

Spatial Information Processing between Hippocampus and Prefrontal Cortex: a Hypothesis Based on Anatomy and Physiology

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The hippocampus and prefrontal cortex are regarded as the highest-order association cortices. The hippocampus has been proposed to store "cognitive maps" of external environments, and the prefrontal cortex is known to be involved in the planning of behavior, among other functions. Considering the prominent functional roles played by these structures, it is not surprising to find direct monosynaptic projections from the hippocampus to the prefrontal cortex. Rhythmic stimulation of this projection patterned after the hippocampal EEG theta rhythm induced stable long-term potentiation of field potentials in the prefrontal cortex. Comparison of behavioral correlates of hippocampal and prefrontal cortical neurons during an 8-arm radial maze, working memory task shows a striking contrast. Hippocampal neurons exhibit clear place-specific firing patterns, whereas prefrontal cortical neurons do not show spatial selectivity, but are correlated to different stages of the behavioral task. These data lead to the hypothesis that the role of hippocampal projection to the prefrontal cortex is not to impose spatial representations upon prefrontal activity, but to provide a mechanism for learning the spatial context in which particular behaviors are appropriate.

The prefrontal cortex (PFC) is known to be involved in higher cognitive functions such as working memory, reasoning, and planning of future actions. It can be regarded as the highest-order association cortex, receiving highly processed inputs from other association cortices and various subcortical structures. It is at the top of the action/reaction cycle, generating an appropriate sequence of future behaviors based on external sensory inputs, internal needs, and memory (Fuster, 1989). In addition the PFC is presumably important for planning of spatial navigation. Movement in space is an essential characteristic of all animal species, and proper spatial navigation is extremely important for survival. The PFC must have access not only to immediate spatial information, but also to spatial memory of an external environment, provided that it is not novel, to generate the most efficient navigational strategy.

The hippocampus has long been thought to be important for spatial memory. Damage to this structure generates a devastating impairment in spatial memory without much affecting animal's ability to navigate in space based on immediate sensory information (O'Keefe

and Nadel, 1978). Also 'place cells' have been found among hippocampal neurons; O'Keefe and Dostrovsky (1971) discovered that pyramidal cells in the rat hippocampus elevate their activities in small restricted regions, or places, of a given environment, but mostly silent outside, so they dubbed these neurons 'place cells'. Based on this finding and other behavioral studies, O'Keefe and Nadel (1978) proposed that the hippocampus encodes 'cognitive maps' of external environments, which is arguably the most influential theory about the hippocampus in this century. The theory has by no means been proven, but the subsequent studies suggest in general that the proposition is largely valid. Many researchers now believe that the hippocampus stores allocentric spatial information, or cognitive maps, of external environments, and the stored information is retrieved by other brain structures to generate appropriate spatial navigation behaviors in a familiar environment.

The above considerations about the PFC and the hippocampus suggest strongly that there has to be a mechanism for the PFC to retrieve spatial information stored in the hippocampus to plan a proper sequence of behaviors, especially spatial navigation, at a given location. Anatomical studies suggest that this assumption is indeed true and the retrieval is done in a rather direct way: the hippocampus sends direct monosynaptic

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projections to the PFC (Swanson, 1981; Ferino et al., 1987; Barbas and Blatt, 1995). This is an exceptional connection pattern for the hippocampus, as most hippocampal inputs from and outputs to other cortices go through the entorhinal cortex (Witter, 1993). The existence of the direct projection suggests that there is something special about the hippocampal and PFC interactions. Retrieval of hippocampal spatial memory for planning of future actions is probably extremely important for survival of an animal so that an exceptional projection system has evolved.

