

POSITIONAL FIRING PROPERTIES OF POSTRHINAL CORTEX NEURONS

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Abstract—Hippocampal cell firing in awake, behaving rats is often spatially selective, and such cells have been called place cells. Similar spatial correlates have also been described for neurons in the medial entorhinal and perirhinal cortices. All three regions receive sensory associational input from postrhinal cortex, which, in turn, is heavily interconnected with visuospatial neocortical regions. The spatial selectivity of postrhinal cells, however, has never been examined. Here, we report the activity of neurons in postrhinal cortex of freely moving rats performing a spatial task on a four-arm radial maze. Data are also reported for visual association cortex neurons.

The four-arm radial maze was defined by multisensory cues on the surfaces of the maze arms (proximal) and complex visual cues at the surround (distal). On each recording day, rats were run in three conditions: baseline, double cue rotation (proximal +90°; distal -90°), and baseline. In this task, hippocampal place field activity is robust and can be controlled by proximal or distal cues. The majority of postrhinal neurons (64%) exhibited positional correlates during performance on the task; however, characteristics of these postrhinal cells were substantially different from those previously described for hippocampal place cells. Most postrhinal cells with firing fields exhibited split or multiple subfields (93%). Unlike hippocampal place fields, the large majority of postrhinal firing fields (84%) adopted new spatial correlates when experimental cues were rotated, but did so neither predictably nor concordantly.

This is the first report of positional firing correlates in the postrhinal cortex. The data are consistent with the idea that postrhinal cortex participates in visuospatial functions by monitoring changes in environmental stimuli rather than encoding stable spatial cues. Thus, postrhinal neurons appear to participate in higher-level perceptual functions rather than mnemonic functions. We propose that the response properties of postrhinal neurons represent an early step in a spatial pathway that culminates in the specific and stable place fields of the hippocampus. © 2003 IBRO. Published by Elsevier Science Ltd. All rights reserved.

Key words: hippocampus, memory, spatial, place field, perirhinal, visual association cortex.

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Abbreviations: ANOVA, analysis of variance; PER, perirhinal cortex; POR, postrhinal cortex; VIS_L, lateral visual association cortex.

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The neuroanatomical connections of the postrhinal cortex (POR) are consistent with a role in processing information about space. The POR receives input from visual association and visuospatial cortex, and is reciprocally connected to the medial entorhinal area (Burwell and Amaral, 1998b). The POR also projects strongly to the perirhinal cortex (PER), but the return projection is relatively weak (Burwell and Amaral, 1998a). Both the POR and the PER are reciprocally connected with the hippocampus and subiculum (Naber et al., 1999). The PER has been implicated in object identification or stimulus-stimulus association (Buckley and Gaffan, 1997; Bussey et al., 2001; Eacott et al., 2001; Gaffan et al., 2000; Liu and Bilkey, 2001; Mumby and Glenn, 2000; Mumby and Pinel, 1994; Otto and Garruto, 1997), but less is known about POR function. Although mixed, there is evidence that the POR is involved in the processing of spatial information in some paradigms (Bussey et al., 1998, 2000a,b; Liu and Bilkey, 2002; Vann et al., 2000). Both the PER and POR are necessary for encoding context in a contextual fear conditioning task (Bucci et al., 2000, 2002). Thus, it may be that the object identification functions of the PER and the visuospatial functions of the POR are necessary for processing information about spatial environments.

Place cells in the hippocampus were first described by O'Keefe and Dostrovsky (1971), and many subsequent studies have replicated those findings. Neuronal correlates of space have since been noted in neighboring areas such as the subiculum (Phillips and Eichenbaum, 1998; Sharp, 1999; Sharp and Green, 1994) and the medial entorhinal area (Quirk et al., 1992). While these place fields are larger than those found in hippocampus and behave differently under certain experimental conditions, they predictably follow spatial cues (but see Sharp, 1999). Cells in PER, in contrast, do not display stable spatial selectivity; only one-third of these cells display spatial correlates, and the firing patterns do not respond predictably to experimental manipulation of cues (Burwell et al., 1998). PER lesions, however, result in decreased stability of hippocampal place fields (Muir and Bilkey, 2001). It is reasonable to hypothesize that the POR, which is connected to visuospatial regions and projects to the PER, medial entorhinal area, and hippocampus proper, may display neuronal activity that reflects the pre-processing of information necessary for the formation of stable place fields in the hippocampus.

The objective of the current study was to record from cells in the POR during a spatial task and determine the spatial firing characteristics of those neurons. Recordings were made from the POR of awake, behaving rats as they

completed the four-arm radial maze task for a water reward. The methods, apparatus, and data analysis procedures were designed to permit comparison of the present results with findings from the hippocampus, subiculum, and PER using similar methods and the same behavioral paradigm (Burwell et al., 1998; Phillips and Eichenbaum, 1998; Shapiro et al., 1997; Tanila et al., 1997a). Accordingly, the results can be directly compared with prior studies of neuronal correlates of spatial behavior in those regions.

EXPERIMENTAL PROCEDURES

Subjects

Subjects were four male Long-Evans rats (290–360 g, 2–5 months old) from Charles River Laboratory, Portage, MI, USA. Animals were housed individually and kept on a 12-h light/dark cycle. Animals had *ad libitum* access to food, but water access other than behavioral rewards during training was limited to 1 h per day for the duration of the experiment. All methods for handling research animals were according to approved IACUC and AAALAC guidelines. Research procedures were designed to minimize suffering of research animals. Experiments were constructed to use the smallest possible numbers of animals.

Surgery

Under halothane anesthesia, two microdriver assemblies were stereotaxically implanted bilaterally in the POR or comparison region in each experimental animal. The implant coordinates were 0.8 mm anterior to lambda, 5.85 mm lateral to lambda, and 4.77 mm ventral to the cortical surface.

Electrodes and microdrivers

One tetrode and one stereotrode (for reference ground) made from twisted 30 μm Formvar-coated tungsten wire (California Fine Wire; Grover Beach, CA, USA) were fixed in a 29-gauge stainless steel guide cannula (Small Parts Inc., Miami Lakes, FL, USA) held in a microdriver assembly. The electrodes were secured to the guide cannula with superglue. The guide cannula was inserted into a larger 24-gauge cannula and could be advanced by the rotation of a 0–80 set screw at 314 μm per full turn. The cannulae were mounted in an amphenol connector and stabilized with a miniature spring. The tetrode wires were cut at 1.5 mm from the bottom of the cannulae and the stereotrode reference wires were cut at 1.0 mm from the bottom of the cannulae.

Recording methods

A data collection system (DataWave Technologies, Inc; Longmont, CO, USA) was used to record extracellular activity in the POR during the behavioral task. Neuronal activity was recorded using tetrode-recording methods. Dual-field effect transistors mounted at the head stage preamplified the tetrode and stereotrode leads. The activity on each tetrode lead was then amplified, filtered, and passed through a time/amplitude window discriminator. When the voltage on any lead reached a user-defined threshold, signals on all four tetrode leads were digitized. Position data were gathered with a video tracking system (DataWave Technologies) that tracked two light-emitting diodes mounted on the head stage. At the end of each recording day, if the tetrode was not in a cellular layer it was lowered 37.5 μm . Otherwise, it was lowered 18.75 μm .

