

Firing Characteristics of Deep Layer Neurons in Prefrontal Cortex in Rats Performing Spatial Working Memory Tasks

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Single cells were recorded with 'tetrodes' in regions of the rat medial prefrontal cortex, including those which are targets of hippocampal afferents, while rats were performing three different behavioral tasks: (i) an eight-arm radial maze, spatial working memory task, (ii) a figure-eight track, delayed spatial alternation task, and (iii) a random food search task in a square chamber. Among 187 recorded units, very few exhibited any evidence of place-specific firing on any of the behavioral tasks, except to the extent that different spatial locations were related to distinct phases of the task. Furthermore, no prefrontal unit showed unambiguous spatially dependent delay activity that might mediate working memory for spatial locations. Rather, the cells exhibited diverse correlates that were generally associated with the behavioral requirements of performing the task. This included firing related to intertrial intervals, onset or end of trials, selection of specific arms on the eight-arm radial maze, delay periods, approach to or departure from goals, and selection of paths on the figure-eight track. Although a small number of cells showed similar behavioral correlates across tasks, the majority of cells showed no consistent correlate when recorded across multiple tasks. Furthermore, some units did not exhibit altered firing patterns in any of the three tasks, while others showed changes in firing that were not consistently related to specific behaviors or task components. These results are in agreement with previous lesion and behavioral studies in rats that suggest a prefrontal cortical role in encoding 'rules' (i.e. structural features) or behavioral sequences within a task but not in encoding allocentric spatial information. Given that the hippocampal projection to this cortical region is capable of undergoing LTP, our data lead to the hypothesis that the role of this projection 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.

Introduction

The human prefrontal cortex (PFC) is thought to play a key role in higher cognitive functions such as working memory, reasoning and planning of future actions (e.g. Goldman-Rakic, 1987, 1996; Fuster, 1989; Kolb, 1990). Lesion (e.g. Goldman and Rosvold, 1970; Goldman *et al.*, 1971), reversible cooling (e.g. Shindry *et al.*, 1994) and metabolic mapping (e.g. Friedman and Goldman-Rakic, 1994) studies of prefrontal cortical regions in nonhuman primates support the idea that this structure is involved in processing multisensory information for sequences of behaviors held in working memory. Most of the detailed information concerning the neural circuit mechanisms underlying PFC function in monkeys has come from recording studies in which single-cell firing rates have been examined during performance of delayed response tasks. Cells in the dorsolateral PFC have been found that increase their firing rates, for example, during the delay component of such a task (i.e. 'delay cells'), and

some cells can be related to complex visuospatial components or identity of stimuli within the task (e.g. Fuster and Alexander, 1971; Niki, 1974a,b; Niki and Watanabe, 1979; Funahashi *et al.*, 1989; Wilson *et al.*, 1993). Prefrontal cortical lesions in rats also cause behavioral disruptions in performance of tasks which require memory for the temporal order of spatial locations (i.e. Sakurai and Sugimoto, 1985; Kesner and Holbrook, 1987; Olton *et al.*, 1988; van Haaren *et al.*, 1988; Chiba *et al.*, 1994; Kolb *et al.*, 1994). Furthermore, prefrontal multi-unit firing rates are selectively altered during the delay period before a 'go' signal in rats that have been trained to perform a delayed go/no-go alternation task (Sakurai and Sugimoto, 1986).

While single-cell data from prefrontal cortical regions in rats are scarce, the behavioral correlates of cells in the hippocampus – a structure to which the PFC is reciprocally connected (in rats, e.g., Swanson, 1981; Jay and Witter, 1991; in monkeys, e.g., Goldman-Rakic *et al.*, 1984; Barbas and Blatt, 1995) – are rather well studied (O'Keefe, 1976). A striking characteristic in common between the firing dependence of hippocampal cells in rats and monkeys is the relation to space, either in absolute coordinates (Ono *et al.*, 1993; Wilson and McNaughton, 1993; Eifuku *et al.*, 1995) or where the monkey directs its gaze or attention (Rolls and O'Mara, 1995). In the present study, it was of particular interest to examine potential spatial correlates of PFC cell activity, taking into consideration its interaction with the hippocampus. Thus, the present experiment was designed to record in PFC areas that received input from the hippocampus, in rats that were free to perform two different spatial working memory tasks: an eight-arm radial maze, spatial working memory task, and a figure-eight track, delayed spatial alternation task. An additional task was included which involved random food search in a square chamber to assess whether spatially selective firing would occur during spatial foraging behavior.

A number of possible behavioral correlates for rat prefrontal cortical cells were hypothesized. One obvious candidate is delay or 'working memory' cells, which have clearly been observed in nonhuman primates. Although the relationship between the rat medial PFC and the primate PFC is debated, it has been suggested that the rat medial PFC is more homologous to the monkey medial PFC than to dorsolateral PFC (Preuss, 1995), where delay cells have often been recorded. Lesion of the rat medial PFC, however, does result in deficits in spatial delayed response tasks (e.g. Kolb *et al.*, 1974; Eichenbaum *et al.*, 1983). Therefore, the hypothesis that spatial working memory cells might be found in the rat medial PFC is not, *a priori*, unreasonable. Hypothetically, a working memory cell on a task such as the eight-arm maze would exhibit activation upon entry to a specific arm, and would remain active for the duration of the trial. Behavior and lesion studies suggest a second potential

correlate for rat medial PFC cells: the cells may encode the rules of a task (Winocur and Moscovitch, 1990). Thus it was also proposed that some rat prefrontal cortical cells may fire in association with specific task components. Third, because hippocampal place cells send monosynaptic projections to the medial PFC in the rat (e.g. Ferino *et al.*, 1987), there may be a direct transfer of allocentric spatial information from the hippocampus to the PFC reflected in PFC cell firing characteristics. In fact, studies employing selective lesions suggest that the medial wall of the rat PFC is preferentially involved in the spatial aspect of PFC functions (Eichenbaum *et al.*, 1983). Thus, potential spatial correlates of the prefrontal cells were also assessed. Because this study was exploratory, in the sense that few single-cell recording studies have been conducted in the rat, we also attempted to identify any other behavioral correlates that consistently occurred in relation to specific behaviors performed by the rats in the different tasks.

Materials and Methods

Subjects

Four male, retired-breeder Fischer-344 rats (aged 9 months) were handled and gentled for at least 1 week upon arrival and then food deprived to ~80% of their *ad libitum* body weight. Lights were on in the colony room between 10.00 and 22.00 h, and experiments were conducted between 07.00 and 17.00 h.

Behavioral Tasks

Rats were trained and tested on three different behavioral tasks. The first task was an eight-arm radial maze, spatial working memory task. The maze arms were 58 cm long and 5.7 cm wide (Fig. 1A). 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 four arms was available to the rat. Once the first four arms were visited, all eight arms were made available. This procedure prevented the adoption of sequential visitation strategies by the animal. In most cases, the rats performed 10 trials (at least one visit to each arm on each trial) in 20–30 min.

The second task was a delayed spatial alternation on a figure-eight track. The dimensions of the track were 100 × 70 × 9 cm (Fig. 1B). The figure-eight track was placed on top of the eight-arm radial maze which was covered by a wooden board. Starting from the center of the track, the animal had to visit alternately two reward sites (L1 and R1 in Fig. 1B) to obtain chocolate cake sprinkles. The animal had to come back to the center from a reward site before visiting the other reward site. The return route was different from the approach route (Fig. 1B). The rat consumed the chocolate at the maze center for ~3–7 s, which served as a delay period. An error was defined by a consecutive visit to the same reward site. Errors were not reinforced. The animal ran a minimum of 15 trials consecutively for each recording session (i.e. 30 choices).

The third task involved random foraging in a square chamber (68 × 68 cm, 51 cm in height; Fig. 1C). The chamber was placed on the same wooden board covered with fresh paper on top of the eight-arm radial maze. The chamber walls were dark gray in color and one was covered with a white card (Muller *et al.*, 1987). The task began with chocolate pellets randomly distributed on the chamber floor. Once all the pellets were retrieved by the rat, more were supplied, so that the animal foraged more or less continuously for 20–30 min.