The hippocampal projection to the PFC is not static, but shows synaptic plasticity. High frequency stimulation of the ventral CA1/subiculum induces long-lasting enhancement of field potentials in the PFC (Laroche et al., 1990). Further, synaptic enhancement requires activation of NMDA receptors (Jay et al., 1995). This result suggests that a Hebbian learning process (Hebb, 1949) is involved in hippocampal-PFC interactions so that they undergo dynamic adjustments. The projections mostly arise from the ventral CA1 and subiculum in the rat, and place cells are found among ventral CA1 pyramidal cells (Jung et al., 1994; Poucet et al., 1994), suggesting that hippocampal spatial information is dynamically incorporated into the PFC. In the present study I tried to confirm long-term potentiation (LTP) in the hippocampal-PFC projection. I especially tested induction of LTP by rhythmic stimulation patterned after hippocampal theta EEG, which has been shown to be optimal for the induction of hippocampal LTP (Larson et al., 1986), after positioning a stimulating electrode in the ventral CA1 cell body layer. Also behavioral correlates of hippocampal versus PFC neurons were compared. Finally, based on these data, a hypothesis is proposed for the role of the hippocampal-PFC projection.

Materials and Methods

Long-term potentiation

Stimulating and recording electrodes were constructed with teflon-coated stainless steel wire (75 μ m, I.D.). The final impedance of stimulating and recording electrodes was 100-300 K Ω m measured at 1 KHz. Fischer-344 rats (male, n=6) were deeply anesthetized with sodium pentobarbital (Nembutal, 40 mg/kg), and a stimulating electrode was lowered to the ventral CA1 cell body layer (6.3 mm posterior and 5.5 mm lateral to bregma) which was identified based on injury discharges. All surgeries described in the present study were conducted according to the N.I.H. guidelines. Recordings were made in the ipsilateral PFC in response to 100-400 μ A, 160 μ S bipolar stimulus pulses. Burr holes were drilled and 3 stainless screws were implanted in the skull for ground, reference and stimulus return lead. Responses were amplified 500x, band-pass filtered at 1-3 KHz, digitized at 20 KHz and stored on

an 80486 personal computer for off-line analysis.

Experiments were started following adjustment of the recording electrode to obtain maximal field potentials and a 30 min waiting period for stabilization of the responses. After a stable baseline was obtained for at least 10 min, two episodes of theta burst stimulation (TBS, 10 bursts repeated at 5 Hz with each burst consists of 4 pulses at 100 Hz) were applied at 1 min intervals, and low frequency (0.1 Hz) stimulation was resumed for minimum of 1 h. More than 10 % increase in the peak amplitude at 30 min following the second TBS was considered as successful LTP. The data are expressed as mean \pm s.e.

Single unit recording

Conclusions and examples in the present study were based on behavioral correlates of single units recorded in the hippocampus and PFC of behaving rats for the past 7 years including previously published results (Jung and McNaughton, 1993; Jung et al., 1994, 1995, 1998; Jung, 1995). Experimental procedures have been already described (Jung and McNaughton, 1993; Jung et al., 1994). Briefly, 'stereotrodes' or 'tetrotrodes' (McNaughton et al., 1983; Recce and O'Keefe, 1989; Wilson and McNaughton, 1993) were implanted in the desired region of the brain and unit signals were recorded via an FET source-follower headstage mounted on the animal's head. Output signals from the headstage were filtered between 0.6-6 KHz, digitized at 32 KHz, and stored on 80486 personal computers for future off-line analysis. The data were transferred to a SUN 4 workstation and units were isolated by projecting the 4 channel relative amplitude data two dimensionally, and applying boundaries to each subjectively apparent unit cluster (McNaughton et al., 1983; Jung et al., 1994). The animal's location and head direction were monitored by tracking two sets of infrared light emitting diodes mounted on the recording headstage.

When well isolated and stable units were found, recordings were made while the rat was performing an 8-arm radial maze, working memory task. For this task, the rat had to visit the end of each arm not previously visited on the current trial to obtain chocolate milk reward. Initially, a random set of 4 arms was available to the rat. Once the first 4 arms were visited, all 8 arms were made available. This procedure prevented the adoption of sequential visitation strategies by the animal. In most cases, the rats ran 10 trials in 20-30 min.