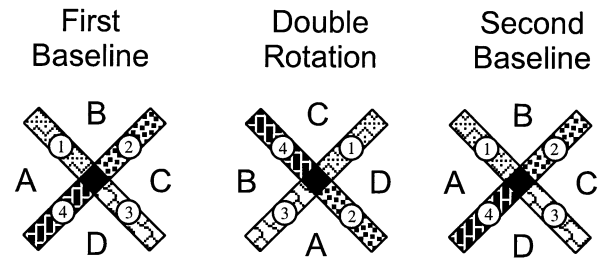


Fig. 1. A schematic view of the behavioral apparatus and procedure. Numbers represent local cues on the moveable arms of the radial maze. Letters represent distal or spatial cues on the curtains surrounding the maze. Animals were run in three conditions: baseline, double rotation in which the distal cues were rotated counterclockwise, while the proximal cues were rotated clockwise, and second baseline in which stimuli were returned to the original configuration.

Behavioral protocol

The experiment was carried out on a four-arm radial maze. The maze consisted of a black octagonal center platform (12 cm per side) raised 69 cm above the ground, with four movable arms protruding at 90° angles (46×10 cm). Four black curtains surrounded the maze and a black mat covered the floor. The environment was illuminated by four 12-W bulbs placed at the top of the black curtains, one at each corner.

The experimental stimuli consisted of both distal and proximal cues (Fig. 1). The distal cues were associated with the curtains surrounding the maze, while the proximal cues were those found on the maze itself. The distal cues consisted of four large shapes on a black background (60×80 cm) differing in form, size, and luminance. The proximal cues, in contrast, consisted of visual stimuli plus tactile and olfactory stimuli. The floors of the maze arms were solid black, or had white diagonal stripes, horizontal stripes, or spots on a black background. The floors of the maze arms were smooth, bumpy, ridged, or sandpapered. Olfactory cues consisted of dilute (25%) artificial flavorings of orange, strawberry, anise, or coconut sprayed on the surface prior to recording. Olfactory cues were always paired with the same arm insets. The top of the maze was covered with a dark canopy that remained in the same position in all conditions.

The task was a standard working memory variation of the radial maze in which the rat received a water reward for correctly visiting a maze arm. A visit to each of four arms of the maze comprised a complete trial. Re-entry of any arm before all arms were visited was an error and was not rewarded with water.

For each recording day, neuronal activity was recorded in three 10-min conditions. The first condition was *baseline*, and did not involve any manipulation of stimuli. The next condition was a *double rotation*. For this condition, the distal stimuli were rotated 90° counterclockwise, while the proximal stimuli (the arms of the maze) were rotated 90° clockwise (Fig. 1). The octagonal center of the maze remained stationary. While the experimenter carried out this manipulation, the rat was contained in the center of the maze in a covered, opaque holding container. Following 10 min in this condition, the experimenter moved the stimuli back to baseline for the *second baseline* condition.

Histology

After a maximum of 10 days of recording, each rat was deeply anesthetized with Nembutal (Abbott Laboratories, North Chicago, IL, USA). Before perfusion, a current was passed through the electrode resulting in the depositing of iron ions around the electrode tip. The animals were then perfused with normal saline, followed by a solution of formalin (4%), potassium ferrocyanide (4%), and glacial acetic acid (4%). A Prussian Blue reaction

marked the cortex around the electrode tips. The brains were coronally sectioned at 40 μm , mounted, and stained for Nissl material according to standard histological procedures.

Data analysis

Using a cluster analysis program (Autocut, DataWave Technologies, Inc), spikes were grouped by similarity according to eight variables. Examples include peak and valley amplitude, peak and valley phase angle, and peak latency of the waveform. Most clusters were distinguished using the peak and valley amplitude of the four tetrode leads. In some cases, these eight variables did not sufficiently isolate clusters and other variables were substituted, for example peak or valley duration. If four leads were not available or a lead was noisy, then analyses were conducted on tritrode or stereotrode data. After the initial cut, clusters were evaluated for the possibility of joined clusters (i.e. two units not isolated). Clusters that appeared upon visual examination to have two areas in which points were clustered at a high density were divided, but this was a rare occurrence. Single unit recordings were considered stable if cluster boundaries successfully isolated units that were observed across conditions.

The clusters were then analyzed for spatial correlates using criteria similar to that used previously for defining hippocampal place fields (Shapiro et al., 1997; Tanila et al., 1997b) and PER firing fields (Burwell et al., 1998). The maze was divided into a 28×28 array of 3×3 cm pixels, and the firing rate of a cluster was determined for each pixel. Firing rate was defined as the total number of spikes in the pixel, divided by the amount of time spent there. In order to maintain the most consistent behavioral performance, data were collected only when the rat was moving at least 2 cm/s. This practice is consistent with other studies using the same paradigm. Each cluster had two additional measures: the grand firing rate and the mean firing rate. The grand firing rate was determined by the number of spikes fired, divided by the amount of time spent in the maze. The mean firing rate was the mean of the firing rates for all pixels within which the rat spent time.

For the purpose of this report, the term "place field" was avoided in describing spatial correlates of POR cells even if they exhibited characteristics of place fields as defined for other studies. Instead, we have substituted the term, "firing field," to avoid implying that behavioral correlates of POR cells are the same as those described for the hippocampus and other regions. Indeed, the aim of this report is to compare the properties of the behavioral correlates of POR neuronal activity to those described for other regions, particularly hippocampal place fields.

A firing field was defined as five adjacent pixels with firing rates above a threshold of three times the grand rate of the cluster. Adjacent pixels included those that shared a side or were diagonally touching. Additionally, a filtering algorithm was used to examine all contiguous regions of high firing rate (Shapiro et al., 1997; Tanila et al., 1997b,c). When firing fields were too small, i.e. less than five pixels, the fields were deleted. If firing fields that did not meet the area criterion were within two pixels of another field, the fields were combined. Thus, use of the filtering algorithm occasionally resulted in the formation of firing fields with discontinuous pixels. Pixels that were visited less than three times or for less than 250 ms were considered to be undersampled, and those data were deleted from further analysis (Shapiro et al., 1997).

Firing field area was the number of pixels that demonstrated firing rates above the threshold criteria. The mean infield firing rate of a cluster was defined as the mean firing rate of those pixels in the firing field. Two additional ratios were calculated in order to further characterize each firing field. Spatial selectivity, a measure of the extent of localization, was the \log_{10} ratio of the mean infield firing rate to the firing field area. Directional tuning was calculated as the ratio of the highest to lowest mean firing rate of the firing field across eight horizontal heading directions. This analysis included all directions that were observed at least once. Thus, if a

rat was only observed to move in the directions of toward and away from the center of the maze, the directional tuning is the ratio of firing rates recorded during movement in those two directions.

The firing fields of cells that were observed to fire in multiple conditions, i.e. fired across conditions, were analyzed for changes between conditions in two ways. First, cells were analyzed for responses to the double rotation of proximal and distal cues. And second, a baseline-to-baseline comparison was conducted.