All behavioral tests were performed in the same room. The testing room was sound-attenuating, moderately illuminated and rich in visual cues. The recording equipment was located outside the testing room. In the light of recent evidence that initial disorientation can cause place cells to exhibit rotational instability from trial to trial (Jung and McNaughton, 1993; Knierim *et al.*, 1995) the rats were introduced into the testing room without intentionally disorienting them.

Electrode Implantation

Surgeries were conducted according to NIH guidelines. The rats were deeply anesthetized with Nembutal (40 mg/kg) and two separate

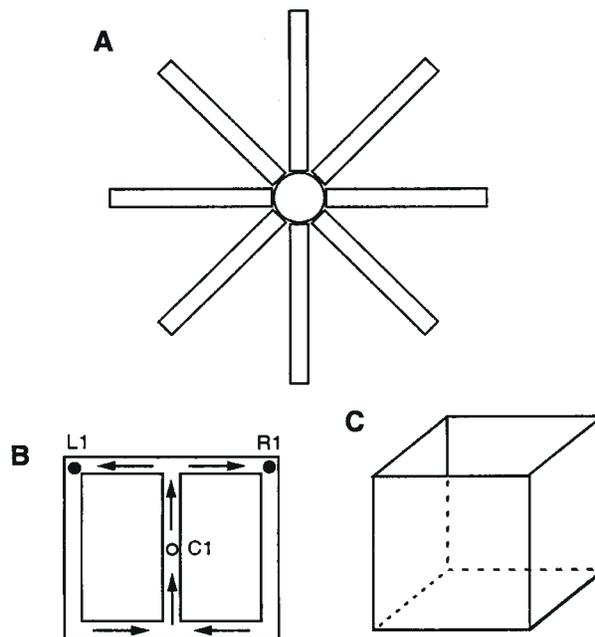


Figure 1. Behavioral tasks. (A) Eight-arm radial maze, spatial working memory task. The rat was trained to visit the end of each arm not previously visited on the current trial to obtain chocolate milk reward. To prevent the adoption of sequential visitation strategies, a random set of four arms was initially available to the rat. When these four arms had been visited, all eight arms were made available. After completion of each trial (eight correct arm choices) all arms were made inaccessible so that the animal had to wait at the center platform until the next trial. The animals typically ran 10 trials within 30 min. (B) Figure-eight maze, delayed spatial alternation task. Starting from the center of the maze, the animal had to alternately visit two reward sites (L1 and R1 are closed circles, left and right goals, respectively from the center) to obtain chocolate morsels. The animal was required to come back to the center from a given reward site before visiting the other reward site. The arrows indicate the direction of travel when going to the left or right goal. The consumption period of chocolate morsels at the maze center (C1 is the center goal, open circle on the center track) served as the delay period in this task (~3–7 s). (C) Random foraging task. The animal was allowed to retrieve chocolate pellets that were randomly distributed on the floor of the chamber (68 × 68 cm, 51 cm in height). Once all the pellets were consumed by the rat, more pellets were supplied so that the animal foraged more or less continuously for 20–30 min.

microelectrode microdrives (McNaughton *et al.*, 1989) were installed on opposite sides of the skull, both aimed at the medial wall of the PFC (2.0–2.6 mm anterior and 0.6–1.3 mm lateral to bregma) at an angle 0–5° toward the midline. The recording electrodes ('tetrodes'; McNaughton *et al.*, 1983; Recce and O'Keefe, 1989; Wilson and McNaughton, 1993) consisted of bundles of four polyimide-insulated nichrome wires (H.P. Reid Co., Palm Coast, FL) twisted together and gently heated to fuse the insulation without short-circuiting the wires (40 μm o.d.). Two tetrodes were mounted together in a guide cannula (30 gauge) on the microdrive. The electrode tips were cut and gold-plated to reduce their impedance to 0.2–1.0 MΩ measured at 1 kHz. The reference electrode was made from Teflon-coated stainless steel wire (114 μm o.d.) with final impedance between 100 and 300 kΩ measured at 1 kHz. One reference electrode was implanted in each hemisphere ~1–3 mm lateral to the recording electrodes and 4–5 mm ventral from the brain surface. Seven anchor screws were implanted in the skull, one of which was used as a ground lead. The entire implant was encased in dental acrylic.

Unit Recording

Multiple single cells were recorded via an FET source-follower headstage mounted on the animal's head. Output signals from the headstage were filtered between 0.6 and 6 kHz, digitized at 32 kHz, and stored on 80486 personal computers for future off-line analysis, using Discovery tetrode acquisition software (Datawave, Inc., Broomfield, CO). The data were transferred from the PCs to a SUN 4 workstation and cluster boundaries were assigned to single cells by projecting the four-channel relative

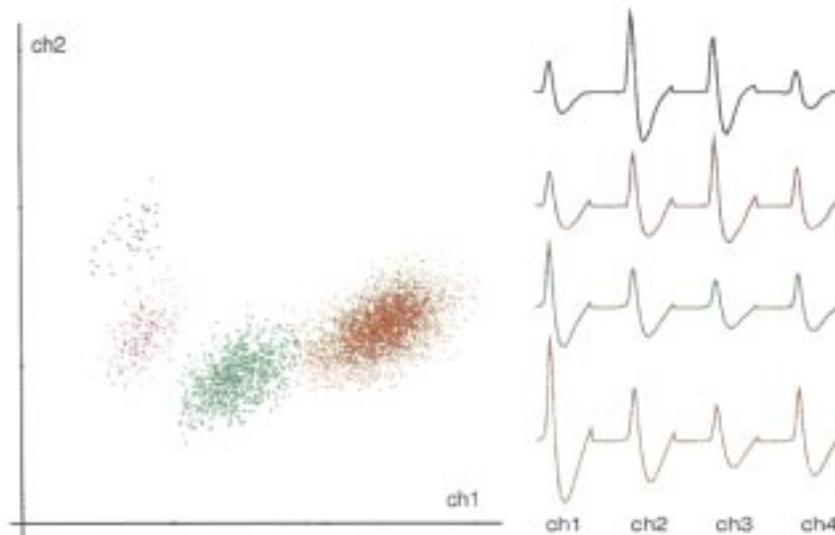


Figure 2. An example of multiple single unit recording with a tetrode. This recording was made in the rat medial PFC during 15 min of slow-wave sleep. Each point in the scatter-plot represents a signal that exceeded the experimenter-defined threshold. The *x*- and *y*-axes represent peak amplitudes of spike signals recorded by channel 1 and 2, respectively, of the four tetrode channels. As shown, individual units tend to form clusters (left, scatter plot). Average spike waveforms recorded by each channel (ch1–ch4) for each cluster are shown on the right.

amplitude data two-dimensionally (McNaughton *et al.*, 1983). Care was taken to apply the same criteria to all cells in the population. An example of a prefrontal tetrode recording is shown in Figure 2.

Two sets of infrared light-emitting diodes were mounted on the recording headstage 12 cm apart, parallel to the longitudinal body axis. The animal's location and head direction were monitored by tracking the relative locations of the large front diode array, containing eight diodes, and the small back diode array, containing only one diode, at 20 frames/s.

Electrode adjustments and baseline recordings were made in the room adjacent to the testing room. When well-isolated and stable units were found, baseline single cell activity was recorded for ~30 min while the animal was sitting quietly on a pedestal. A typical behavioral testing sequence was: 10 trials on the eight-arm radial maze working memory task; 30 choices on the figure-eight track delayed alternation task; and finally, recording sessions in the random food search task in the square chamber. In some cases ($n = 13$) the figure-eight track session was omitted. Following behavioral testing, the rat was returned to the same pedestal and post-behavior recording was made again during quiet wakeful or sleep states for ~30 min, in order to confirm stability of the recorded units. Cells that were not present in both the pre-behavior and post-behavior recording sessions on the pedestal were not included in the analysis.

Analysis

Place-specificity

Eight-arm Radial Maze. To assess spatially selective firing properties of the PFC units, spatial information content per spike (Skaggs *et al.*, 1993) was first calculated. In addition, firing rates on individual arms over multiple visits were compared using an ANOVA in order to test whether or not unit firing was evenly distributed over all eight arms. Finally, for those units whose firing showed a significant position dependence on the maze, further assessment was conducted to compare the spatial firing patterns to those characteristic of hippocampal 'place cells'.

