The Hippocampus and Space: Are There "Place Neurons" in the Monkey Hippocampus?

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Since the findings by Scoville and Milner (1957), the hippocampus has been presumed to have an important central function in memory. As they reported, amnesic patients with medial temporal lobe damage did not show deficits in every kind of memory or learning ability. It is now accepted by many investigators in the field of memory and learning that memory can be divided into several subtypes, and damage of the hippocampus does not impair all kinds of memory. One critical aspect of this forum seems to be the determination of suitable memory subtypes. As Nadel described in the lead article, which is based on the cognitive map theory, involvement of spatial factors is a strong candidate for this rule because spatial memory is reported to be severely impaired by hippocampal damage, not only in the rat, but also in the monkey (Parkinson et al., 1988; Gaffan and Harrison, 1989) and human (Smith and Milner, 1981; 1989). The existence of "place neurons" in the rat is presumed to provide strong evidence for foundation of the cognitive map theory (O'Keefe and Nadel, 1978). Thus, if one is to discuss whether spatial cognitive mapping is also applicable to the primate hippocampus, it becomes critical to determine if there are neurons that change their firing rates in particular locations in the environment. Although investigation of this is very rare in humans, because it must be limited to clinical examination of the results of accidental damage, more complete evaluation is possible in the monkey. The first study of this subject has recently been reported (Ono et al., 1991). Although there are still far less data than there are for the rat, we believe it will be useful for us to describe some of our results here.

Locale Neurons in the Monkey Hippocampus

During the past several years we have used single neuron recording to investigate involvement of the monkey hippocampus in central information processing. During taxonomic tests (Fig. 1Bc) of the monkey hippocampus, we tested the presentation of stimuli extempore from various directions. To our surprise, we found direction-related responses to stimulation under conditions in which the amygdala had not previously responded (Ono et al., unpublished observations). Examples of these hippocampal responses are shown in Figure 1.

As a consequence of these results, we devised a complete experiment with more rigid controls (Tamura et al., 1990). In this experiment on the monkey hippocampus, we recorded single neuron activity during presentation of various visual or auditory stimuli from several directions around the monkey without changing the location of the monkey (Fig. 1A). This verified the existence of neurons with space-related activity changes (space-related neurons). About 10% of the neurons sampled in the hippocampus were space-related, that is, these neurons responded strongly when visual or auditory stimuli were presented from unique directions around the monkey, but responded less or not at all if the stimuli were presented from other directions (Fig. 1Ba,b). Some of these neurons were stimulus-selective (Fig. 1Bc) and others were not. These space-related neurons were classified into two types, egocentric and allocentric neurons, identified by rotating the animal around a fixed axis. Responsiveness of egocentric neurons maintained constant bearing from the monkey, and that of allocentric neurons remained in place in the environment independent of the monkey's position. An example of the responses of an allocentric space-related neuron is shown in Figure 1Ba,b. This neuron responded strongly to human movement in the right anterior direction from the monkey, but not to the same stimulus in any other direction (spatial-selectivity) (Fig. 1Ba). It also did not respond to other stimuli from right anterior direction (stimulus-selectivity) (Fig. 1Bc). Responsiveness to walking at the right anterior remained fixed in the environment and did not follow the monkey when the monkey was rotated 45° to the left (Fig. 1Bb).