In the first analysis, cells were assessed for changes associated with manipulation of cues, i.e. changes from the first baseline to the double rotation or, if the cell began firing in the double rotation, between the double rotation and second baseline. The behavior of each firing field was designated as belonging to one of five categories: unchanged relative to the room, rotated related to proximal or distal cues, changed unrelated to manipulation of cues, appeared, or disappeared. The presence of multiple or split fields made determinations of disposition of firing fields challenging because of the difficulty of identifying individual firing fields across conditions. Thus, some assumptions had to be made about the identity of firing fields, and disposition was determined in a pre-set order. First it was determined whether, after double rotation, a firing field was located in the same place relative to the room or not. If the field was found to have changed, then it was determined whether the field had rotated related to cues or changed unrelated to cues. The determinations were made in the following order. 1) A firing field located on an arm was first characterized as located in the inner, middle, or outer third of a particular arm. If after double rotation, a field appeared on the same arm in the same portion of the arm, the field was characterized as unchanged. 2) If there was no field at the same location, but a field appeared on an adjacent arm in the same portion of the arm, that field was characterized as rotated. A clockwise rotation was considered to correlate with the manipulation of proximal cues, and a counterclockwise rotation was considered to correlate with the manipulation of distal cues. 3) If the number of fields did not change across conditions, any fields that were neither unchanged nor rotated were characterized as changed unrelated to cue manipulation. 4) If the number of fields increased in the double rotation, the new firing fields were considered to have appeared. 5) Finally, if the number of fields decreased, the number by which fields decreased was considered to have disappeared. For example, if two fields appeared in the first baseline and one appeared in the double rotation, one field was said to have disappeared.

To examine possible changes of positional firing correlates between the first and second baselines, the data were analyzed in two ways. First, cross correlations for isolated cells were performed on pixels that met the visit criteria in both baselines. Next, the location of firing fields in the first baseline was visually compared with the location of firing fields in the second baseline in order to determine the number of firing fields located in the same place relative to the room in both baselines.

Because of the tendency of POR cells to have multiple firing fields and because the number of firing fields could change across conditions, we also calculated a measure termed the *maximum number* of firing fields. This measure was calculated as the number of firing fields in the condition that exhibited the most firing fields. For example, if the cell had two firing fields in the first baseline, three in the double rotation, and two in the second baseline, the maximum firing fields was calculated as 3.

Finally, a post hoc correlation analysis was conducted in which clusters were analyzed for stability within a session. For the first baseline session for units with positional correlates, filtered firing rate and locations of firing were analyzed for the full 10-min session, the first 5-min block, and the second 5-min block. If a cell did not fire in the second 5 min of the session, the first 5 min was subdivided into two 2.5-min blocks. Because the firing rates are relatively low for POR cells, a larger grid size was used for these analyses. The maze was divided into a 10×10 array of 11.4×11.4

cm pixels, and the firing rate of a unit was determined for each pixel as described above. Pearson r correlations were calculated for the first and second blocks of the session.

Additional statistical tests including analysis of variance (ANOVA) and χ^2 analyses were conducted using SAS V.6.1 (SAS Institute, Inc., Cary, NC, USA). An α level of 0.05 was adopted for these analyses.

RESULTS

Histology and behavior

Implant placement was evaluated for each subject in Nissl-stained coronal sections. In three out of the four rats, implants were located in anterior POR, which was the intended anatomical location (Fig. 2A, C, left). In the fourth rat, however, the electrode was located in an area slightly anterior to the POR, in lateral visual association cortex (VIS_L) according to Swanson (Swanson, 1998), (Fig. 2B, C, right). Because of this difference in placement, the recordings from the fourth rat provided a useful comparison for the cells recorded from POR. For one rat the electrode became dislodged before data were collected in the behavioral protocol. Thus four tetrodes were located in the POR and two in a comparison region, VIS_L . All rats learned the behavioral task equally well within a few days, rapidly adopting a stereotyped strategy such that each arm was visited in succession and very few errors were made. We recorded from a total of 50 cells during the 10-day protocol.

Postrhinal neuronal firing characteristics

Thirty-three cells were recorded from electrodes placed in POR. POR cells had a mean firing rate of 0.16 Hz and a mean number of firing fields of 1.45 (Table 1). POR cells tended to fire in bursts such that single spikes were rarely observed. Some cells fired in multiple conditions such that 21 cells were recorded in the first baseline, 19 in the double rotation, and 19 in the second baseline (Table 2). Fig. 3 shows a representative set of waveforms for a POR cell recorded in the three experimental conditions. Mean firing rates differed significantly over subsequent conditions [$F(2, 56)=4.09, P<0.02$]. Contrasts indicated that the difference was accounted for by significantly lower firing rates in the second baseline as compared with the first ($P<0.005$). Proportionately fewer cells had firing fields in each subsequent condition, 76%, 63%, and 53%, respectively. The mean number of subfields, however, did not differ significantly across conditions ($P>0.33$).

Examination of characteristics of POR firing fields indicated that there were no significant differences across conditions for firing field area, infield firing rate, spatial selectivity, or directional tuning (Table 2).

POR firing field characteristics and disposition

Of the 33 POR cells, 21 cells exhibited firing fields (Table 1). For those cells, the mean number of place fields was 1.85 ± 0.18 . The mean place field area was 8.36 pixels, the mean infield firing rate was 2.62 Hz, the mean spatial selectivity was 1.14, and mean directional tuning was 18.24.

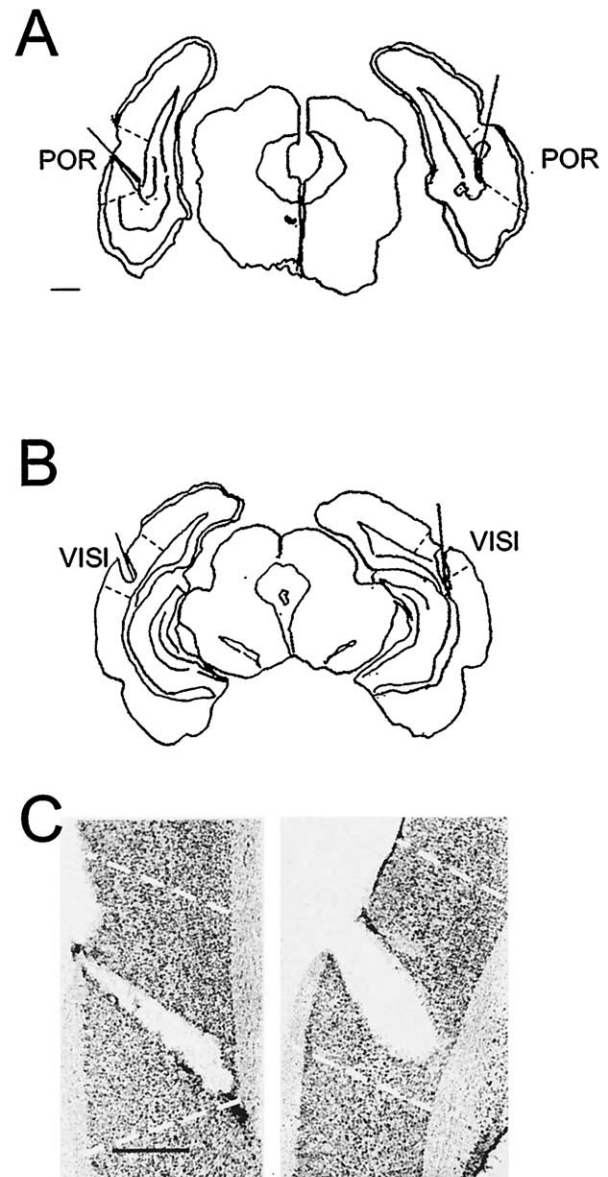


Fig. 2. Reconstruction of representative electrode tracks for POR (A) and VIS_L (B) implants. (C) Nissl-stained tissue showing cannula tracks for the left POR electrode in panel A and the left VIS_L electrode implant shown in panel B. Scale bar=500 μm .