Figure-eight Track. Spatial information content per spike was assessed as for the eight-arm radial maze. Second, firing rates on the left versus right sides of the figure-eight track were compared using an ANOVA.

Square Box. Spatial information content per spike was assessed, and then spatial firing patterns of individual units were examined for place-specific firing and comparison with hippocampal place cells.

Delay-dependent Firing and Working Memory

A careful search was made for cells that changed their firing rates during the delay interval on the radial eight-arm maze or on the figure-eight track. Such delay cells have been found in monkey PFC (e.g. Fuster and Alexander, 1971; Kubota and Niki, 1971).

Eight-arm Radial Maze. If a single cell participates in spatial working memory, then it might increase its firing rate after visitation of a particular arm and maintain that firing rate until the end of the trial. Thus, as a population, higher firing rates should be observed on the last arm in a given trial. Population firing rates on the first versus last arm were therefore compared using an ANOVA. Because comparison of firing rates on the entire arm may be a somewhat stringent test for working memory, firing rates were also calculated just for the period between entering an arm and reaching the goal on the first versus the last arm choice. Finally the animal's behavior and unit firing were examined off-line to subjectively assess possible working memory components that may have been missed by statistical analysis (see below).

Figure-eight Track. It was first determined if there were units that exhibited significantly different firing rates during the delay period (at the reward site in the center, Fig. 1B) based on the previously visited goal locations (L1 and R1, Fig. 1B) using an ANOVA. The hypothesis tested is that the animal would hold memory of the previously visited reward site (by changes in firing rates of individual cells) until the correct choice of the next goal site was made. For this analysis units were selected, based on a Student's *t*-test, that exhibited significantly changed firing rates during either of the goal-dependent delay periods on this two-choice task. Finally, those units that exhibited altered firing patterns during some portion of the delay period were further examined to test whether this activity was maintained over the entire delay period.

Other Behavioral Correlates.

Correlations between unit firing and the animal's speed, acceleration, head direction or angular velocity were calculated for the radial maze and the figure-eight track. Peri-event time histograms (PETH, time interval = 2 s, bin size = 100 ms) were constructed for the radial maze and figure-eight track sessions. For the radial maze, PETHs for nine events (one overall plus eight individual arms) were examined for each arm entry, crossing the middle of an arm in the outward direction, reaching the goal, turning inbound at the goal, crossing the middle of an arm in the inbound direction and returning to the center. PETHs for the beginnings and endings of trials were also examined. The selected events for the

figure-eight track were: returning to the central section, reaching the central reward site, leaving the central section (branch point for heading either left or right), reaching the left or the right goal (L1 and R1), crossing the middle of the side track and crossing the lower corner of the maze. Significant firing rate change associated with each event was determined by an ANOVA. Third, unit firing over time (in 250 ms bins) for each trial was constructed for both behavioral tasks. This was useful for the detection of continuously elevated neural activity for certain periods, which may not be easily detectable by PETHs. Finally, the correlation between unit firing and the animal's behavior was subjectively examined for each unit. This was done by displaying the animal's position and movement on a computer (Sun 4 SPARC station) screen in semi-real time and listening to unit firing as audio output signals through the computer's audio port, and determining whether 'significant' behavioral correlates could be detected by such examination. For the events that were analyzed with PETHs, only those that satisfied both statistical and subjective criteria were included as significant behavioral correlates.

Cells were initially examined for correlation with the animal's immediate behaviors such as speed, angular velocity, turning and head direction, and then for correlation of firing patterns with various phases of the task.

Histology

When recording was complete, an electrolytic current (50 μ A cathodal, 5 s) was applied through one of the recording electrodes. After waiting several days, the animal was deeply anesthetized and perfused with buffered 10% formal-saline while the electrode remained *in situ*. The electrodes were not removed from the brain for at least 24 h, to aid the reconstruction of electrode tracks. The brain was then removed, left in formal-saline for 3-7 days, and then transferred to a 10% formal-saline/30% sucrose solution for 3-5 days until it sank to the bottom. Sagittal sections (40 μ m) were cut on a sliding microtome and alternately stained with cresyl violet for cell bodies and with a silver stain for axons. Tracks and lesion sites were located under a light microscope.

Results

Histology

Under a light microscope, tracks and lesion sites were unequivocally identified for three of the four rats. The tissue from the fourth rat was lost due to a procedural error. The regions of unit recording are indicated in Figure 3. Recordings were made in the frontal area 2, anterior dorsal cingulate gyrus, prelimbic cortex and infralimbic cortex. These brain regions include the intended recording sites for the remaining one rat from which 20 units were recorded. All tracks traversed the deep (IV-V) layers.

Unit Classification

A total of 187 well isolated units were recorded from the PFC. Units were classified into two categories based on their baseline discharge characteristics: fast spiking cells (FSCs) and regular spiking cells (RSCs) (Connors and Gutnick, 1990). In general, FSCs had spike waveforms with large after-hyperpolarizations (unlike RSCs), and their firing rates were substantially higher than those of RSCs (Fig. 4). The latter is reflected in high-frequency components in the autocorrelation histograms and interspike interval histograms (Fig. 4). Average firing rates of FSCs and RSCs are summarized in Table 1. Twenty-one RSCs fired in bursts to various degrees, and thus may comprise a distinct cell population, although they are not analyzed separately here because they had overlapping behavioral correlates with the other RSCs.

Spatial Firing Characteristics

Eight-arm Radial Maze

The overall spatial information content (Skaggs *et al.*, 1993) for

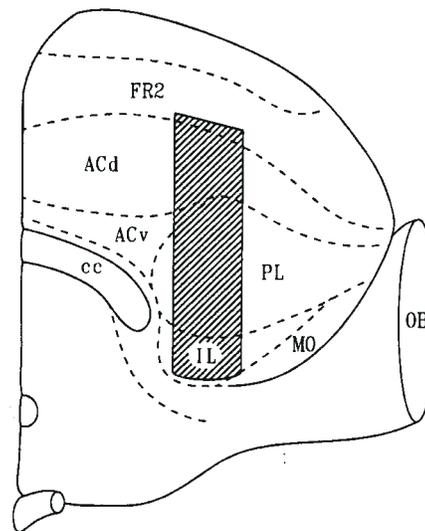


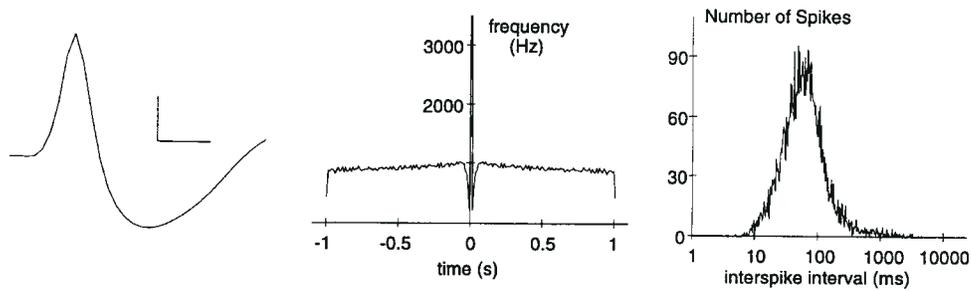
Figure 3. Recording locations. Tetrode recordings were made from the rat PFC including medial precentral area (PrCm), dorsal anterior cingulate cortex (ACd), prelimbic area (PL) and infralimbic area (IL), as indicated by the shading. All recordings were made from deep layer neurons (layer IV-V). ACv: ventral anterior cingulate cortex; MO: medial orbital cortex; cc: corpus callosum; OB: olfactory bulb.

PFC units on the radial maze was 0.31 ± 0.02 for RSCs and 0.10 ± 0.02 for FSCs (Table 1), which is lower than that of hippocampal place cells recorded with tetrodes in the dorsal hippocampus under various conditions including the eight-arm radial maze (1.09-1.54; Jung *et al.*, 1994; Markus *et al.*, 1994). Visual examination of spatial firing patterns indicated that PFC units did show spatially biased firing, but their discharge characteristics were quite different from those of hippocampal place cells. Almost all PFC units which were active on the maze fired on all eight arms (Fig. 5). This is unlike hippocampal place cells which usually fire on only one or two arms. Although some PFC units were active exclusively at the maze center (Fig. 5B), this firing rate change was related to the intertrial interval rather than to a spatial location on the maze. That is, these PFC units showed elevated firing rates only during intertrial intervals, but not during trials when the animal was crossing the maze center (Fig. 6B). Comparison of firing rates on the maze arms also indicated that only 24 units out of 187 (13%) showed significant ($P < 0.05$) arm-specific dependence of firing rates.

