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Object and Place Memory in the Macaque Entorhinal Cortex

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Suzuki, Wendy A., Earl K. Miller, and Robert Desimone. Object and place memory in the macaque entorhinal cortex. *J. Neurophysiol.* 78: 1062–1081, 1997. Lesions of the entorhinal cortex in humans, monkeys, and rats impair memory for a variety of kinds of information, including memory for objects and places. To begin to understand the contribution of entorhinal cells to different forms of memory, responses of entorhinal cells were recorded as monkeys performed either an object or place memory task. The object memory task was a variation of delayed matching to sample. A sample picture was presented at the start of the trial, followed by a variable sequence of zero to four test pictures, ending with a repetition of the sample (i.e., a match). The place memory task was a variation of delayed matching to place. In this task, a cue stimulus was presented at a variable sequence of one to four ''places'' on a computer screen, ending with a repetition of one of the previously shown places (i.e., a match). For both tasks, the animals were rewarded for releasing a bar to the match. To solve these tasks, the monkey must *1*) discriminate the stimuli, *2*) maintain a memory of the appropriate stimuli during the course of the trial, and *3*) evaluate whether a test stimulus matches previously presented stimuli. The responses of entorhinal cortex neurons were consistent with a role in all three of these processes in both tasks. We found that 47% and 55% of the visually responsive entorhinal cells responded selectively to the different objects or places presented during the object or place task, respectively. Similar to previous findings in prefrontal but not perirhinal cortex on the object task, some entorhinal cells had sample-specific delay activity that was maintained throughout all of the delay intervals in the sequence. For the place task, some cells had location-specific maintained activity in the delay immediately following a specific cue location. In addition, 59% and 22% of the visually responsive cells recorded during the object and place task, respectively, responded differently to the test stimuli according to whether they were matching or nonmatching to the stimuli held in memory. Responses of some cells were enhanced to matching stimuli, whereas others were suppressed. This suppression or enhancement typically occurred well before the animals' behavioral response, suggesting that this information could be used to perform the task. These results indicate that entorhinal cells receive sensory information about both objects and spatial locations and that their activity carries information about objects and locations held in short-term memory.

INTRODUCTION

The structures of the medial temporal lobe have long been thought to play an important role in normal memory function. Neuropsychological studies of humans with damage to the medial temporal lobe as well as functional imaging studies in humans support the idea that medial temporal lobe structures participate in a variety of different kinds of memory tasks, including those requiring memory for objects, locations, or memory for the location in which a particular object was shown (Aguirre et al. 1996; Cave and Squire 1991; Milner 1972; Owen et al. 1996; Smith 1988; Smith and Milner 1981, 1989; Squire et al. 1988; Warrington and Baddeley 1974). Similarly, medial temporal lobe damage in monkeys produces impairments in memory for visually presented objects (Mishkin 1978; Zola-Morgan and Squire 1985), tactile memory (Murray and Mishkin 1984; Suzuki et al. 1993), and memory for the spatial location of objects (Angeli et al. 1993; Parkinson et al. 1988).

Within the medial temporal lobe, the entorhinal and perirhinal cortices both appear to contribute to object recognition memory as measured in the delayed nonmatching to sample task. In this task, animals are first shown a novel stimulus as the sample, followed after a variable delay interval by the same stimulus paired with a novel test stimulus. The animal is rewarded for selecting the novel test stimulus (i.e., the nonmatching test item). Combined lesions of perirhinal and entorhinal cortices (Eacott et al. 1994; Meunier et al. 1993) or perirhinal and parahippocampal cortices (Suzuki et al. 1993; Zola-Morgan et al. 1989), or lesions of the perirhinal cortex alone (Meunier et al. 1993), significantly impair performance on the delayed nonmatching to sample task. Lesions limited to the entorhinal cortex result in milder memory impairments (Leonard et al. 1995; Meunier et al. 1993), but adding an entorhinal lesion to a perirhinal lesion significantly exacerbates the impairment on the delayed nonmatching to sample task compared with lesions of the perirhinal cortex alone (Meunier et al. 1993).

Neurophysiological studies indicate that both the perirhinal and entorhinal cortices receive sensory information about visual objects. Like cells in adjacent area TE, perirhinal cells have large, bilateral receptive fields that typically include the center of gaze and have complex stimulus selectivity (Desimone and Gross 1979; Lueschow et al. 1994; Miller et al. 1993). Entorhinal cortex receives powerful inputs from perirhinal cortex (Insausti et al. 1987; Suzuki and Amaral 1994a; Van Hoesen and Pandya 1975), but little is known about the sensory properties of entorhinal cells in the monkey except that the do appear to respond selectively to different complex visual stimuli (Fahy et al. 1993; Riches et al. 1991).

Neurophysiological studies also suggest that perirhinal and entorhinal cells contribute to object recognition memory, although far more is known about the properties of perirhinal cells than entorhinal cells. Most studies of perirhinal cortex have recorded the properties of cells while monkeys performed versions of the delayed match to sample (DMS) task. In this task, a sample stimulus is followed, after a delay, by a matching or nonmatching test stimulus, and the animal is rewarded for responding to the matching stimulus (Brown et al. 1987; Fahy et al. 1993; Li et al. 1993; Miller and

Desimone 1994; Miller et al. 1991b, 1993; Nakamura and Kubota 1995; Riches et al. 1991). In our studies, we used a sequential version of the DMS task in which the sample stimulus was followed by a variable sequence of several test stimuli, the last of which matched the sample. For example, a stimulus sequence on one trial might consist of A. . .B. . . C. . .D. . .A, and the animal would be rewarded for responding to the final A.