Results

Long-term potentiation

Stimulation of the ventral CA1 evoked field potentials in a widespread area of the PFC as shown in Fig. 1. There was a restricted region of the PFC in which the

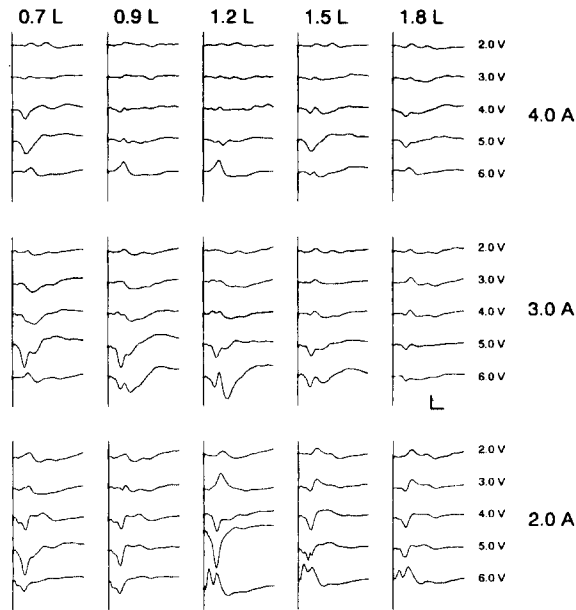


Fig. 1. Distribution of evoked field potentials in the PFC in response to stimulation of the ventral CA1 cell body layer. A stimulating electrode was lowered in the ventral CA1 cell body layer (6.3 mm posterior and 5.5 mm lateral to bregma, and 3.0 mm ventral from the brain surface) and a 400 μ A, 160 μ S bipolar stimulus pulses were delivered. The distribution of evoked field potentials was mapped in the PFC by systematically changing recording locations. Each column represents a lateral distance from bregma in mm (e.g., 0.7 L=0.7 mm lateral to bregma) and three panels represent anterior-posterior distances from bregma (e.g., 4.0 A=4.0 mm anterior to bregma). The rows within each panel indicate depth of the recording electrode (e.g., 2.0 V=2.0 mm ventral to the brain surface). Each trace is an average of 10 responses. Stimulus parameters were kept constant throughout the experiment. As shown, stimulation induced field potentials in widespread areas of the PFC. Calibration: 20 ms by 1 mV.

maximal field potential was induced, however. The latency to peak of the negative potential was about 20 ms, which is similar to the previous report (Laroche et al., 1990).

Two episodes of TBS induced stable LTP following initial depression in 4 out of 6 animals. The average magnitude of potentiation measured at 30 min following TBS was $16.5 \pm 3.0\%$ above baseline. An example of LTP is shown in Fig. 2.

Single unit activity

Almost all principal neurons of the hippocampus were either silent or exhibited characteristics of 'place cells' in a given environment on the 8-arm radial maze. In contrast, inhibitory neurons in each subfield fired at high rates all over the maze with much lower spatial selectivity. Basic spatial firing characteristics were similar among granule cells and pyramidal cells in Ammon's horn. In general, place cells in each subfield had quite specific firing fields, were not dependent on animal's direction in an open field, were not affected by animal's ongoing behavior, and were anchored to remote visual cues. Some differences were found, however, in such indices as the number of firing fields