Discharge patterns of four PFC units were classified as spatially selective (Table 2). One unit showed quite a broad spatial bias and eight units showed specific elevation of activity on a particular arm. Two of these cells also had other behavioral correlates (Figs 5A and 7E).

Eight units showed directional bias on the maze (Table 2). Of the four units with a single conspicuous behavioral correlate, three showed higher firing when the animal was facing outward and one unit when the animal was facing both outward and in a southeastern direction at the same time. The remaining four units showed absolute directional bias and had multiple behavioral correlates. As shown in Figure 6A, directional bias of these units was quite broad, unlike head direction cells that have been found in postsubiculum and anterior or lateral dorsal thalamus (Taube *et al.*, 1990; Mizumori and Williams, 1993; Knierim *et al.*, 1995; Taube, 1995), but not unlike many head direction cells found in posterior cortex in the rat (Chen *et al.*, 1994).

Regular Spiking Cell



Fast Spiking Cell

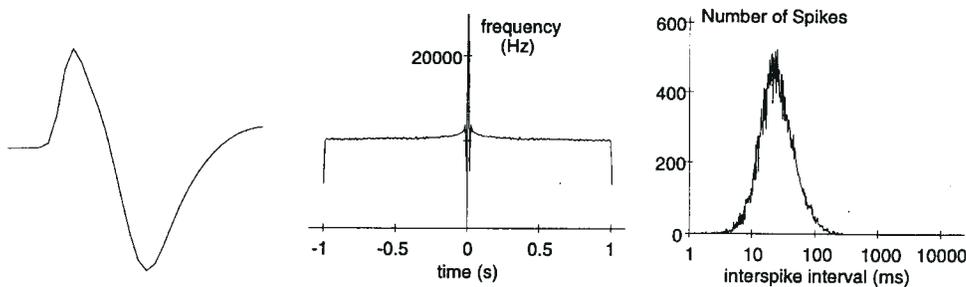


Figure 4. Classification of units. An average spike waveform, autocorrelation histogram and interspike interval histogram for a typical regular spiking cell and a fast spiking cell are shown. Regular spiking cells typically had waveforms with small after-hyperpolarizations, whereas fast spiking cells had more pronounced after-hyperpolarizations. The autocorrelation function (second column) represents the expectation density of spike discharge at times $\pm \Delta t$ given the occurrence of a spike at time 0. The ordinates represent firing rate in a time-lag interval (the number of spikes divided by the width of the interval (10 ms) expressed in Hz. It can be seen that fast spiking cells fired at much higher rates (second column), and had shorter interspike intervals (third column). Note that the x-axis of the interspike interval histogram is logarithmic.

Table 1

Number, mean rate and spatial information content of PFC neurons during different behavioral tasks

	RSC				FSC			
	Base	8-arm	F8	Chamber	Base	8-arm	F8	Chamber
Number of units	172	172	113	31	15	15	7	0
Rate (Hz)	2.07 \pm 0.16	2.21 \pm 0.21	2.34 \pm 0.26	1.83 \pm 0.49	15.62 \pm 2.20	14.56 \pm 2.17	11.50 \pm 2.42	–
Spatial information content per spike	–	0.31 \pm 0.02	0.28 \pm 0.02	0.27 \pm 0.03	–	0.10 \pm 0.02	0.14 \pm 0.04	–

RSC, regular spiking cell; FSC, fast spiking cell; base, baseline recording outside the maze room; 8-arm, eight-arm radial maze, spatial working memory task; F8, figure-eight maze delayed spatial alternation task; chamber, random food search task in a square chamber. Data are expressed in mean \pm SEM.

Figure-eight Track

The overall spatial information content of PFC units on this alternation task was similar to that on the radial maze: 0.28 \pm 0.02 for RSCs and 0.14 \pm 0.04 for FSCs (Table 1). Comparison of firing rate on the left versus right side of the track, excluding the central section, indicated that 38 out of 120 units (32%) had significantly higher firing rates on one or the other side of the track. Visual examination also revealed that a substantial portion of cells showed consistent spatially asymmetrical firing patterns (Fig. 7B,D), and at least one cell showed quite selective spatial firing (Fig. 7A).

Square Chamber

Thirty-one RSCs and no FSCs were recorded in the square chamber following recording on the eight-arm maze ($n = 13$) or the figure-eight track ($n = 18$). The average spatial information

content was 0.27 \pm 0.03 in the square chamber. Unlike hippocampal place cells, spatial location was not well correlated with discharge of PFC units in the chamber. While an animal was occupying one location, discharge of a PFC unit changed unpredictably, presumably due to changes in the internal state of the animal.

Working Memory

Eight-arm Radial Maze

It was hypothesized that a ‘working memory’ cell would be one that would increase (or decrease) its firing rate at some point during the task (i.e. after visiting a particular arm) and would maintain this change in firing rate until the end of the trial, when the memory of that arm was no longer needed. This would mean that the overall firing rate in the population of cells would tend

to be higher on the last arm than on the first arm, as more cells would be activated over the eight arm choices. Comparison of firing rates on the first versus the last arm in the present study using an ANOVA indicates that only 40 units had significantly different firing rates between the first and last arm choice (18 units increased and 22 units decreased their rates from the first to the last arm choice). Thus, contrary to the 'working memory cell' prediction, there was no tendency for the PFC units as a population to fire at higher rates on the last arm than on the first arm. Subjective examination of each of these units suggests that only two cells maintained increased firing rates after visiting one arm until end of a trial. In each case, however, continuously elevated firing was observed only for one trial, not over all trials in the session.

Figure-eight Track

ANOVA indicated that 15 out of 113 units showed differential firing during the delay period (on the central section of the maze), depending upon the previously visited goal location. Among the 15 units, only three had significantly higher firing rates during the delay period than on the rest of the maze. Two out of the three units maintained elevated firing rates for the entire delay period. Thus only two units met the criteria of a 'delay cell'. An example is shown in Figure 8A. These two units elevated their firing rates regardless of which goal the animal was coming from.

Many units increased their firing rates at certain stages of the delay period such as approaching the central reward site. Among these, activities of seven units showed strong dependence on the previous goal location. As shown in Figure 8B, these units elevated their firing exclusively, and reliably, when the animal returned from a particular reward site. Figure 8C shows an example of a cell that fired during the delay, but had no dependence on the previous goal location.

Other Behavioral Correlates

Eight-arm Radial Maze

One hundred and forty out of 187 PFC units had clearly discernible behavioral correlates during the eight-arm radial maze, spatial working memory task. The remaining units were either silent on the maze (mean rate <0.1 Hz with no obvious correlate; $n = 24$) or had no reliable behavioral correlates that could be detected ($n = 23$). Among the 140 units, 69 had a single conspicuous correlate and 71 had multiple correlates (summarized in Table 2). Only two units were associated with the

animal's immediate movement. One unit increased its firing rate, and another decreased its rate whenever the animal made any type of movement. The rest tended to fire with different phases of the task, as described below.

Behavioral correlates of 74 units (20 single correlate units and 52 multiple correlate units) were related to the goal. Among these, the firing activity of 11 units were correlated with approach to the goal; 29 units had briefly elevated or decreased activity when or a little after arriving at the goal; 33 units had elevated firing rates at the goal either as continuous activity ($n = 24$), slowly decreasing activity ($n = 7$), or slowly increasing activity ($n = 2$); and two units maintained decreased firing rates at the goal. Some examples of these are shown in Figures 5C,D,K,I and 7H.

Twenty-two units (6 single and 16 multiple correlates) were correlated with the animal's turning behavior at the goal. Among these, three units increased their firing rates slightly before turning, ten during turning, four at the end of turning. Five cells showed decreased firing rates during turning (Table 2). Examples are shown in Figures 5E,F and 7C.

Thirty-five units were correlated with the animal's movement on the maze (Table 2). One unit showed elevated firing for both inward and outward running; 23 units showed outward direction-selective changes in firing (15 increased and 8 decreased firing rates); 11 cells changed their rates during inward running behavior (6 increased and 4 decreased their rates); and one unit increased its firing rate only on the proximal portion of all arms. Examples are shown in Figures 5G and 7K.