As shown in Table 3, the disposition of POR firing fields in response to a double rotation was quite heterogeneous. Six of a total of 48 firing fields were characterized as unchanged. Fig. 4A shows an example in which two of four firing fields were determined not to have changed. Thirty firing fields either appeared or disappeared with cue manipulation. Ten changed unrelated to manipulated cues. Two rotated with distal cues and no fields were determined to have rotated with local cues.

Examination of the disposition of individual POR firing fields for each cell indicated that each of the 21 POR cells with positional correlates adopted new spatial correlates (remapped) with manipulation of cues. There was little evidence that any individual firing fields followed manipu-

Table 1. Properties of single units recorded in various brain regions during performance on the four-arm radial maze

Properties	Postrhinal cortex	Visual association	Perirhinal cortex ^a	Hippocampal field CA1 ^b	Hippocampal field CA3 ^b
Total cells	33	17	43	73	73
Mean firing rate (Hz)	0.16±0.027	Ψ0.35±0.10	0.32±0.08	*	*
Mean no. place fields	1.45±0.23	0.65±0.21	0.70±0.08	1.20±0.08	0.84±0.07
Cells with place fields (PF)	21 (64%)	8 (47%)	14 (33%)		120 (82%)
Cells firing across conditions	14 (64%)	0 (0%)	2 (5%)	*	*
Mean PF area (pixels)	8.36±0.44	8.00±1.04	6.59±0.47	8.06±0.59	7.60±0.66
Mean infield firing rate (Hz)	2.62±0.16	ΨΨ3.90±0.40	4.50±2.46	3.10±0.42	3.40±0.44
Mean spatial selectivity	1.14±0.04	1.16±0.11	0.91±0.03	1.9±0.07	2.5±0.10
Mean directional tuning	18.24±2.05	21.41±8.12	12.86±2.16	13.9±4.1	14.3±3.6

Here the term *place cell* refers to any cell with positional correlates meeting the criteria for place fields regardless of neuroanatomical location. The top three rows show properties of total cells. The bottom six rows show properties for place cells. Fourteen POR cells with firing fields fired across conditions. Significant differences between POR and VIS_L cortex cells: Ψ P <.05; ΨΨ P <.005. Four of 14 PER single units had two place fields. In all cases both fields responded to the double rotation (DR) in the same way. In contrast, in the POR, only one cell with multiple place fields showed concordance. * Cannot be determined from published study. ^a Data from Burwell et al. (1998) study. ^b Data from Shapiro et al. (1997) study. Total numbers of hippocampal place fields were not distinguished by CA field in Shapiro et al (1997) and thus have been combined, i.e., 120 place fields for a total of 146 cells.

lated cues. In the best example, the cell remapped with the double rotation, and a firing field that had changed unrelated to cues with the double rotation appeared to follow distal cues with the return to the baseline configuration (Fig. 4B). The disposition of the subfields for the 14 cells that fired across conditions can be described as follows: For two cells, firing fields appeared in only one condition. The fields of one cell responded to cue manipulation concordantly. In that case, two fields at the end of one arm changed with the double rotation to the opposite arm, but appeared to maintain the same spatial relation to one another. The fields of four cells changed unrelated to manipulated cues or one another (Fig. 4C). The fields of three cells moved closer to the center of the maze with cue manipulation (Fig. 4D). Finally, the fields of four of the cells split and/or moved farther apart to define the same arm or diagonal across conditions (Fig. 4E). The cell shown in Fig. 4A was placed in this group.

A total of seven POR cells exhibited firing activity in both the first and second baselines. Six of those seven had firing fields. For those cells, the location of firing fields was examined visually, and cross file correlations were computed based on firing rates of pixels that met the visit

criteria. Three cells had two firing fields in the first baseline and one or two in the second baseline, but none in the same place (Fig. 4B, C). Pearson R values ranged from 0.0–0.11. One cell had three firing fields in the first baseline and two in the second baseline, but only one was in the same place (R value not available due improper backup of files). Two cells had one firing field in the same location in the first and third baselines (e.g. Fig. 4E, $r=0.06$ and 0.39). To summarize, firing patterns were generally not similar in the first and second baselines.

VIS_L neuronal firing characteristics

Seventeen cells were recorded from electrodes placed in VIS_L (Table 2). Mean firing rate was 0.35 Hz, and the mean number of firing fields was 0.65 (Table 1). Eight cells were recorded in the first baseline, two in the double rotation, and seven in the second baseline, and none of those cells fired in more than one condition. In general, there were no significant effects of condition for VIS_L cells. Mean firing rates were numerically higher in the first baseline (Table 2), but did not differ significantly across conditions ($P>0.15$). Likewise, the mean number of subfields was not

Table 2. Properties of single units recorded in POR and VIS_L in three conditions on the four-arm radial maze

Properties	Postrhinal cortex (N=33)			Visual association cortex (N=17)		
	First baseline	Double rotation	Second baseline	First baseline	Double rotation	Second baseline
Total cells per condition	21	19	19	8	2	7
Mean firing rate (Hz) ΨΦ	0.23±0.03	0.17±0.03	0.12±0.02	0.49±0.14	0.25±0.01	0.24±0.09
Mean number of firing fields Φ	1.5±0.26	1.4±0.25	0.95±0.22	0.88±0.08	0±0	0.57±0.30
Cells with firing fields (FF)	16 (76%)	12 (63%)	10 (53%)	5 (63%)	0 (0%)	3 (43%)
Total firing fields	30	26	18	7	0	4
Mean FF area (pixels)	9.30±0.88	7.84±0.47	7.44±0.76	7.71±1.19	N/A	8.50±2.17
Mean infield rate (Hz) Φ	2.82±0.27	2.15±0.22	2.86±0.31	3.93±0.34	N/A	3.84±1.04
Mean spatial selectivity	1.16±0.07	1.17±0.07	1.13±0.05	1.03±0.15	N/A	1.38±0.11
Mean directional tuning	17.91±5.64	21.33±5.20	14.84±6.03	19.56±6.72	N/A	24.64±21.00

Significant differences across condition for POR cells, Ψ. Significant differences between POR and VIS_L cortex cells, Φ.