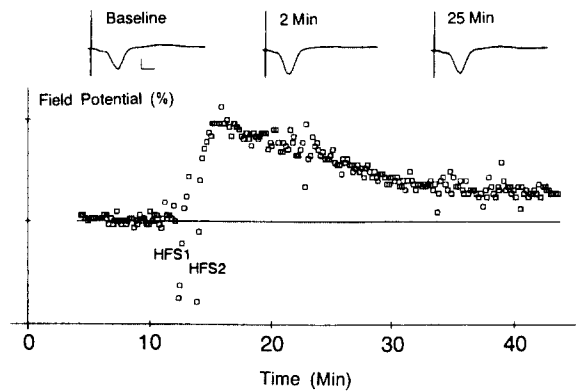


Fig. 2. Long-term potentiation of the hippocampal projection to the PFC. The experiment was performed with the same subject as in Fig. 1. The stimulating location and parameters were identical as in Fig. 1 except that the current was reduced to 250 μ A. The recording was made in the prelimbic area. Top: Field potentials during baseline and 2 min and 25 min after the second high frequency stimulation are shown. Bottom: Abscissa and ordinate represent time (min) and peak amplitude of field potential (% control). Baseline recordings were made for 10 min at 0.1 Hz stimulation frequency and 2 episodes of high frequency stimulation (HFS1 and HFS2) were delivered at 1 min interval. Theta burst stimulation was used for high frequency stimulation, which consists of 10 bursts repeated at 5 Hz with each burst containing 4 pulses at 100 Hz. High frequency stimulation induced initial depression followed by long-lasting potentiation. Calibration: 10 ms by 1 mV.

and spatial information content (Jung, 1995). Some examples of place cells recorded in the rat dorsal hippocampus are shown in Fig. 3.

Firing patterns of the medial PFC neurons were quite different from those of hippocampal neurons. Few neurons exhibited arm-specific firing patterns on the 8-arm radial maze. Almost all units showed radially symmetrical firing patterns. When a unit is active on a certain part of a maze arm, it was usually active on the corresponding parts of all other arms. PFC neurons showed diverse behavioral correlates, but

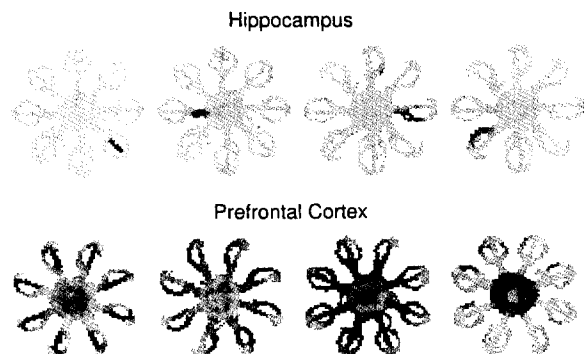


Fig. 3. Comparison of hippocampal and PFC unit activity. Each plot represents a spatial firing rate map of a hippocampal or PFC neuron on an 8-arm radial maze. The cumulative trajectory of an animal is depicted by light gray and firing rate is indicated in gray scale, so that dark gray indicates high firing rate at that location. Rats were allowed to run about 10 trials of a spatial working memory task in 20-30 min. (A) Place cells recorded in the dorsal hippocampus. Most hippocampal place cells exhibited strong spatial bias toward particular arms. (B) Medial PFC units. As shown, PFC unit activities were correlated to distinct phases of the task. Example units were correlated to (from left to right) approaching reward sites, staying at reward sites, coming back to the central platform and intertrial intervals. Note that unit activities are more or less radially symmetrical

most units were correlated to distinct phases of the task (Jung et al., 1995, 1998). Some examples of PFC neurons are shown in Fig. 3.

Discussion

Radial mazes have been widely used for allocentric spatial memory tasks (Olton, 1987). The beauty of a radial maze is that all arms are radially symmetrical, therefore it is extremely difficult to keep track of visitation of particular arms based on other than external cues. This is particularly true for the rat which is innately a 'spatial' animal (O'Keefe and Nadel, 1978). To solve the spatial working memory task used in the present study, an animal has to remember visited versus unvisited arms within a current trial to obtain reward. Then radially symmetrical neural activity does not contain spatial information required to solve the present task, since no information about a specific arm is available. Spatial information is conveyed by neural activity biased toward particular arms. Comparison of hippocampal and PFC neural activity on the 8-arm radial maze demonstrates a striking contrast. As shown in Fig. 3, hippocampal neurons fired at specific locations, often on only single arms of the maze. In contrast, almost all PFC neurons fired at distinct phases of the task without much spatial bias toward a particular arm. Thus hippocampal neurons convey information about 'where on the maze', whereas PFC neurons about 'what stage of the task', respectively, as a population. This pattern of single unit activity is consistent with the previous behavioral studies that suggested that the hippocampus and PFC are important for encoding spatial memory and 'rules' of a task, respectively (Winocur and Moscovitch, 1990).