Thirty-one units showed firing rate changes in relation to the period between turning inward at a goal and reaching a new goal (Table 2). Six of these cells showed increased rates, and two cells showed reduced firing rates for the entire period. The remainder changed their rates over only a part of this period (examples in Fig. 5E,F). Five units showed elevated activity during the period between coming back to the central platform and entering a new arm, i.e. while the animal appeared to be selecting the next arm to visit at the central platform. Eight additional units showed elevated firing rates as the rat entered the arm. Examples of cells with these properties are shown in Figures 5H-J and 7C.

Eleven units were correlated with trial onset. Three cells increased firing rates coincident with trial onset (Fig. 6C), and eight cells before trial onset. The latter cells typically fired 10–30 s before a new trial began, which may be an indication of the animal's 'anticipation' of trial onset. Sixteen units were correlated with trial end. Six units showed brief firing rate

Figure 5. Spatial firing rate maps of PFC neurons selected on the basis of their behavioral correlates on the eight-arm radial maze. Each pair represents the spatial distribution of the firing rate (number of spikes/occupancy time) for one cell which was recorded on the eight-arm radial maze and subsequently on the figure-eight track. Red indicates maximal firing rates, which are different for each firing rate map, and dark blue indicates no firing. The minimum value for the maximum firing rate was set at 1 Hz. These cells increased their firing rates during various phases of the eight-arm maze spatial working memory task. Some of these cells also had correlates (usually different ones) on the figure-eight track. (A) A unit with spatially selective firing. This unit reliably fired when approaching a particular goal (10 o'clock direction). It also elevated its firing rate at the trial end, as shown by several spots of high activity at the proximal portions of the maze arms, and when the animal was returning to the maze center from goals. On the figure-eight track, the unit was very active when returning to the center. Maximum firing rates (red) of the maps are 1 Hz (radial maze) and 2.9 Hz (figure-eight maze). (B) A cell whose firing was associated with the intertrial interval. This cell was largely silent during the eight-arm maze trial, but elevated its firing rate during intertrial intervals at the maze center. It was silent on the figure-eight track. Maximum rates are 4 and 1 Hz respectively. (C,D) Goal-related units. Cell C elevated its firing rate when approaching goals (ends of maze arms) and cell D fired at a high rate while the animal remained at the goals. Maximum rates are 4.5 and 1 Hz (C) and 3.9 and 5 Hz (D). (E,F) Turning-related units. Both cells were active when the animal turned at the goal, with slightly different firing phase characteristics in the turn. The cell shown in (E) was recorded only on the radial maze (maximum rate 4.5 Hz). Note that the animal was biased towards making left turns on this trial. Maximum firing rates are 7 and 5.5 Hz for the radial and figure-eight mazes respectively in (E). (G) This unit was active when the animal ran outward on the maze arms (maximum rate 4.5 Hz). On the figure-eight track, it was active when the rat approached reward sites (maximum rate 7 Hz). (H–J) Units that were active during the period between turning inward at a goal and reaching a new goal. Cell H was active during the entire period. The average firing rate at the central platform is low due to little movement during intertrial intervals. Cell I was particularly active during the period between when the animal came back to the central platform and when it entered a new arm, i.e. while the animal appeared to be deciding which arm to visit next. Cell J elevated its firing rate during the entire period between turning at a goal and reaching a new goal, but the firing rate was also particularly high at the central platform. Maximum rates for the radial and figure-eight mazes are 3.6 and 4 Hz (H), 2.6 and 1 Hz (I), and 6.5 and 1 Hz (J). (K,L) Units with multiple correlates. Cell K showed increased firing during intertrial intervals and when occupying goal locations (maximum rates 3.6 and 7.5 Hz). Cell L fired when approaching the goal and when occupying goal locations (maximum rates 6 and 10.5 Hz).

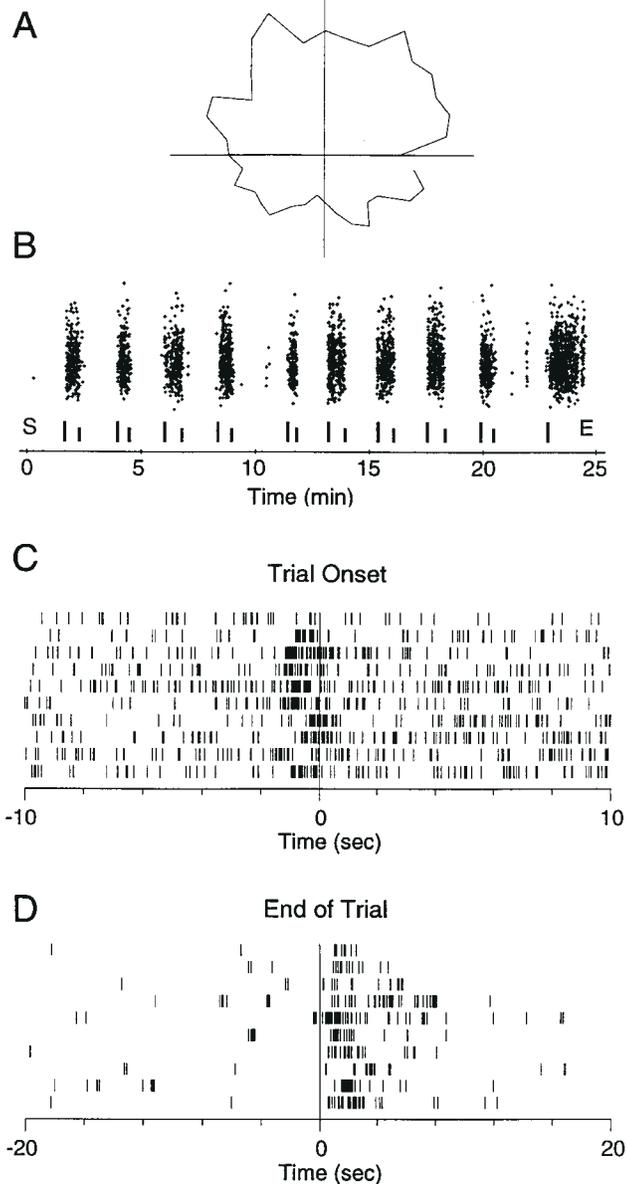


Figure 6. Other behavioral correlates of PFC neurons on the radial maze. (A) A directional unit. A tuning curve of a PFC neuron was constructed by dividing the number of cell discharges when the rat faced a particular direction (in bins of 10°) by the amount of time the rat faced that direction. The activity of this unit was broadly biased towards north. (B) A unit that fired during the intertrial interval. The x-axis represents time and shows entire recording period. Each point represents discharge of the unit. This cell fired at high rates during intertrial intervals and was silent during trial performance, as indicated by the clustered cell discharges. S: start of the session; E: end of the session. Tick marks indicate beginning (long tick) and end (short tick) of the intertrial intervals. (C,D) Units that briefly increased their firing rates in association with trial onset (C) or offset (D). Time 0 indicates trial onset (C) or end of a trial (D) of the eight-arm radial maze, spatial working memory task.

elevation when a trial ended (Figs 5A and 6D), six fired shortly (a few seconds) after trial end, and four fired continuously when trials were over, for up to 30 s.

Forty-three units showed firing rate changes within the intertrial interval (Figs 5B, 6B and 7J). Twenty-four units maintained constant firing rates during the entire intertrial interval; three units slowly increased, five slowly decreased, and four slowly increased then decreased their firing rates during the intertrial interval. Seven other units fired intermittently during this period.