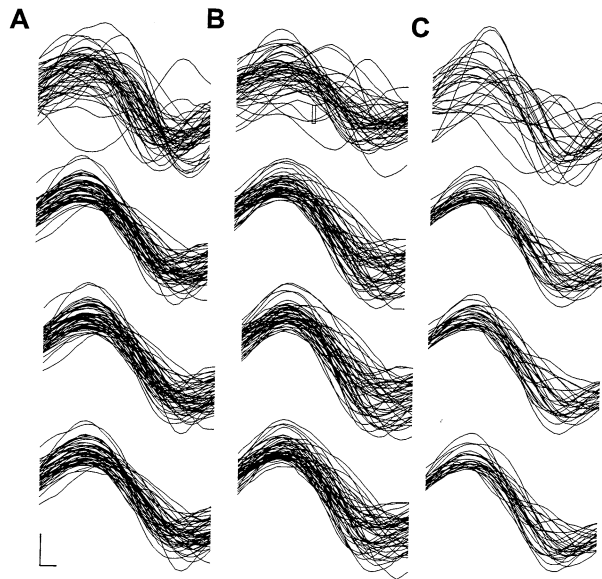


Fig. 3. Representative waveforms for a tetra recording of a POR cell. Waveforms are shown for the four leads (top to bottom) for the three conditions (A, B, and C, respectively). Scale bar=50 μ V \times 50 μ s.

different across conditions ($P>0.44$). Seven of eight cells recorded in the first baseline had firing fields, and three of seven cells recorded in the second baseline had firing fields. For those cells, the mean number of place fields was 1.38 ± 0.26 . Neither of the two cells recorded in the double rotation condition exhibited firing fields. Examination of cross-condition characteristics of VIS_L firing fields revealed no significant differences between the first and second baselines (Table 2).

Regional comparisons

POR cells were significantly more likely to fire in multiple experimental conditions on the same recording day [$\chi^2(1)=4.9$, $P<0.027$]. Some firing characteristics of cells located in POR differed from those of cells located in VIS_L (Table 1). Mean firing rate was significantly lower in POR cells as compared with VIS_L cells [$F(1,48)=5.12$,

$P<0.028$]. POR cells exhibited significantly more firing fields [$F(1,48)=5.32$, $P<0.026$].

The data were also analyzed for differences in raw numbers of spikes. Cells were grouped by region (POR versus VIS_L) and by spatial characteristics, i.e. whether or not they had firing fields (SPATIAL versus NONSPATIAL). POR cells averaged 133 spikes per session and VIS_L cells averaged 262 spikes per session. ANOVA indicated that POR cells had significantly fewer total spikes than VIS_L cells [$F(1,48)=4.60$, $P<0.037$]. Cells with spatial characteristics did have higher numbers of spikes than cells without spatial characteristics [$F(1,48)=5.30$, $P<0.026$]. However, this cannot account for the positional firing characteristics of the cells in each location as there was no interaction of region and spatial characteristics ($P>0.55$). POR cells with spatial firing characteristics had a mean of 170 spikes and those without spatial characteristics had a mean of 61 spikes. By comparison, VIS_L cells with spatial firing characteristics had a mean of 352 spikes and those without spatial characteristics had a mean of 171 spikes.

Both POR and VIS_L cells exhibited positional correlates; 64% of POR cells and 47% of VIS_L cells exhibited firing fields. POR firing fields differed from those of VIS_L in that infield firing rates were significantly lower [$F(1,82)=8.73$, $P<0.004$]. Firing fields of cells recorded in the two locations were not significantly different in field area ($P>0.94$), spatial selectivity ($P>0.83$), or directional tuning ($P>0.86$). POR cells with positional correlates differed from those recorded in VIS_L in the number of subfields, or split firing fields, per cell calculated as the sum of the maximum number of firing fields observed across the three conditions for each cell with firing fields [$\chi^2(3)=8.1$, $P<0.044$]. Sixteen of 21 POR cells with positional correlates exhibited two or three subfields whereas the large majority of VIS_L cells with positional correlates (six of eight) exhibited only one firing field. POR cells with firing fields exhibited 48 fields for 21 cells as compared with 11 fields for eight VIS_L cells (Table 3).

Unlike POR firing fields, none of the 11 VIS_L firing fields was present in more than one condition (Table 3). A total of 7 VIS_L fields were present in the baseline condition,

Table 3. Disposition of place or firing fields with double rotation by region

Spatial characteristics of single units	Postrhinal cortex	Visual association	Perirhinal cortex ^a	Hippocampal CA1 and CA3 ^b
Cells with place fields	21	8	14	120
Total maximum place fields	48	11	18	144
Unchanged	6 (13%)	0	0 (0%)	17 (13%)
Appeared with DR	10 (21%)	4 (36%)	7 (39%)	2 (1%)
Disappeared with DR	20 (42%)	7 (64%)	9 (50%)	30 (21%)
Changed unrelated to cues	10 (21%)	0	1 (5.5%)	32 (22%)
Rotated with distal cues	2 (1%)	0	1 (5.5%)	41 (28%)
Rotated with local cues	0	0	0 (0%)	22 (15%)

Again, *place cell* refers to any cell with positional correlates meeting the criteria for place fields regardless of neuroanatomical location. Maximum number of firing fields refers to the number of firing fields in the condition with the most firing fields, e.g. if a cell had three fields in the baseline and one disappeared in the double rotation, the maximum number of place fields is 3. Four of 14 PER single units had two place fields. In all cases both fields responded to the DR in the same way. In contrast, in the POR, only one cell with multiple firing fields showed concordance. ^a Data from Burwell et al. (1998) study. ^b Data from Shapiro et al. (1997) study.