There are massive monosynaptic projections from the ventral CA1 to the PFC in the rat (Swanson, 1981; Ferino et al., 1987). Place cells have been found in the rat ventral CA1, although average spatial selectivity is lower than that in the dorsal counterpart (Jung et al., 1994; Poucet et al., 1994). Also, long-term potentiation can be induced at the hippocampal-PFC projection (Fig. 2; Laroche et al., 1990). These results suggest that hippocampal spatial information is incorporated into the PFC and this may be exhibited as place-specific firing of PFC neurons. Contrary to the prediction, however, activities of PFC neurons are correlated mainly to distinct phases of the task, not to spatial locations (Fig. 3). It is therefore reasonable to conclude that the hippocampal projection does not impose spatial representations on the PFC.

What is the role of the direct hippocampal projection to the PFC? It is not unreasonable to assume that allocentric spatial information is incorporated into the PFC via this projection. Considering the role of the PFC in planning of behavior, one role for this projection may be to enable the animal, after learning a task, to generate appropriate behaviors based on spatial

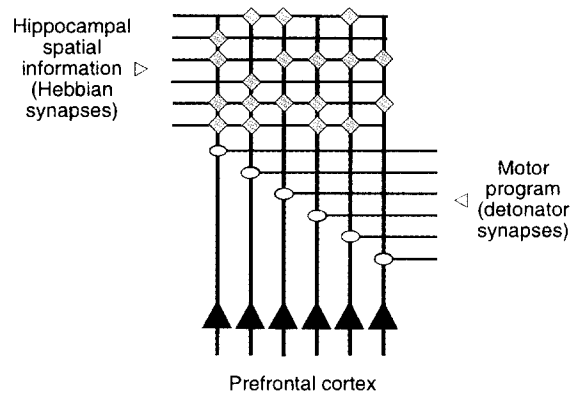


Fig. 4. A hypothetical neural network in the PFC that may implement association between spatial locations and generation of appropriate behaviors. The hippocampal projection to the PFC supports NMDA receptor-dependent LTP (Jay et al., 1995). If the PFC receives motor programs via detonator synapses, spatial information will be associated with generation of particular behaviors by modifying synaptic weights of the hippocampal-PFC projection. After learning, the animal can generate appropriate behaviors solely based on spatial information.

information. Fig. 4 shows a hypothetical neural network in the PFC that may mediate this function. The hippocampal-PFC projection supports NMDA receptor-dependent LTP (Jay et al., 1995), thus the synapses are modified following the Hebbian learning rule. Assume that the PFC receives detonator synapses that carry motor programs. 'Detonator' means that its activity induces unconditional discharge of the post-synaptic neuron. Assume that an animal always makes, say a turning behavior at location A. Then synapses carrying spatial information of 'location A' onto PFC neurons, that organize 'turning behavior', will be strengthened following the Hebbian learning rule. If the synaptic weights are enhanced enough to drive PFC neurons without detonator inputs, then the animal can generate 'turning behavior' solely based on spatial information of 'location A' that is provided by the hippocampal projection.

Further investigations are required to elucidate the exact role of the direct hippocampal projection to the PFC and the mode of hippocampal-PFC interactions. This information may contribute to understanding general principles of hippocampal interactions with other cortical areas, an important subject for understanding how the brain organizes memory. Simultaneous recordings from the hippocampus and PFC are expected to generate particularly valuable information. A recent development of a parallel unit recording technique (Wilson and McNaughton, 1993) is encouraging for this reason.

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