Table 2

Behavioral correlates of PFC neurons recorded during an eight-arm maze, spatial working memory task (numbers in parenthesis indicate fast spiking cells; the rest are regular spiking cells)

	Units with single correlates (<i>n</i> = 69)		Units with multiple correlates (<i>n</i> = 71)	
Silent (<i>n</i> = 24)				
No clear correlates [<i>n</i> = 23(2)]				
Directional	4	4	4	4
Outward		3		0
Inward		0		0
Absolute directional bias		0		4
Outward and absolute directional bias		1		0
Spatial	1			3
Specific		1		2
Broad		0		1
Movement related	2		0	
When moving		1		0
When not moving		1		0
Turning at goal	6		16(3)	
When turning		3		7(1)
Shortly before turning		1		2
When turning is over		1		3
Rate decreases when turning		1		4(2)
Goal related	20(3)		53(4)	
Continuously active at goal		6		18(2)
Briefly when or after arriving at goal		5(2)		19(1)
Rate slowly decreases at goal		3		4
Rate slowly increases at goal		1		1
Goal approach		5(1)		6
Rate briefly decreases when or after arrival		0		3(1)
Continuously inactive at goal		0		2
Running on arm	11(1)		26(2)	
Both inward and outward running		1		1(1)
Outward running (rate increased)		8		7(1)
Outward running (rate decreased)		1(1)		8
Inward running (rate increased)		1		5
Inward running (rate decreased)		0		4
Inward running (only on proximal arm)		0		
Between turning and reaching new goal	9		22(1)	
After turning until reaching new goal		2		4
After turning until entering new arm		2		2
Back to center until reaching new goal		4		0
At center when selecting next arm		0		5
When entering arm		1		7
Rate reduced between turning and new goal		0		2(1)
Rate reduced between turning and new arm		0		2
Trial onset	3		8(1)	
When trial begins		1		2
Before trial begins		2		6(1)
End of trial	2		14	
Briefly when trial ends		1		5
Continuously when trial ends		0		4
After trial ends		1		5
Intertrial interval	12(4)		31(2)	
Continuously active at a constant rate		6(2)		18
Rate slowly increased		1(1)		2(1)
Rate slowly decreased		3(1)		2
Rate going up and down		1		3(1)
Intermittent		1		6
Total number of correlates	69		177	

Figure-eight Maze

PFC units also had diverse behavioral correlates during the rats' performance of the figure-eight track, delayed spatial alternation task. Twelve units were silent (mean rate <0.1 Hz), and 37 units had no obvious behavioral correlates. Twenty-five units had a single conspicuous behavioral correlate and 39 had multiple correlates (Table 3). Two cells satisfied the criteria for being considered a working memory delay cell (Fig. 8A), two units were associated with the movement of the animal, and one fired during rightward turn behaviors (Fig. 7J). Two units showed

strong spatial bias for one side of the maze or the other (Fig. 7B), and six cells exhibited elevated firing rates during the entire delay period (on the central section of the maze) without significant dependence on the previous goal location.

Eleven units increased firing rates at the branch point, when the rat was selecting paths to the left or right goals (Fig. 7G,L). Seven of these increased firing rates regardless of the animal's selection of goal. The remaining four units showed selective elevated firing for a specific goal (Table 3). All 11 of these units had behavioral correlates in addition to path selection.

The activities of 68 units were related to the goal in some manner. Twenty-six units showed elevated firing when the animal was at the goal, 30 when approaching the goal, six briefly when the rat arrived at the goal, and six when the rat left the goal. Some cells changed firing rates at all goals, some at only one goal (Table 3). Examples of such goal-related units are shown in Figures 5G,K,L and 7F,H,I,K,L.

Twenty-six units increased firing rates when the animal returned to the track center (Table 3). Some units showed elevated firing rates for the entire return phase from the reward to the center, and some changed firing on only a selective portion of the track before returning to the track center after reward ($n = 8$). Eight cells increased their firing rates at different phases (combinations of above) of the return path depending on the initial goal location (L1 versus R1). Several examples of these units are shown in Figures 5A,L and 7C,K,L.

Behavioral Correlates of Fast Spiking Cells

FSCs were separately examined to test whether they were associated with any particular behavioral correlate. As shown in Tables 2 and 3, there was no consistent trend for FSCs to fire following specific behavioral conditions on the eight-arm radial maze or figure-eight track. As might have been expected by their high baseline firing rates, no FSC unit was silent in either behavioral condition.

Relationship Between Behavioral Correlates in Different Tasks

Among 187 total units, 110 units were recorded both on the eight-arm maze and on the figure-eight track. Examination of the behavioral correlates of single cells in these two tasks suggests that activity in one condition did not predict the activity in the other. Because the structure of the two tasks was different, some of the correlates did not have a 'comparison correlate' in the other task. Comparison can be made, however, for such behaviors as goal-related behaviors and returning to the maze center. A unit was regarded as a 'common correlate unit' as long as it had one common correlate on both mazes, even if the cell had multiple correlates (there were no single correlate units that shared this common property in both test conditions). Based on these loose criteria, four units with 'goal approach', one with 'arrival at goal', seven with 'at goal' and one with 'leaving goal' correlates (total = 13) were determined to share these correlates on both tasks. Six units were silent on both mazes and five had no clear correlates on both mazes.

Discussion

Single cells were recorded in the deep layers of the medial PFC, including those regions that are targets of hippocampal projections. Although PFC neurons exhibited diverse behavioral correlates, several general conclusions can be drawn from the present experiment. First, few neurons exhibited spatially

selective firing in a manner similar to hippocampal place cells. Second, few units exhibited continuous activity during delay periods that might mediate working memory of previously visited locations. Third, PFC neurons tended to change their firing rates during distinct phases of the working memory tasks. Fourth, the behavioral correlates of a cell in one task was not simply related to the same behavior in another task.

Spatial Selectivity

To solve the allocentric spatial memory task used in the present study, a rat must remember visited versus unvisited arms within a current trial to obtain reward. Radially symmetrical neural activity cannot provide specific information about arms visited in the task. Of the 187 neurons recorded, few exhibited arm-specific firing patterns on the eight-arm radial maze. Rather, when a cell was active on a certain part of a maze arm, it was usually active on the corresponding parts of all other arms. Asymmetric firing was generally associated with non-spatial aspects of the task, such as the onset or end of trials. Although many neurons exhibited a spatial bias on the figure-eight track, it is likely that the differential firing was related to the behavioral requirements of the task, rather than to allocentric spatial coordinates. In support of this interpretation, no PFC units showed place-specific firing characteristics reminiscent of hippocampal place cells in the random food search task in the square chamber. Whereas activity of a hippocampal place cell is relatively independent of an animal's behavioral state, PFC units changed their activities in an unpredictable way at a given location. Because spatial location was a poor predictor of PFC unit activity, specific information about external environments may not be represented in the rat medial PFC. This result is consistent with a recent study by Poucet (1997) in which few units of the rat prelimbic cortex were found to have spatially selective firing, during a random, food-searching task in a cylinder, of the sort observed in hippocampal place cells.

Working Memory

It was hypothesized that the rat medial PFC would contain cells that maintain their altered activity during the period in which an animal must retain information about a previously visited location (i.e. delay cells, as have been found in primate PFC). Contrary to this expectation, however, few cells showed such delay characteristics. In fact, in the two units that did show elevated firing rates after visitation of one arm, which were maintained until the end of a trial on the eight-arm radial maze, these cells only exhibited this delay-related property for a single trial. Several units showed a consistent change in firing rates in the delay period of the figure-eight track, spatial alternation task, although only two of these cells passed the criteria necessary to be considered 'delay cells'.

How, then, does a rat maintain working memory of previously visited locations? Several possibilities are suggested by the present results. First, working memory may be maintained in regions other than those PFC regions recorded in the present study, including the more superficial layers of the medial PFC. Second, working memory of the present tasks may be maintained by changes in synaptic weights. Third, working memory may be maintained as continuous neural activities of a population of neurons. Clear differences in firing rates depending on previously visited goal locations were shown by seven units that elevated their firing rates during part of the delay period on the figure-eight maze. Such units cannot mediate working memory of previously visited goal locations during the entire delay period