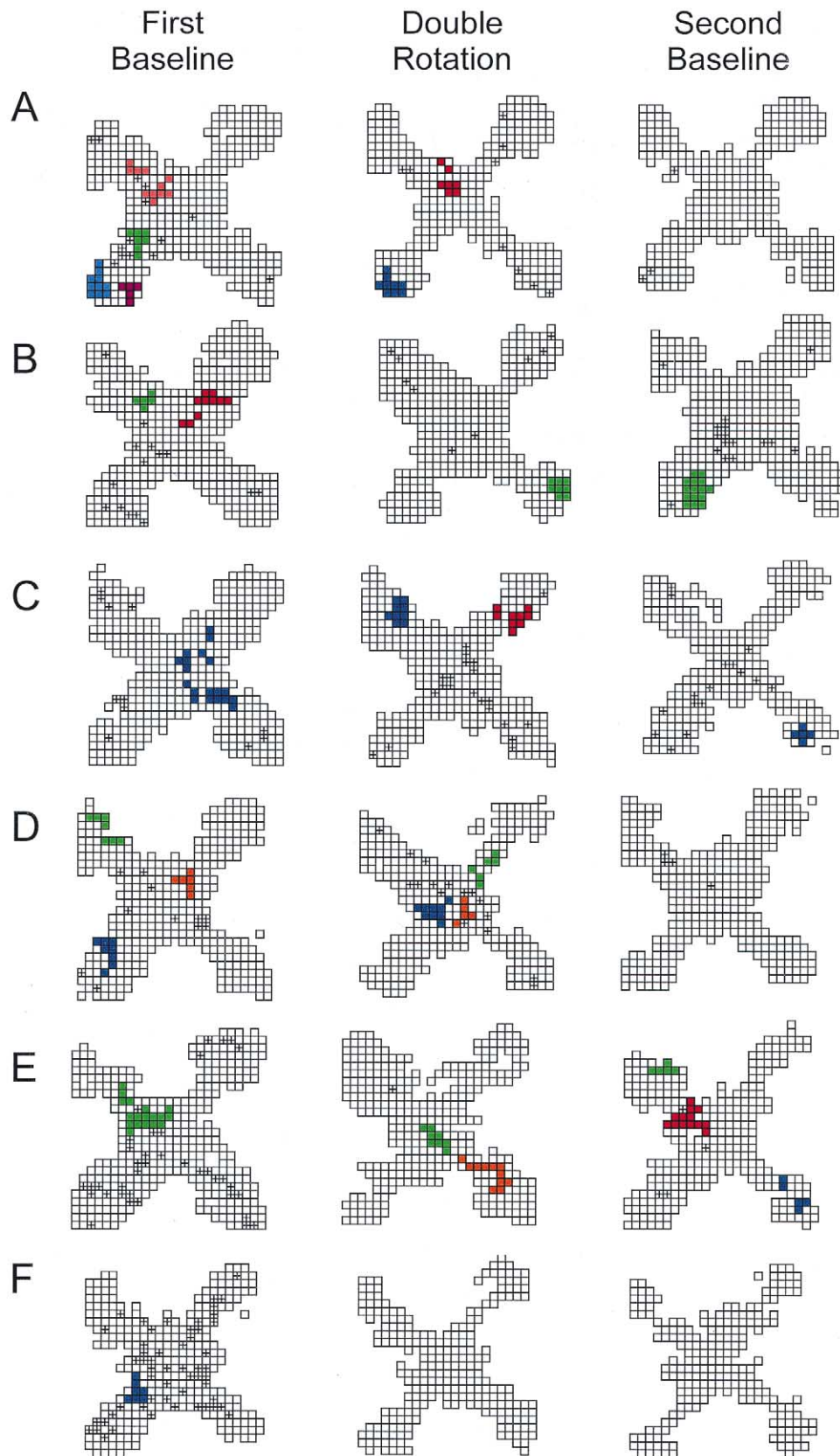


Fig. 4. (Caption overleaf).

disappeared with the double rotation, and did not reappear (e.g. Fig. 4F). Four VIS_L fields appeared in the double rotation or the second baseline condition. For the two cells that exhibited multiple subfields, the fields behaved concordantly, i.e. appeared together or disappeared together.

Stability within a session

Because POR firing fields tended to change spatial correlates across conditions, stability within a session was addressed with post hoc statistical and descriptive analyses. The analysis was conducted on the first baseline session for POR and VIS_L cells with firing fields. Three cells (2 POR and 1 VIS_L) could not be analyzed because the files were not properly backed up leaving 19 POR and 7 VIS_L cells available for this analysis. We divided the initial baseline session of each cell with positional coordinates into two 5-min blocks and evaluated the patterns of raw firing rates for each block. If a cell did not fire in the second 5 min of the session, the first 5 min was subdivided. This situation occurred for three POR cells and 1 VIS_L cell, but the same pattern of results was observed when these cells were dropped from the analysis.

Repeated measures ANOVA of the first condition revealed a main effect of Group on firing rates such that POR cells showed overall lower firing rates than VIS_L cells (Table 4). Numerically, POR cells decreased firing rates across blocks, and VIS_L cells did not. Statistically, however, there was no overall effect of Block and no Block×Group interaction. Post hoc univariate analysis indicated a trend toward a block difference for the POR cells ($P<0.08$), but not for the VIS_L cells ($P>0.87$). For POR cells, six of 19 cells showed increased firing rates as compared with two of seven VIS_L cells.

It has been shown in a similar paradigm that the spatial correlates of hippocampal place cells develop over time (see pp. 5158–5160, Tanila et al., 1997a; see abstract and p. 5172 for discussion, Tanila et al., 1997c). Thus, in a second analysis we evaluated magnitude of the delay to firing onset for each POR and VIS_L cell for the first baseline session. Cells were categorized as to whether they began firing in the first half minute, the second half minute, or after the first minute (Fig. 5). Nine POR cells and 5 VIS_L cells began firing in the first half minute. Thus, both POR and VIS_L cells with firing fields began firing early in a session.

Persistence of the location of firing across blocks was also examined. Within-session correlations of filtered firing rates for POR cells were highly variable and usually low ranging from $r=-0.10$ to $r=0.36$. VIS_L cells also exhibited low correlations (ranging from $r=-0.12$ to $r=0.29$). The low correlations are likely due to relatively short session blocks (2.5 or 5 min), relatively low mean firing rates, and

Table 4. Within-session firing rates

Block	POR	VIS _L
First	0.490±0.100	0.761±0.229
Second	0.260±0.067	0.706±0.334

Firing rates for the first and second 5-min blocks of the first baseline session for cells with firing fields ($n=15$). If the cell stopped firing in the second five minutes ($n=4$), the first 5 min was divided into two 2.5-min blocks. Values represent (mean Hz±S.E.M.).

a tendency to decrease firing across blocks. Visual observation across the session blocks permitted some additional conclusions about the within-session stability of positional firing correlates. Location of firing for a cell was categorized as similar if firing was observed in the same parts of the maze (parts being the four arms and center) for the first and second blocks. For example, if firing was observed when the rat was in the center and the upper two arms in both blocks, the location was categorized as similar. Location was categorized as changed if firing was observed in different parts of the maze for the first and second blocks. Despite low correlations, localization of firing of POR cells was largely similar across session blocks (14 of 19 cells). For example, the location of firing activity for the first and second blocks of the session for the POR cell shown in Fig. 6A was uncorrelated ($r=-0.04$), but that for the POR cell shown in Fig. 6B exhibited a positive correlation ($r=0.36$). As is evident in the figure, both showed similarities across the two session blocks, i.e. in 6A firing is evident in the NW and SW arms and in 6B firing is evident in all four arms. Localization of firing changed for the remaining five POR cells (e.g. Fig. 6C). Visual examination of VIS_L cells showed that four cells exhibited similar location of firing (Fig. 6D) and three showed changed location of firing (Fig. 6E).

A frequency analysis was conducted to determine whether the magnitude of delay of onset of firing was related to the stability of the location of firing. This was conducted only for POR cells as there were not sufficient numbers of VIS_L cells to complete the analysis. POR cells with early onset of firing were significantly more likely to exhibit similar localization of firing across the session [$\chi^2(2)=6.1$, $P<0.047$]. Indeed, all nine POR cells that began firing in the first half minute of a session were categorized as showing similar firing across session blocks.

