S +) – appeared on the monitor, the monkey could lick to obtain a fruit juice reward, and if a square of the same area and luminance – the negative discriminative stimulus (S –) – appeared, the monkey had to withhold licking in order to avoid aversive hypertonic saline. A 0.5-s signal tone (400 Hz) preceded the presentation of the stimulus, and if the monkey was fixating correctly before the stimulus appeared, he had suf-

ficient time to perform the discrimination and obtain multiple licks of the fruit juice tube in the short (1.0 s) period in which the stimulus was on. This procedure was designed to ensure fixation of the stimuli[18], and was also used in the serial object–place memory task. The order of presentation of the stimuli was randomized. The EOG recordings confirmed that this procedure resulted in consistent fixation of the stimuli. The only other task on which the monkeys were trained was a serial recognition task[17], in order to provide evidence on whether any neurons active in the object–place memory task might be responsive on the basis of the novelty as compared to the familiarity of visual stimuli, independently of any spatial component to the task. It was found (data in preparation), that 2.4% of hippocampal neurons did respond differentially in the serial recognition task to novel and familiar stimuli. However, these neurons were not differentially active in the tasks described in this paper, and are not considered here further.

Recording techniques

The activity of single neurons was recorded with glass-insulated tungsten microelectrodes (after Merrill and Ainsworth[6], but without the platinum plating) in both the left and right hippocampal formations and the parahippocampal gyri (areas TF and TH) of two rhesus macaque monkeys (*Macaca mulatta*) (weight 3.0–6.5 kg) seated in a primate chair using techniques that have been described previously[15]. (The monkeys were trained on the tasks described above, and in addition knew a conditional spatial response task[9], and a multiple object–place memory task[16]. The recordings in these monkeys were made only in the areas just noted.) The monkeys had been implanted under thiopentone sodium anesthesia with stainless steel holders on which an adaptor could be fitted for the later daily recording sessions. The action potentials of single cells were amplified using techniques described previously[18], converted into digital pulses using the trigger circuit of an oscilloscope, and analyzed on-line using a PDP11 computer. The computer collected peristimulus rastergrams of neuronal activity for each trial and displayed, printed and stored each trial, as well as computing the peristimulus time histogram by summing trials of a given type. To facilitate latency measurements, the cumulative sum distribution was calculated from the sum peristimulus time histogram. For each trial the number of action potentials occurring in a 500-ms period (and a 250-ms period) starting 100 ms after the stimulus onset was printed. This period was chosen because the neurons studied responded to visual stimuli with latencies which were typically 100 ms or more, and the monkeys consistently fixated the stimuli for more than 500 ms. Fixation of the stimuli was confirmed using permanently implanted silver/silver chloride electrodes for EOG recording. The EOG recordings provided eye position with an accuracy of 1–2 degrees within each trial, and were sampled by the computer every 10 ms and saved with the action potentials for each trial.

X-radiographs were used to locate the position of the microelectrode on each recording track relative to permanently implanted reference electrodes and bony landmarks such as the posterior tip of the sphenoid bone[1]. The position of cells was reconstructed from the X-ray co-ordinates taken together with serial 50-μm histological sections stained with Cresyl violet which showed the reference electrodes and micro-lesions made at the end of some of the microelectrode tracks.

Treatment of results

For each cell, measures of responses were calculated from the total number of action potentials occurring on each trial during the sample stimuli, delay period, and match stimuli. *t*-tests were then performed on the responses of each cell to the left and right positions during the sample, delay, and match periods, using data from between 13 and 48 trials of each type. In the figures, the mean firing rate and its standard error are shown, calculated for trials with correct performance. (The monkeys' performance was typically at 90% or better correct, but if error trials did occur, the neuronal responses were analyzed separately to provide evidence on whether the neuronal activity recorded was locked to the motor responses made.) Cells were classified as showing differential responses if the *t*-test was significant at the

0.05 level, but for most of the cells described here with differential responses, the differences were significant at beyond the 0.01 level.

The latency of neuronal responses, or the differential latency of the neuronal response, that is, the latency at which it fired significantly differently for left as compared to right, was determined using cumulative sum and running mean statistics. The cumulative sum[23] was calculated online, using 18 prestimulus bins as the reference. The point at which the slope of the cusum changed was taken as the latency. Running mean *t*-tests, which compared the mean number of neuronal spikes in 18 prestimulus bins with the mean number of spikes in 2, 3, 4 or 5 poststimulus bins, were performed over the sums of trials of any one condition, over the difference of the sums of trials of two conditions, or over the cumulative sums of these arrays of values.