The number of space-related neurons in the primate hippocampus (about 10%) seemed to be very small compared to the number (more than 50% of complex-spike cells) in the rat hippocampus (O'Keefe, 1990). It was considered that one factor influencing these proportions might be the ability of the rat to move freely in space and change its location, whereas the movement of the monkey was severely restricted. To overcome this, at least in part, we developed a movable cab by means of which the monkey could change its location by its own manipulation (Fig. 2A). By using this device, we were able to find about 40% of monkey hippocampal neurons (place-related neurons) that were presumed to correspond to the place neurons reported in the rat hippocampus (Ono et al., 1991). Responses of a typical place-related neuron are shown in Figure 2B. The monkey could have moved to any location within a 2.5 × 2.5 m area, but for practical reasons the actual positions allowed were limited to the stations P0–P24 (Fig. 2Ab). This provided enough loci, with enough space between loci, to allow analysis of the spatial preference of neuronal activity. If the room lights were on and the monkey could see the experimental room, the activity of the neuron depicted in Figure 2B consistently increased in and around locations P8–P10 when the monkey moved the cab from any direction to these locations (Fig. 2Ba). When the room lights were off, the activity of this neuron was still place-related, although it was to a much lesser extent than with the lights on (Fig. 2Bb). These place-related neurons also showed spatially differentiated egocentric or allocentric responsiveness.
to visual stimuli, some with and some without stimulus-selectivity.

DISCUSSION

Space-related neurons and place-related neurons

Consistent with previous studies (Watanabe et al., 1985; Cahusac et al., 1989; Miyashita et al., 1989; Rolls et al., 1989), our data indicate that some monkey hippocampal neurons are certainly involved in central processing of spatial information. We have not found and have seen no reports of neurons, except for hippocampal neurons, that code space nonegocentrically.

The ratio of place-related neurons among the neurons sampled in the hippocampus was much greater (about 40%) than the ratio of space-related neurons (about 10%). This indicated that the ability of the monkey to control its own change of location may be an essential factor in the responsiveness of hippocampal neurons. When the monkey can change its position itself, more nonegocentric spatial information processing must be required than when it does not move. Since more neurons related to a process might be presumed to become active when an animal is required to use the process, it seems reasonable that the hippocampus should be considered important for nonegocentric spatial information processing.

In many reports of rat place neurons, influence of spatial parameters (e.g., direction and velocity of the animal) on the activity of place neuron was emphasized, but the influence of nonspatial parameters (e.g., kinds of stimulation and biological significance) was not emphasized. Although we have not yet completely analyzed the effects of nonspatial parameters on the activity of place-related neurons in the monkey hippocampus, our impression is that the responsiveness of place-related neurons depends not only on spatial, but also on nonspatial parameters. We also found that some hippocampal neurons responded differentially to only nonspatial aspects of stimuli, such as familiarity–unfamiliarity and reward–aversion (Ono et al., 1990; Tamura et al., in press). Recently, Wiener et al. (1989) reported that when the same hippocampal neurons in a rat were tested in a spatial navigation task and a simultaneous-cue odor-discrimination task, many neurons with spatial correlates in the place task also had striking behavioral correlates (including nonspatial correlates) when the rat performed the odor task in the same environment. These data suggest that hippocampal processing may not be limited to the representation of spatial location, although the representation of spatial location is apparently a major function.

Place neurons and retrieval of place

O'Keefe and Speakman (1987) concluded that the hippocampal spatial map system is a memory system and that this internally represented memory of the environment, in combination with information about movement, permits the updating of place-field representations and the correct unfolding of both neural activity and navigational behavior. If we think of the memory function of the human hippocampus in terms of spatial orientation, the conclusion of O'Keefe and Speakman is reasonable and interesting, since spatial disorientation occurs in patients with hippocampal damage. If we think about our own memory concerned with space, one can envision various places without going to or envisioning the route to such places. Is this kind of place retrieval also reflected in the place-field representation formed by the population of hippocampal place neurons? To our knowledge, there are no positive data at this level of unit recording. That is, if we assume that responsiveness of a place neuron in a spatial memory task would reflect retrieval of a place in the form described above, and that the animal could retrieve "that place" when it is in another place (start box, or on the way to "that place," for example), the neuron must respond when the animal is in other places as well as in "that place." However, the place neurons increased their firing rate in the spatial memory task only when the animal was in "that place" (the firing field of the neuron). Neurons that we recorded, although we could not identify them specifically as memory neurons, displayed a similar characteristic (Fig. 2B): they fired in "that place" only, and not during travel toward "that place." Of course, we do not yet know how an animal solves the problems of spatial memory, nor how the animal retrieves "that place" when it is in another place, but we think it is very interesting and important to know whether the place neurons are directly involved in such kinds of place retrieval, or if they are driven by different populations of neurons that are involved in this function.