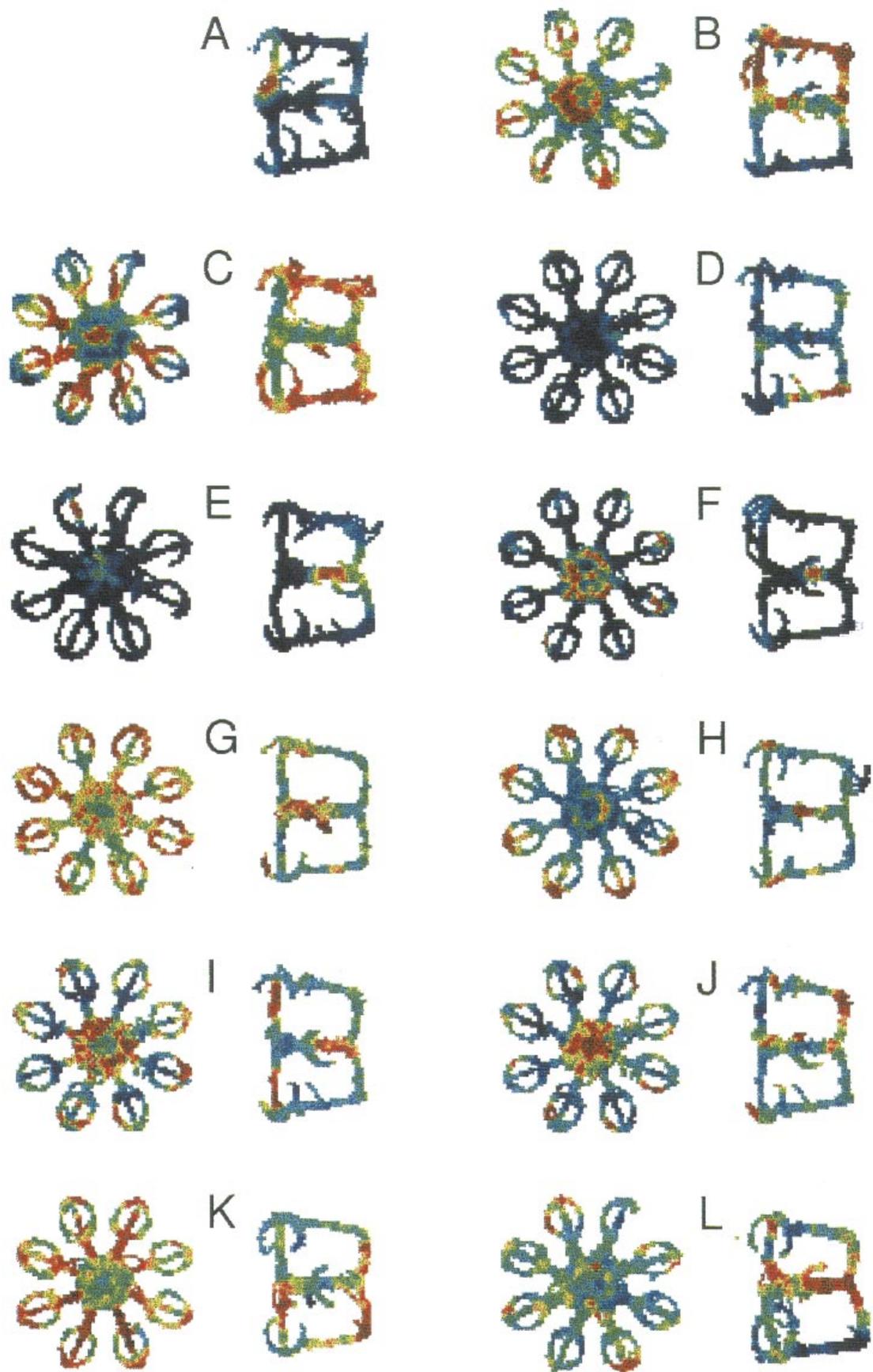


Figure 7. Spatial firing rate maps selected on the basis of behavioral correlates on the figure-eight track. Pairs of spatial firing maps were constructed as in Figure 5, except that these units were selected based on their distinct behavioral correlates on the figure-eight track. Firing rates of 0 Hz are indicated by blue in the examples. (A) This unit exhibited elevated firing in a small restricted region of the maze (maximum rate 6.4 Hz). It was not recorded on the radial maze. (B) This unit showed strong spatial bias toward the right side (upward direction) of the figure-eight track. In the center track, the unit showed a higher firing rate when the animal's previous goal location was the right goal (maximum rates 2.1 and 1.4 Hz for the radial and figure-eight mazes respectively). (C,D) Units that were active in the return phase on the figure-eight maze. Cell C was active during the period between turning at a goal and reaching a new goal on the radial eight-arm maze. Maximum rates were 7.5 and 5.5 Hz. Cell D showed asymmetric firing on the figure-eight maze and was silent on the radial maze (maximum rates for both mazes were 1 Hz). (E,F) Units related to the entire (E) or part (F) of the delay period on the figure-eight track. Activity in cell F was dependent on the previously visited goal location. On the eight-arm radial maze, the units fired when approaching a specific goal and at trial ends (E) and in the intertrial interval and arrival at goal (F). Maximum rates for the radial and figure-eight mazes were 1.7 and 10.1 Hz (E) and 1 and 3.5 Hz (F). (G–I) Goal-related units. Cell G was especially active while the rat was occupying and leaving the central goal. Cell H was active at all three goals on the figure-eight track, and cell I elevated its firing rate when approaching goals on the track. Cell H was also active at goal locations on the eight-arm radial maze. Maximum rates for the radial and figure-eight mazes were 2.4 and 1.1 Hz (G), 2.3 and 2.2 Hz (H), and 1.1 and 2.3 Hz (I). (J) Turn-related unit. Cell J elevated its firing rate whenever the animal made a turning movement toward the right on the figure-eight track. Note that it was also active when animal swung its head towards the right while staying at the goals. Maximum rates on the radial and figure-eight mazes were 1 and 3.3 Hz. (K,L) Units with multiple behavioral correlates. Many units had multiple correlates on the figure-eight track as shown in the examples. Maximum rates on the radial and figure-eight mazes were 6.5 and 6.3 Hz (K) and 2.1 and 1.5 Hz (L). Cells I and J fired on intertrial intervals on the radial maze, and cell K fired while the rat ran outward on the maze arms.

single-handedly. In principle, however, working memory may be maintained in a network of such units that are interconnected and sequentially activated.

Encoding Rules

Firing patterns of the PFC units were mostly correlated with distinct phases of the present working memory tasks. On the eight-arm radial maze, many cells fired in relation to the structure of a given trial, such as intertrial interval or trial onset or offset. When PFC cells were active within a trial, such as when the rat ran towards a goal, the cells showed radially symmetrical firing patterns (i.e. active on all eight arms) across all trials. As a population, the sorts of cells that were recorded in the PFC in the present study could convey information about which stage, or behavioral sequence of the task the animal is engaged in, or about to become engaged in. Cells in the PFC also showed altered firing properties in relation to distinct phases of the figure-eight track, delayed spatial alternation task. These correlates included goal approach, selection of paths and returning to the maze center. Thus, activity of the PFC units may best be described to be correlated with subcomponents of the behavioral tasks. It is possible that an internal representation of these subcomponents is necessary for the extraction of higher-order, context-specific 'rules' of behavior, a function of this region suggested by Winocur and Moscovitch, (1990) on the basis of lesion studies; however, no direct evidence on favor of such an hypothesis was obtained in these studies.

The properties observed in the present study are somewhat reminiscent of cells that have been recorded in other areas, such as the orbitofrontal and pyriform cortex (Shoenbaum and Eichenbaum, 1995a,b) or perirhinal and entorhinal cortices (Young *et al.*, 1997) of rats in olfactory discrimination tasks. These cells tend to fire selectively during salient trial events, such as trial initiation or odor sampling. The properties observed here are also quite comparable to properties observed in rat