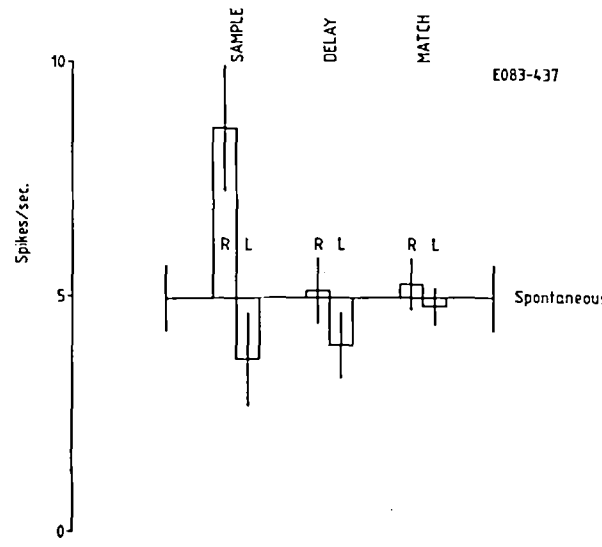

Fig. 1. Histograms representing the firing rates for the sample, delay and match periods during the object–place task. This single neuron recorded from the TF-TH area of the parahippocampal gyrus showed significantly higher activity to the right sample stimulus. The baseline from which the histograms are plotted is the mean spontaneous firing rate ± S.E.M.

RESULTS

Object–place memory task

The activity of 600 neurons was recorded during the performance of the object–place memory task in two monkeys. Similar results were found in the 4 hemispheres from which recordings were made. Of the neurons analysed, 181 (30%) showed some alteration of firing rate in the task. Twenty-seven (4.5%) neurons showed differential activity to the different conditions in the task. The response properties of the 23 (3.8%) neurons which responded differently when objects were shown in left as compared to right positions on the screen in the sample, delay, or match periods are described first. The responses of most (68%) of the hippocampal formation neurons which responded in this task consisted of an increase of firing rate. The mean spontaneous firing rate of these neurons was 8.0 spikes/s, and the mean rate during the response was 15.3 spikes/s. For the 32% which responded by decreasing their firing rate, the mean spontaneous rate was 19.6, and the mean rate during the response was 12.7 spikes/s.

An example of how a single parahippocampal (TF-TH area) neuron responded in the object–place memory task is shown in Fig. 1. This neuron fired more when an object was shown on the right than on the left during the sample period. The neuron did not respond during the match period, so that its activity did not reflect just the presentation of a stimulus on the right, but rather the fact that a novel stimulus had been presented on the right in a task in which the monkey had to remember both what the sample stimulus was, and where it had been shown.

The parts of the task in which the 23 neurons with differential right/left responses in the task showed the differential activity are indicated in Fig. 2A. Thirteen neurons responded differentially in the sample period. These differential neuronal responses to stimuli presented on opposite sides cannot be related to any behavioral response being prepared by the monkey, for it is not until the period in which the match/nonmatch stimulus is shown that the behavioral response can be determined. Consistent with this evidence that the activity of these neurons reflects spatial information about stimuli is that 8 of these also responded differentially in the match period (see Fig. 2A).

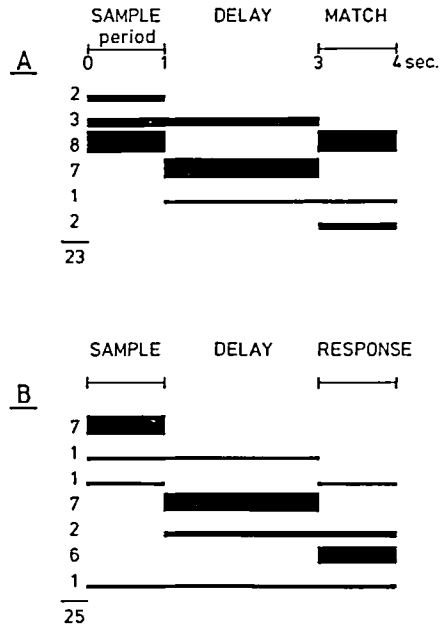

Fig. 2. A: representation of the parts of the object–place memory task in which different hippocampal neurons showed differential activity (as determined by a *t*-test) for stimuli presented on the left as compared with those presented on the right. The numbers of hippocampal neurons with differential activity in each part of the task are indicated by the numbers at the left and by the thickness of the horizontal bars. B: representation of the parts of the delayed response task, illustrating the numbers of differentially responsive neurons over the various periods in the task.