CONCLUSION

Here, we return to the original theme of the forum, "Is the hippocampal formation preferentially involved in spatial behavior?" We think the answer to this question has to be "Yes." However, as we suggested above, we do not think that hippocampal processing is limited to the representation of spatial location.

There are still many unsolved, interesting problems. For example: (1) Does the hippocampus have limited or unlimited (or virtually unlimited) capacity for spatial memory? (2) How does the hippocampus handle the problem of capacity of spatial memory? (3) Are there place neurons in the human hip-

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Fig. 1. (A) Schema of early experimental situation. Directions of visual and auditory stimulation sources. Various kinds of visual and auditory stimuli were presented from several directions in succession around the monkey. Solid lines, visual stimulation; broken lines, auditory stimulation. (B) Allocentric space-related neuron responses. (Ba) Spatially differentiated responsiveness to human walking. Note strong responses at right anterior. (Bb) Spatially differentiated responsiveness to human walking after the animal was rotated 45° left from initial position. Note responsiveness to human walking at right anterior (Ba) remained fixed in the environment when the monkey was rotated (Bb). (Bc) Comparison of responses to various visual or auditory stimuli. This neuron tested with 16 visual stimuli and 12 auditory stimuli (not all results shown) and responded to visual or auditory stimuli, such as walking or standing up, apple approaching, clap, or crash. M, monkey; histograms in B, mean ± SD of three 1.0-second firing rate measurements after stimulation.
Fig. 2. (A) Schema of later experimental situation. (Aa) Movable monkey cab. Monkey, restrained painlessly in a stereotaxic apparatus by a previously prepared, surgically attached head holder, sat in a chair in the cab (0.7 \times 0.8 \text{ m}, 0.85 \text{ m} \text{ high}). Front, left, and right walls of the cab half-mirrored, rear wall made of steel and equipped with two speakers. Five bars and indicator light-emitting diodes on lower half of cab front. Double half-mirrored shutter (15 \times 15 \text{ cm}) in upper half of cab front wall opened to deliver food. Lamp in food bay to show object in bay. The cab is on a turntable rotatable \( \pm 180^\circ \). OSC. oscillator. (Ab) Range of linear movement of cab. Monkey cab motorized to move in 2.5 \times 2.5 \text{ m} \text{ space}. The monkey usually faced in +Y direction in the spatial moving task. Entire apparatus in experimental shielded room (5 \times 6 \text{ m}). Monkey could see room environment through right, front, and left half-mirrored walls if room was illuminated. Locations where monkey could get reward and was to remain until next trial were numbered P0–P24. Monkey shown here in position P24. Each session consisted of a block of 30 trials, starting from P0 and returning to P0. One route and sequence shown by arrows, but alternative routes and sequences were also used. Tele, telemeter; Contr, controller for spatial moving task; ATAC, minicomputer ATAC 3700; Oscillo, oscilloscope; Stereo, rat experiment apparatus; Refr, refrigerator. (B) Examples of neural activity of a place-related neuron. (Ba) When room lights were on, neural activity increased in and around P8–P10 during spatial moving task trials. (Bb) When room lights were off, activity increase of this neuron was still limited to P8–P10, but magnitude was less. Responses: firing rate of place-related neuron as function of location within field. Calibrations: 3 spikes/s.
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ARE THERE "PLACE NEURONS" IN THE MONKEY HIPPOCAMPUS? (4) What computations are performed in brain areas closely related to the hippocampus (parahippocampal cortices, septal area, etc.)? (5) How are the place neurons placed in the circuit in the hippocampus when an animal experiences a novel environment? (6) Are the questions related to this problem limited or unlimited (or virtually unlimited)?

References