To summarize, the evidence shows that POR firing fields were not stable across sessions. Rather, they tended to remap with changes in the environment even when the change was a return to the baseline condition. Within a session, positional correlates were largely the same, but firing rates tended to decrease as the recording session

Fig. 4. Disposition of POR firing fields across the three experimental conditions. The reference frame is fixed relative to the room. Firing fields are color coded such that all pixels meeting the criteria for a place field are the same color. Any pixels having a firing rate that was below threshold for a subfield is indicated by a cross in the pixel. (A) Example of a cell for which two subfields did not change in response to cue manipulation and two disappeared. (B) One cell appeared to have a firing field that rotated with distal cues between the double rotation and the second baseline. (C) Example of a cell for which the fields changed largely unrelated to manipulated cues. (D) Example of a cell for which the fields moved closer together. (E) Another type of cell became less selective spatially, but seemed to become more selective by representing a diagonal on the maze. (F) Example of a representative cell with positional correlates recorded in VIS_L.

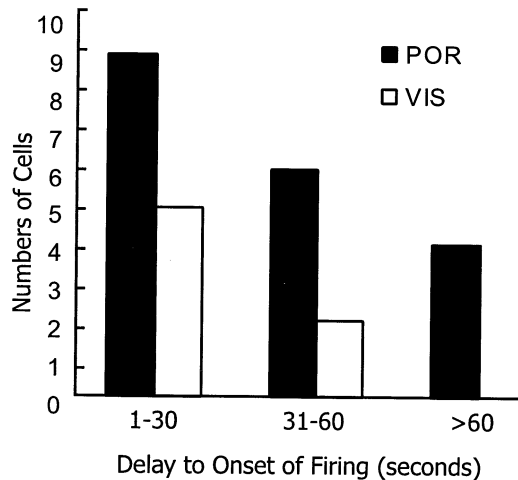


Fig. 5. Delay to onset of firing for POR and VIS_L cells. Numbers of cells with firing fields exhibiting onset of firing in the first 30 s, the second 30 s, or later are shown for POR and VIS_L. For both regions onset of firing tends to be early, within the first 30 s.

proceeded. POR cells that began firing early in a session exhibited greater stability in localization of firing.

DISCUSSION

The POR is reciprocally connected with the medial entorhinal cortex (Burwell and Amaral, 1998b), the hippocampus, and the subiculum (Naber et al., 1997). Cells with spatial firing correlates have been identified in each of these regions. This study examined whether cells in the POR also display spatial firing properties. Because the POR is interconnected with the hippocampus, it might be expected that POR cells exhibiting positional firing correlates would show the same properties as place cells recorded in the hippocampus, i.e. would be sensory bound and would reliably follow experimentally manipulated cues. Alternatively, if one considers the hippocampus to be at the top of a hierarchy of spatial information processing, it might be expected that the POR is involved in the pre-processing of information in a way that permits the formation of sensory-dependent place fields observed in the hippocampus.

To summarize the evidence presented here, we found that 64% of cells recorded in the POR during performance in the four-arm radial maze task contained one or more firing fields during at least one condition. While this is lower than the 82–85% of the cells that contain place fields in the hippocampus in the same task (Phillips and Eichenbaum, 1998; Shapiro et al., 1997), it is higher than the percentage found in the PER (33%) (Burwell et al., 1998) and for VIS_L (47%). Indeed, almost two-thirds of the cells in the POR fell within the definition of a place cell, i.e. their firing patterns reliably reflected the physical location of the animal in the maze during a recording session. POR firing fields remapped when the experimental cues were manipulated and did not return to baseline configuration when the cues were returned to their original locations.

Within a session, firing rates of POR cells tended to decrease and localization was similar but more restricted

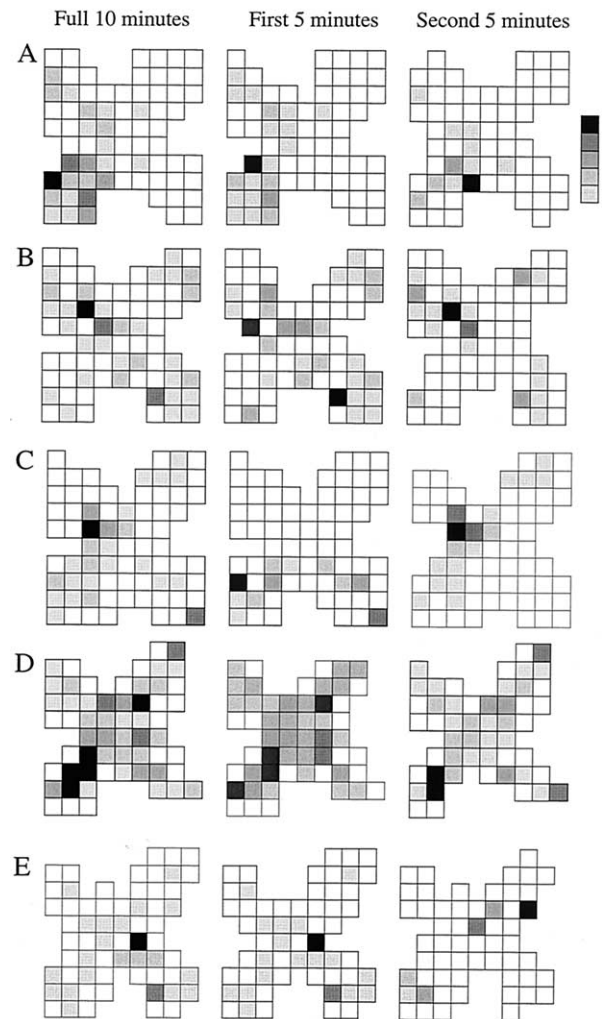


Fig. 6. Stability of neuronal activity within a session. The reference frame is fixed relative to the room. Firing rates are shown for an entire baseline 10-min session, the first block, and second block (left, middle, and right columns, respectively). (A and B) Representative POR units in which firing rates decreased and positional correlates were similar as the recording session continued. (C) One of the few POR units for which firing rates increased and positional correlates changed as the recording session continued. (D) Firing rates for a representative VIS_L cell for which firing rates and positional correlates were similar across first and second blocks of the session. (E) Firing rates for a VIS_L cell for which localization of firing changed across blocks. Gray scale: The mean firing rate for pixels meeting the visit criteria was divided by five to provide a five-level linear gray scale. White designates pixels for which there was no firing. Peak firing rate for panels A–E was 2.3, 2.2, 1.3, 3.8, and 2.4 Hz, respectively.

with continued exposure to the environment. This differs from the findings for hippocampal cells in the same paradigm in which firing onset is often delayed (Tanila et al., 1997a). Firing onset for 70% of hippocampal cells in the same paradigm is after the start of the second four-arm radial maze trial and for 30% is after the fourth to fifteenth trial. These findings are consistent with the idea that POR neuronal activity in the four-arm radial maze task is signaling changes in the environment rather than encoding place as hippocampal place cells seem to do.

Firing characteristics of VIS_L cells differed significantly from those of POR cells on several measures. VIS_L cells exhibited higher firing rates and fewer split fields. VIS_L firing did not fire in more than one condition. It may be that the cells in VIS_L were responding to highly specific visual stimuli. Such stimuli would be transient because of changes in the appearance of the maze and the location and head direction of the animal would be expected to preclude stable representation of highly specific cues. Thus, by disappearing or appearing with cue manipulation, VIS_L firing fields behaved as would be expected.