Eleven of the neurons tested in the object–place memory task responded differentially in the delay period (see Fig. 2A). These differential neuronal responses to stimuli presented on opposite sides cannot be related to any behavioral response being prepared by the monkey, for it is not until the match period that the behavioral response can be determined. Nor can these differential neuronal responses reflect spatial sensory information, for the stimuli were not visible in the delay period. These neurons thus show differential activity in a period in which the monkey must remember the spatial position of stimuli. Three of these neurons with activity in the memory period started to show their differential activity while the sample stimulus was being shown (see Fig. 2A).

Eleven of the neurons tested in the object–place memory task responded differentially in the match period (see Fig. 2A). Eight of these also had differential responses in the sample period, consistent with the evidence that the activity of these neurons reflects spatial information about stimuli as noted above.

Of the 23 neurons with differential responses to stimuli in different spatial positions, in 12 cases the neuronal response was greater to the left, and in 11 to the right.

Two neurons responded significantly differently to novel as compared to familiar stimuli. For one of these neurons, this difference between the response to a novel and to a familiar stimulus was found irrespective of the side on which the stimulus was shown, and for the other neuron the novel-familiar difference occurred only on one side. The latter neuron thus required a combination of information about the stimulus (whether it was novel or familiar) and about the position in which the stimulus was seen.

A number of further examples of neurons with comparable place specificity were found in a variation of the object–place memory task in which the sample stimulus was the same as the match on any one trial, and the monkey had to respond when the position of the sample and the match stimuli on a trial was the same. Of 92 neurons tested, 4 displayed differential right/left spatial responses of the kind already described above. One of these cells responded differentially to position during presentation of the sample stimulus. One responded to one side during the match period, another to one side during both sample and match periods, and a final neuron responded when the match stimulus corresponded to the sample. The results in this task confirm the results described above.

None of the left–right differential responses of these neurons could be accounted for by reinforcement (although 4 neurons were found which were simply response-related), since reward could be obtained following both left and right trials. Further, these differential responses to stimuli in different spatial positions could not be explained by reward or by movements required in the task such as the initiation of licking, as shown by measurements of firing rate made during the performance of the visual discrimination task in which the same licking response was required and the same reinforcement was given.

The neurons which did not have differential spatial responses in this task, but which showed some change in activity during the task, did this for example during the tone period. Analyses of the responses of other hippocampal neurons in other tasks are given elsewhere[9,16].

Delayed spatial response task

The activity of 436 neurons was recorded during the performance of the delayed spatial response memory task in two monkeys. Of these neurons, 186 (42.6%) were active in the task. Twenty-six (6%) neurons responded differentially to the different conditions of the task. The response properties of the 25 (5.7%) neurons which responded differently when stimuli were shown in the left as compared to the right position on the screen in the sample, delay, or response periods are described first. The responses of most (66%) of the neurons which responded in this task consisted of an increase of firing rate. The mean spontaneous firing rate of these neurons was 11.1 spikes/s, and the mean rate during the response was 23.5 spikes/s. For the 34% which responded by decreasing their firing rate, the mean spontaneous rate was 24.8, and the mean rate during the response was 15.4 spikes/s.

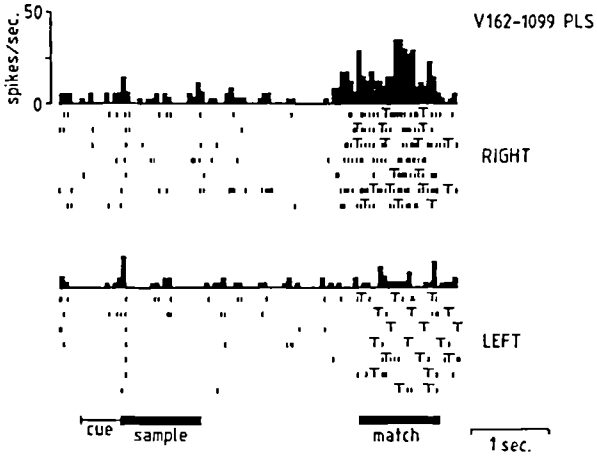

Fig. 3. Rastergrams and peristimulus time histograms of the firing of a neuron recorded from the CA1 field of the hippocampus during the delayed spatial response task. The neuron showed little activity during the sample and much of the delay periods, but fired differentially towards the end of the delay and during the match period when the monkey was required to respond to the right side. Left and right trials were run in pseudorandom order but have been separated into right (top of figure) and left (bottom) trials for the purposes of presentation. Note that the neuron continued to respond although the monkey failed to elicit the behavioral response (see middle trial of upper series).