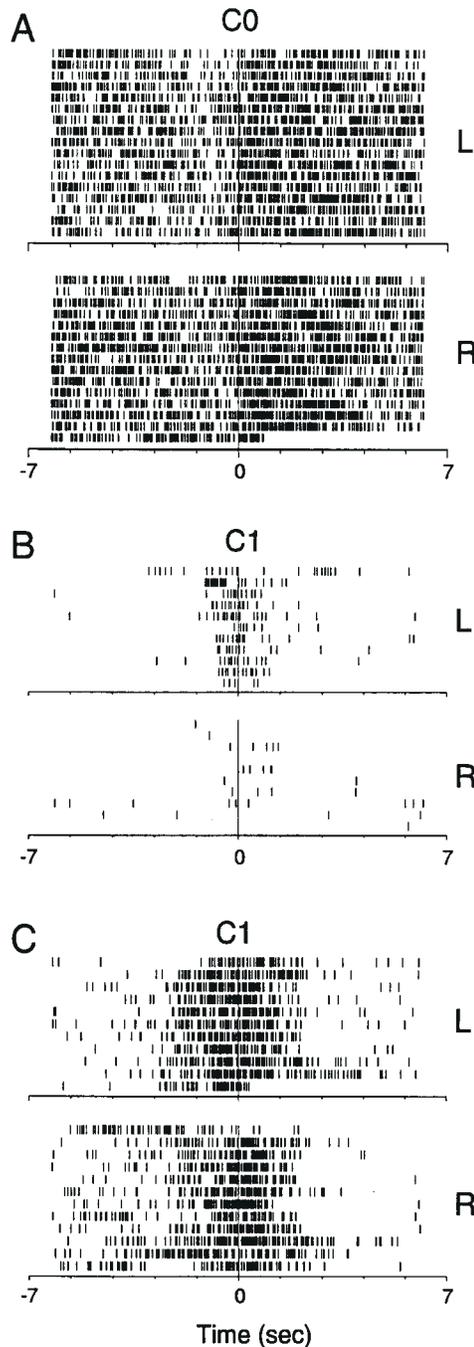


Figure 8. Units that fired during the delay period of the figure-eight track spatial alternation task. Each spike raster represents unit activity on the central section of the maze that was constructed based on the previously visited goal locations. L, R: trials in which the animal returned to the center of the track from the left and right reward site respectively. (A) One of two units that satisfied criteria for delay cells which may mediate working memory of previous visited goal locations as continuous activities. This unit elevated its firing rate during the entire delay period. It fired at significantly higher rates when the animal was returning from the right reward site. Note that the unit still elevated its firing rate when the animal was returning from the left reward site. Time 0 represents the animal's arrival at the central portion of the track (C0, beginning of the delay period). (B) An example of the units that showed differential firing rates during certain parts of the delay period, depending on which goal location the animal previously visited. This unit was active when arriving at the central reward site (C1), but only when the animal was returning from the left goal. (C) This unit elevated its firing rate when the animal was arriving at the central reward site (C1) regardless of previous goal locations. Note that the rat's posture was often different at the central reward site depending on which direction it arrived from. Therefore, influences on firing rate other than 'working memory' cannot be excluded.

Table 3

Behavioral correlates of PFC neurons recorded during a figure-eight maze, delayed spatial alternation task (numbers in parenthesis indicate fast spiking cells; the rest are regular spiking cells)

	Units with single correlates (<i>n</i> = 26)	Units with multiple correlates (<i>n</i> = 38)	
Silent (<i>n</i> = 12)			
No clear correlate [<i>n</i> = 37(1)]			
Working memory delay cell	2(1)	0	
Movement related	2(1)	0	
Turning (right turn)	1	0	
Overall strong left or right bias	2	0	
Delay period	1	5	
At goal	6	20(2)	
At all three goals	3		8(2)
At left and right	1		3
At center only	2		5
At left or right only	0		
At center and either left or right	0		3
Goal approach	6	24(3)	
All three goals	2		3(1)
Left and right	1		3
Center only	2		6
Left or right only	0		8
Center and either left or right	1		4(2)
Briefly when arriving at goal	1	5	
All three goals	1	2	
Left and right	0	1	
Left or right	0	2	
Leaving goal	1	5(1)	
All three goals	1		2
Left and right	0		1
Left or right only	0		2
Center only	0		1(1)
Selection of paths (C2)	0	11(2)	
When moving toward both goals	0	7(1)	
When moving toward either left or right goal	0	4(1)	
Return to center	4	22(4)	
Similar on return paths from both left and right rewards	3		15(4)
Left and right return path different	1		7
Total number of correlates	26	92	

posterior cortex (HL, Oc2M, Oc2L, RSA) during performance of the radial eight-arm task (Chen *et al.*, 1994a,b; McNaughton *et al.*, 1994). In the latter studies, many cells responded in relation to specific behaviors such as turning or running forward, and some of these were selective for particular phases of the task (e.g. running inward but not outward, turning at the arm ends but not in the center). Thus the parsing of a repeated behavioral task into distinct components seems to be a rather widespread neocortical phenomenon.

Relationship Between Two Tasks

Neurons were recorded while the rats were performing the radial eight-arm maze and the figure-eight track tasks sequentially, in the same recording room with the same visual cues. Although the room features were similar, there was no obvious relationship found for firing during similar behaviors across the two tasks. Only 13 units were determined to have similar behavioral correlates on both mazes, and even these units had additional behavioral correlates other than the common correlates. These results are perhaps not surprising in view of the fact that few cells appeared to fire in relation to immediate sensory input or motor patterns. Because most cells could be associated with distinct phases of the tasks, these results further

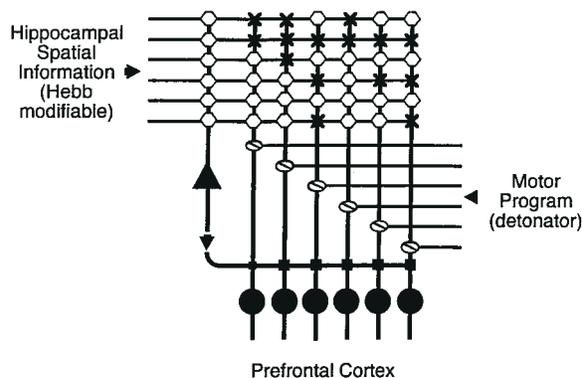


Figure 9. A plausible hypothesis on the role of the hippocampal projection to the PFC is that it may permit learning of the spatial contexts in which certain behaviors are appropriate. The figure represents a hypothetical neural network in the PFC that may implement associations between spatial locations and generation of appropriate behaviors. The hippocampal projection to the PFC supports NMDA receptor-dependent long-term potentiation (e.g. 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 spatial context information may be sufficient to drive the appropriate motor program, perhaps making the behavior more 'automatic'.

support the conclusion that the representations in the PFC are not strictly sensory- or motor-bound, but related to more abstract features of task performance.

Role of Hippocampal Projection to the PFC

There are monosynaptic projections from the ventral hippocampus to the PFC in the rat (Swanson, 1981; Ferino *et al.*, 1987), and place cells have been observed in ventral CA1 (Jung *et al.*, 1994; Poucet *et al.*, 1994). Furthermore, long-term potentiation can be induced in this projection system (Laroche *et al.*, 1990). These results led to the hypothesis that PFC cells may be influenced by this hippocampal projection and exhibit certain place-specific firing characteristics. Contrary to this prediction, however, the firing properties of PFC neurons could not be directly related to spatial locations. If the hippocampal projection does not impose some form of spatial representation in the rat PFC, then what is the role of this projection? In certain highly constrained situations, such as conditioning experiments, hippocampal neurons appear to model response components or behavioral contingencies (e.g. Berger *et al.*, 1980; Foster *et al.*, 1987; McEchron and Disterhoft, 1997). One might argue that such activity, when projected to the PFC might contribute to the development of representations of task components of the sort observed here; however, in the types of tasks used in the present experiments, there is no evidence for hippocampal representation of task components *per se*. Otherwise the hippocampal activity would exhibit symmetrical correlates consistent with the symmetries of the behavioral task. Therefore, given the role of the PFC in the planning of behaviors in appropriate sequences, a reasonable hypothesis is that the hippocampal projection may enable the PFC to learn the spatial contexts in which particular components of these sequences are appropriate.

Figure 9 shows a hypothetical neural network in the PFC that could mediate this function. The hippocampal–PFC projection supports NMDA receptor-dependent long-term potentiation (Jay *et al.*, 1995), thus the synapses are modified following the Hebbian learning rule. This model assumes that the PFC receives a strong input ('detonator synapses') carrying motor program information, which induces unconditional discharge of the post-

synaptic neurons. If an animal always makes a turning behavior at a 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 detinator inputs, then the animal can generate 'turning behavior' appropriate to the task, based solely on spatial context information from the hippocampus.

In summary, the single units recorded in PFC of freely behaving rats in the present study appear to encode specific features of the working memory tasks performed by the rats, but do not appear to participate in maintaining active states corresponding to the items to be remembered (i.e., they are not 'working memory cells' *per se*). Although the hippocampus itself encodes allocentric spatial information, its projection to the prefrontal region does not impose strong spatial selectivity on most prefrontal neurons.

Notes

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