Firing characteristics and behavioral correlates of POR cells were compared with those of other regions that have been tested in similar paradigms. Methods used in the present study differ slightly from prior studies of neuronal correlates of hippocampal (Shapiro et al., 1997) and PER (Burwell et al., 1998) cells in the four-arm radial maze. Perhaps the most important procedural difference between studies is that the minimum place field size was three pixels in earlier studies of different regions as opposed to five in the present study. The minimum subfield area was adjusted because of a concern that noisier firing patterns might yield artifactually high numbers of split firing fields. POR cells exhibited more split fields despite the more conservative threshold for field area. Another difference is that animals were rewarded with lateral hypothalamic stimulation in the prior studies, but water in the present study. In the earlier studies, rewarding stimulation might have been more motivating for some animals such that a sufficient number of trials could be completed in less than 10 min. Indeed, sessions were 5–10 min in the prior studies. In the present study, all sessions were at least 10 min.

Despite the more conservative criteria for defining firing fields, the POR yielded proportionately more cells with positional correlates than the PER but fewer than the hippocampus (Table 1). The spatial selectivity of POR firing fields was higher than those of PER, but lower than for hippocampal place fields. Notably, the directional tuning of POR cells was higher than that of place cells in the other regions. Although a relatively small proportion of POR cells recorded had positional correlates, a large proportion of those POR cells (93%) exhibited a greater number of multiple or split fields as compared with place cells recorded in other brain regions. This is illustrated in Fig. 7, which shows the frequency of occurrence of multiple fields for the POR (this study), the PER (Burwell et al., 1998), and the hippocampus (Shapiro et al., 1997).

Compared with place cells recorded in the hippocampus under the same conditions, POR firing fields were much more likely to remap in response to changes in experimental cues. Thus, POR positional correlates were not stable across sessions. Indeed, all 21 POR cells with positional correlates remapped with cue manipulation. That is, one or more firing fields appeared, disappeared, or changed unrelated to manipulated cues. One concern is that POR fields that disappeared resulted from losing a cell; however, when fields disappeared or cells stopped firing, in all cases, other cells isolated for the same animal on the same day continued to fire across sessions. As is

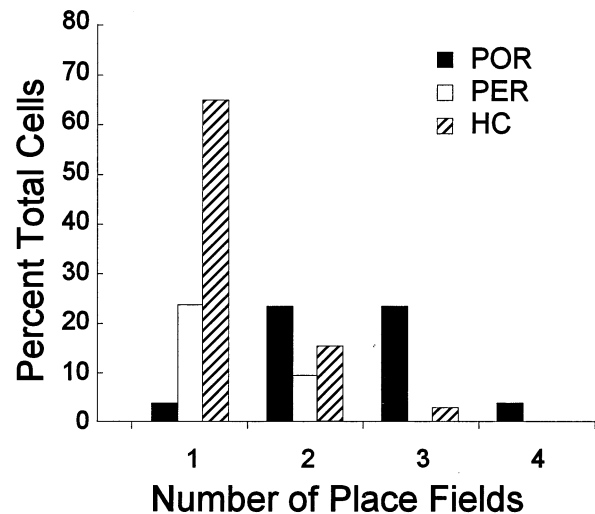


Fig. 7. Numbers of place/firing fields in the POR, PER (Burwell et al., 1998), and hippocampal fields CA1 and CA3 (Shapiro et al., 1997). The POR has more cells with firing fields than the PER and less than the hippocampus. POR cells with firing fields had a greater tendency to exhibit split or multiple firing fields than PER or hippocampal place cells.

more common for hippocampal place cells, only one POR firing field returned to the original baseline configuration with the second baseline. Taken together, the data are consistent with the idea that the POR is involved in pre-processing of information about the environment and that the intact hippocampus confers stability upon POR input about place.

Although the interpretation that POR cells remap with cue manipulation is consistent with the data, data for four cells might be interpreted differently. An example is shown in Fig. 4E. Although individual fields of a postrhinal cell changed unrelated to manipulated cues, taken together the group of firing fields described an arm or diagonal either in a stable manner or in a progressively more selective manner. One possibility is that these POR cells differ from the remaining cells because they reflect subicular output. This is consistent with a model of ventral subiculum proposed by Phillips and Eichenbaum (1998) in which ventral subicular neurons encode complex configural cues based on converging input from multiple CA1 neurons (see also Sharp, 1999).

Most POR cells with positional correlates exhibited split or multiple fields, which did not exhibit concordance across session. Only one cell had fields that changed concordantly in response to cue manipulation. In contrast, the firing fields of all four of 14 PER cells that exhibited multiple place fields responded concordantly to cue manipulation. Hippocampal place cells with multiple fields tend to be mixed with some showing field concordance and others not (Tanila et al., 1997b).

The firing properties of neurons in the POR during performance on the four-arm maze suggest that this area is involved in processing information about the environment; however, the low spatial selectivity and the tendency of POR cells to remap indicate that the area does not

maintain a precise or stable representation of place. One interpretation of these data is that the POR, along with the PER and medial entorhinal area, relays visuospatial information to the hippocampus. The hippocampus then integrates information from the POR and other areas to create a stable representation of space reflected by place cell activity. This interpretation encompasses the possibility that the POR is simply a conduit for the information. Given its neuroanatomical connections, however, it is more likely that the POR performs particular computations on visuospatial input. For example, the POR may participate in visuospatial functions, by automatically monitoring the spatial environment for changes in environmental stimuli and reflecting that information in its signal output. To test this hypothesis, future studies could examine postrhinal responses in a visuospatial attention-orienting task.

The above notion is interesting in light of an outstanding issue about medial temporal lobe functions, i.e. how are stimuli tagged for more focused processing when either relevant to a task, such as object discrimination, or when needed for spatial functions such as spatial navigation. One possibility is that POR neuronal firing correlates reflect the current environmental or spatial stimuli and signal changes in those stimuli. By this view the functions of the POR would be characterized as perceptual rather than mnemonic. This is consistent with recent functional imaging studies of the human parahippocampal area suggesting that the region is involved in processing new perceptual information about the appearance and layout of scenes (Epstein et al., 1999). Thus, the POR might provide a background upon which stimuli are selected for more focused processing by other medial temporal lobe structures, for example, the PER (for object identification functions) or the hippocampus (for spatial memory). According to this view, the relational or configural functions of the hippocampus may be dependent upon serial processing of information by the POR and the PER. This is consistent with the medial temporal lobe anatomy in that the POR projection to the PER is much stronger than the return projection. It is also consistent with recent findings that both the PER and POR contribute to the processing of contextual information (Bucci et al., 2000, 2002).

To summarize, this is the first demonstration of positional firing correlates for POR. POR cells with firing fields differed markedly from the classically defined place cell described for the hippocampus. Hippocampal place cells in classical paradigms typically have a single place field that is stable across conditions, whose location can usually be predicted by identifiable sensory cues. In contrast, POR cells exhibit multiple firing fields that are changeable across conditions, but that change neither concordantly nor predictably with respect to controlled cues. The evidence suggests that POR cells with positional correlates are repeatedly remapping with changes in the environment. Thus, response patterns of POR neurons may reflect an early step in a spatial pathway that produces the selective, stable place fields of the hippocampus.

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