Rastergrams and peristimulus time histograms of the activity of a single hippocampal (CA1 field) neuron in the delayed response memory task are shown in Fig. 3. This neuron fired more at the end of the delay period and during the match period after a sample stimulus had been shown on the right than on the left.

Of the 25 neurons with right–left differential responses in the task, 10 responded differentially in the sample period (see Fig. 2B). One of these also responded differentially in the match period, one other responded differentially in the delay period, and one other responded differentially in the sample, delay and match periods.

Eleven of the neurons tested in the delayed response task responded differentially in the delay period (see Fig. 2B). (This includes the two just noted.) Two of the 11 neurons responded differentially in both the delay and the match periods. An example of a neuron showing a significant differential response only during the delay is shown in Fig. 4.

Ten of the neurons tested in the delayed response task responded differentially in the match period, including the 4 noted above (see Fig. 2B).

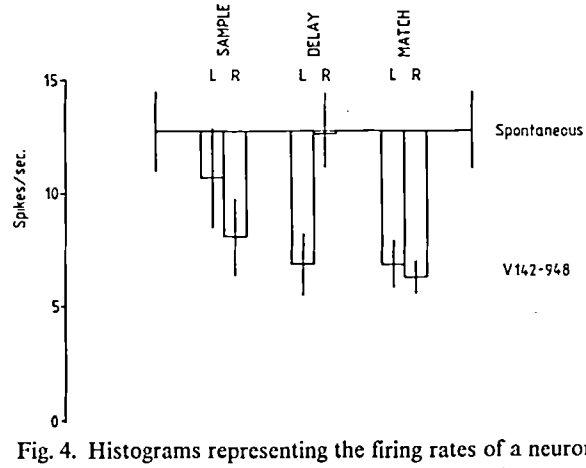

Fig. 4. Histograms representing the firing rates of a neuron recorded from the dentate gyrus during the delayed response task. The neuron showed a decrease in firing from the baseline spontaneous level during most periods of the task except during the delay following the presentation of a stimulus on the right hand side.

Of the 25 neurons with differential spatial responses, in 9 cases the neuronal response was greater to the left, and in 16 to the right.

None of the left–right differential responses of these neurons could be accounted for by reinforcement (although one neuron of the total sample responded only to reinforcement), since as noted above for the object–place task, reward could be obtained following responses to both left and right sides.

Comparison of the activity of single neurons in the two tasks

Of the 16 neurons with differential activity in the object–place memory task and/or delayed response tasks which were investigated during the performance of both tasks, only 8 had differential activity in both tasks. Further, only 3 neurons showed a response in the two tasks which was consistent (such as a response during the left sample period). The other 4 neurons which responded in both tasks had responses which were not consistent across the tasks. For example, one neuron responded more to right sample trials in the object–place memory task, and more to left trials in the delay and response periods of the delayed response task. Thus although both tasks engaged hippocampal function, the particular neural systems activated in the hippocampal formation were different for the two tasks.

The sites at which these neurons were recorded are shown in Fig. 5. (The results from the 4

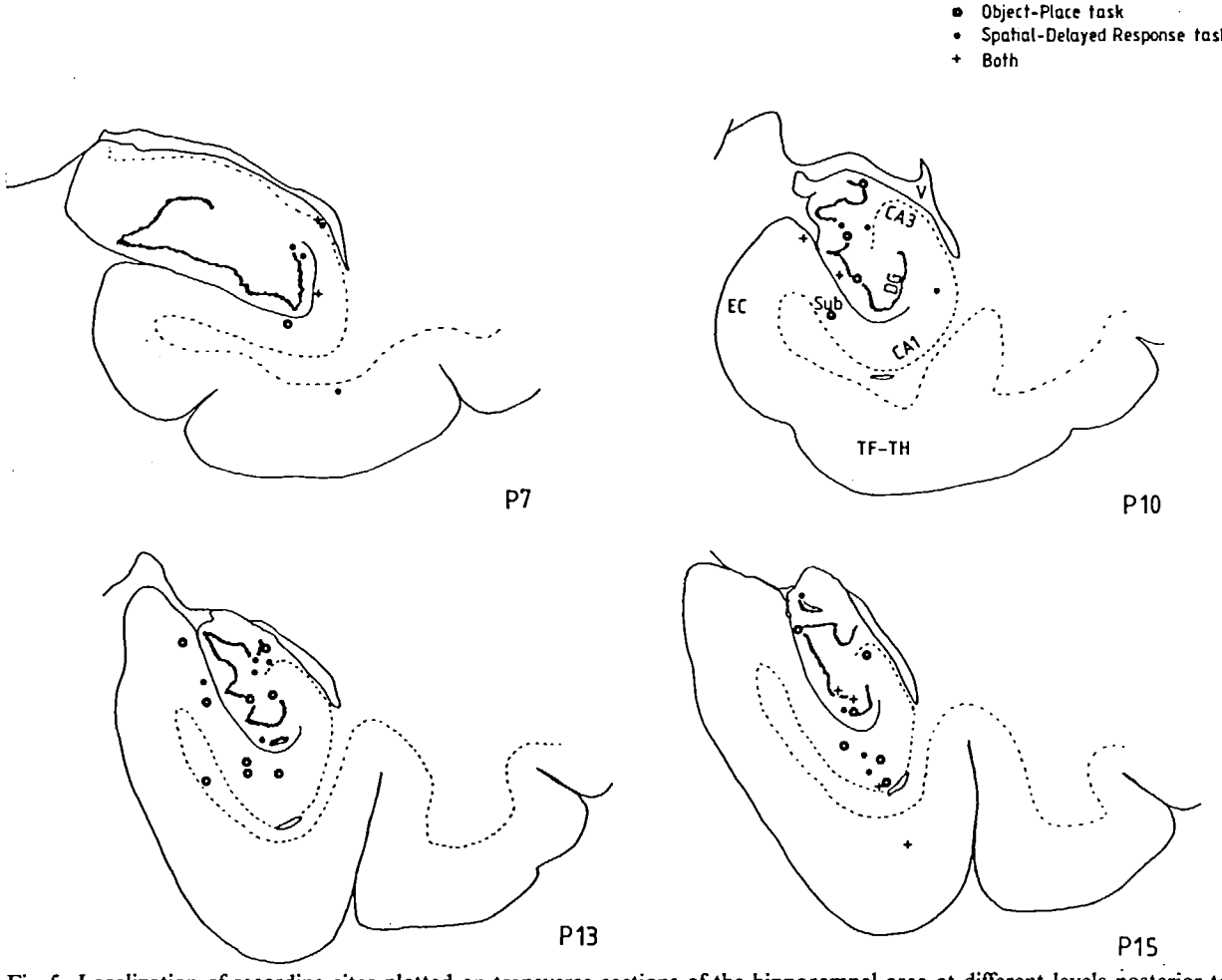

Fig. 5. Localization of recording sites plotted on transverse sections of the hippocampal area at different levels posterior to sphenoid reference (posterior 7–15 mm). DG, dentate gyrus; CA3, CA1, two subfields of the hippocampus; Sub, subiculum; EC, entorhinal cortex (anterior levels only); TF-TH, area in parahippocampal gyrus; V, lateral ventricle.

hemispheres were combined, as similar types of responsive neuron were found in all 4 hemispheres sampled. Similar numbers of neurons were sampled in both hemispheres. The number of neurons sampled in monkey 1 was 792 and in monkey 2 85.) The majority of the responsive neurons were in the dentate gyrus or the CA fields, but some were in the parahippocampal gyrus. The activity recorded from the hippocampus proper could not easily be classified in terms of the 'theta' versus 'complex spike' types found in subprimate species such as the rat and rabbit[11]. This was in agreement with electroencephalographic studies in the primate showing a paucity of theta-like activity (e.g. Halgren et al[5]., in human). A wider survey, including the present study, was made of the types of activity observed in over 1500 neurons of the hippocampus and hippocampal formation. Only 22 neurons had activity of the complex spike type, and none of the differentially responsive neurons in the present study described above were of this type: 163 neurons showed bursting activity, each burst containing between 2 and 6 spikes; 4 (8%) responsive neurons showed this type of activity. Neurons with complex spike and bursting activity were almost exclusively confined to the hippocampus proper. The majority of neurons (1111) showed irregular firing activity (ranging from 3 to 60 Hz firing rate), and a proportion of these (241) showed occasional bursts of activity; 33 (67%) responsive neurons displayed this type of activity; 79 neurons had rhythmic or phasic activity, showing clusters of short duration action potentials. Each cluster typically lasted between 100 and 350 ms of 100 Hz firing, with an inter-cluster interval of 100–400 ms. Many of these neurons were located in the dentate gyrus; 2 (4%) responsive neurons belonged to this category. Finally, 167 neurons displayed fairly regular firing activity that was neither bursting nor clustered, and 10 (20%) responsive neurons were of this type.

DISCUSSION

The findings in the object–place memory task show that some neurons in the hippocampal formation of the monkey can respond differentially with respect to the place in which a stimulus is shown. These were the neurons which responded to the sample and/or match stimuli more when they were shown on one side than on the other. The results were obtained in a task impaired by hippocampal damage in which the monkey must remember the positions in which particular stimuli have been seen[3,4,12]. The performance of a similar task is impaired in humans with right temporal lobe damage[20]. Although only a small number of hippocampal neurons (3.8%) responded differently when stimuli were shown on the left and on the right, these statistically significant responses did not arise by chance for the following reasons. First, if a neuron had spatial responses at all, then these were much more likely to be evident in two or more of the four periods (sample, first part of the delay period, second part of the delay period, and match period) than would be predicted if the statistically significant results were distributed randomly across the cells and periods (Fisher exact probability test comparing the distribution found with that predicted from a binomial distribution, $P < 0.004$). Second, the statistically significant spatial responses were far more likely to occur in the sample period than in the other periods (18 vs 4, 8, and 4 in the other periods) than would be predicted if differences were occurring by chance (Chi-square = 16.3, df = 3, $P < 0.001$). Third, if a neuron had a differential response to one side in one period of the task, it was more likely to have it to the same than to a different side in another period of the task (7 vs 1, binomial test, $P = 0.03$). Moreover, the spatial responses described are being confirmed in a subsequent study in which, interestingly, given that a wider range of space is being investigated, a higher proportion of neurons with spatial responses is being found[16].

In the object–place memory task, it is extremely unlikely that the neuronal activity reflected preparation of a motor response or a mediating motor response, for the following reasons. First, when a stimulus was shown in a given position, the monkey could not code for any motor response at that time, but had to wait until the match period before he could determine whether to make response. Mediating motor responses in

such a situation are unlikely. Second, the response which was made by the monkey in the task was a non-spatial response, that of licking a tube in front of the mouth, so that the differential responses of the neurons to the different positions in which stimuli were shown could not have been due to a spatial response requirement of the task. Third, the majority of the neurons did not respond differentially to a novel as compared to a familiar object–place combination, so that differential motor responses are not likely to account for the differential responses of the neurons. Fourth, the responses of the neurons could still occur when a stimulus was shown in a particular position when the monkey was performing the task incorrectly or was not performing the task, providing further evidence that the responses of these neurons are not related simply to motor responses. Fifth, the neurons did not respond in a visual discrimination task in which the same motor response (of licking), and the same reinforcement (fruit juice) was given, providing further evidence that the motor response required or the reinforcement obtained cannot account for the responses of these hippocampal formation neurons. Sixth, given that in the delayed response task the response can be prepared in the delay period, but that the majority (13/16) of neurons with differential responses in the object–place memory task did not have differential activity during the response preparation period in the delayed response task, it is unlikely that the neuronal responses in the object–place task were related to response preparation. Seventh, if the activity of these neurons reflected eye movement responses which were made to the side of the sample stimulus during the sample period, and the task was solved by the monkey holding his eyes (or attention) in that position and then performing a match/non-match for the stimulus in that position (cf. Brown[2], who analysed hippocampal neuronal activity in a Konorski task with non-spatial stimuli), then differential activity should have been found in the delay period as much as in the sample period, whereas in fact differential spatial activity was much more common in the sample than in the delay period (see Fig. 2). (Further, the EOG recordings showed that in the delay period the eyes were not held stationary looking at the place where the sample had been shown.) These points provide evidence that these neurons in the monkey code for the place in which a stimulus is shown, rather than the response required to a particular spatial position.

Most of these neurons responded similarly to a stimulus on one side whether it was the sample or the same or a different stimulus in the match period. Thus these neurons appeared to reflect primarily information about the side or position in space in which a stimulus was located. However, some of the neurons responded when a stimulus was novel in a particular position (that is, during the sample stimulus [or during the match period if it was a different stimulus on the side to which that neuron responded best]), but responded less when the same stimulus was shown on the same side. Although the response latencies of the neurons were not always sufficiently short for them to play a part in the performance of the object–place memory task, in some cases their responses did precede the responses made by the monkey in the object–place memory task. This, together with the evidence that hippocampal lesions impair object–place memory tasks[3,4,12], is consistent with the view that some of these neurons provide information useful in performing this task. The neurons with responses to stimuli in one place may provide a representation of space useful when a combination of a particular position and a particular stimulus must be detected. Neurons with responses which depend on whether a stimulus has been seen recently in a particular location reflect the combination of position and novelty, and a population of neurons with information of this type distributed across it would contain the information necessary to perform the object and place memory task for which the hippocampus is required. Indeed, confirmation that such neurons are present in the hippocampus is being obtained in current investigations in which the monkey must remember for multiple places in space, whether or not he has seen a particular stimulus in that place before[16].

These neurons may be compared with 'place' cells recorded in the rat hippocampus (see refs. 8 and 9). The 'place' cells which have been de-

scribed 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. The exact information which leads 'place' cells in the rat to respond, and the nature of any mapping which may be being performed by the hippocampus, has not been easy to define. It should be possible in the monkey, by requiring different eye fixation positions in the object–place memory task, and by moving the monitor screen relative to the monkey's body, to determine whether the spatial neurons in the monkey reflect information coded in retinotopic, egocentric, or allocentric space. The finding that a relatively small proportion (3.8%) of hippocampal neurons in the monkey had activity which responded differentially to the spatial position of stimuli in the object–place memory task does not necessarily imply that spatial cells are less common in the monkey than in the rat hippocampus, for the spatial positions in the monkeys' environment which were tested in the present experiments were limited to positions on a screen in front of the monkey, whereas in the rat larger areas of space were investigated as the rat locomoted and explored[10,11].

Consistent with the results of Watanabe and Niki[22], some neurons with differential activity in the sample, delay or response parts of the delayed spatial response task were found. Although only a small number of hippocampal neurons (5.7%) responded differently when stimuli were shown on the left and on the right, these statistically significant responses did not appear to arise by chance. For example, if a neuron had differential responses to the two sides in the delayed response task, then these were much more likely to be evident in two or more of the four periods (sample, first part of the delay period, second part of the delay period, and response period) than would be predicted if the statistically significant results were distributed randomly across the cells and periods (Fisher exact probability test comparing the distribution found with that predicted from a binomial distribution, $P < 0.004$).

It is of interest that most neurons that were tested in both the object–place and delayed response tasks did not show similar activity in the two tasks. In particular, of the 16 neurons with differential activity in at least one of the tasks which were tested in both tasks, only 3 neurons showed activity which was consistent in both tasks. This is an indication that largely different populations of hippocampal neurons have activity (differentially) related to these tasks. This was true even though in the two tasks the sample stimuli and delay periods were operationally identical, with the exception that the monkey depressed the observing response key in the delayed response task. A major difference of the delayed response task is that the response can be prepared, although it must not be performed, as soon as the sample stimulus is shown. Thus it is likely that the neurons active in the delay of the delayed spatial response task (in both the experiment described here and that of Watanabe and Niki[22]) reflected the movement about to be performed, rather than memory of the stimulus and its position. They could reflect a mediating response (such as leaning to one side), or they could reflect preparation of the response about to be performed, or they could be related to holding in memory the response which it was required to perform after the delay. Thus these neurons appear to be related to spatial response encoding. In contrast, the largely different population of hippocampal neurons with activity related to position in the object–place memory task appear to have activity related to that task not because a response is being prepared, but because a stimulus has been shown on one side or is being remembered as having been shown on one side.

In this paper we have thus shown that primate hippocampal neurons with spatial responses in a delayed spatial response task reflect primarily spatial response encoding, and have shown in addition (using the object–place memory task) that there is a separate population of hippocampal neurons with responses related to the positions of stimuli in space, and to the memory of those stimulus positions. The functions of the primate hippocampus is spatial response encoding and in spatial stimulus encoding and memory are taken up elsewhere[9,16,14,14a].

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