In both the sequential and standard versions of DMS, we and others have found that the responses of many perirhinal cells to test stimuli that matched the sample were suppressed relative to nonmatching stimuli (Brown et al. 1987; Fahy et al. 1993; Li et al. 1993; Miller and Desimone 1994; Miller et al. 1991b, 1993; Nakamura and Kubota 1995; Riches et al. 1991). Because this suppressive effect occurred before the time of the behavioral response, it has been proposed that it might mediate working memory for the sample stimulus. However, it was later found that the suppressive effect also occurred when a behaviorally irrelevant nonmatching stimulus was repeated in the sequence (e.g., A. . .B. . .B. . .A), indicating that suppression occurs automatically for any type of stimulus repetition (Miller and Desimone 1994). Thus, ''repetition suppression'' apparently does not depend on active working memory. Relatively long-term response suppression is also found when initially novel stimuli are repeated over the course of a recording session (Brown et al. 1987; Fahy et al. 1993; Li et al. 1993; Miller et al. 1991b; Riches et al. 1991). Repetition suppression may contribute to priming and novelty effects in memory as well as behavioral habituation.

In addition to the perirhinal cells showing repetition suppression, other perirhinal cells gave enhanced responses to stimuli matching the sample (Miller and Desimone 1994). Unlike repetition suppression, the enhancement occurred only for the test stimulus that matched the sample stimulus actively held in memory and did not occur when nonmatching stimuli were repeated in the test stimulus sequence. Thus the enhancement effect in perirhinal cortex appears to depend on active working memory.

In addition to its effects on the responses of perirhinal cells to test stimuli in the DMS task, the memory of the sample stimulus is also reflected in the activity during the delay. For many perirhinal cells, the activity in the delay following a preferred sample is higher than in the delay following a nonpreferred sample (Miller et al. 1993; Miyashita and Chang 1988). It has been proposed that the delay activity in perirhinal cortex actually maintains an explicit representation of the sample stimulus that the animal is holding in memory (Miyashita and Chang 1988). However, the sample-specific delay activity in perirhinal cortex is not maintained following the intervening nonmatch stimuli in the sequential DMS task, even though the animal clearly maintains a memory of the sample that survives intervening stimuli (Miller et al. 1993). By contrast, delay activity in prefrontal cortex does survive intervening stimuli in the same sequential DMS task used in perirhinal cortex (Miller et al. 1996).

Much less is known about the role of entorhinal cells in object memory. Some entorhinal cells do, however, exhibit repetition suppression (Fahy et al. 1993; Riches et al. 1991). Likewise, nothing is known about the role of monkey entorhinal neurons in place memory. However, anatomic studies not only support the notion that the entorhinal cortex contributes to both object and location memory, but provide predictions concerning which portions of the entorhinal cortex may be particularly involved in these functions. Object information from the ventral stream is potentially sent to entorhinal cortex via the perirhinal cortex, which projects primarily to anterior and lateral portions of the entorhinal cortex (Suzuki and Amaral 1994a). By contrast, visuospatial information from the dorsal stream pathway projects strongly to posterior portions of the entorhinal cortex via the parahippocampal cortex (Andersen et al. 1990a; Cavada and Goldman-Rakic 1990; Suzuki and Amaral 1994a,b). In addition, a prominent disynaptic projection also exists from the parahippocampal cortex to anterior and lateral entorhinal cortex via the perirhinal cortex (Martin-Elkins and Horel 1992; Suzuki and Amaral 1994b). These projection patterns suggest that all anterior-posterior levels of the entorhinal cortex may be involved in processing visuospatial information.

To examine the neural correlates of object memory in the entorhinal cortex, the responses of entorhinal cells were recorded as animals performed a version of the DMS task. The task was the same sequential version of DMS that has been used in our laboratory to examine mnemonic properties of cells in both the perirhinal and prefrontal cortices (Miller et al. 1993, 1996). This task was chosen to allow comparisons across all three areas. As a further comparison with the results on object memory, an additional animal was studied with the use of a newly developed task of location memory, the sequential delayed match to place (DMP) task. This task was roughly similar to the DMS task, except that the monkey was required to remember locations rather than objects.

METHODS

Subjects and surgical procedures

The subjects were three rhesus monkeys (*M1*, *M2* and *M3*) weighing 7–9 kg. *Animals M1* and *M2* were previously used in studies of visual object memory in the inferior temporal cortex by Lueschow et al. (1994) and Miller et al. (1993), respectively. Brain images taken in the stereotaxtic plane were obtained for all three animals with the use of magnetic resonance imaging. Following the technique described by Alvarez-Royo et al. (1991) with slight modifications, brain ''atlases'' were prepared from the individual sets of magnetic resonance imaging scans and appropriate coordinates for placement of the recording chamber on the dorsal surface of the skull were determined. The recording chamber, head restraint post, and scleral eye coil used to monitor eye position (Robinson 1963) were all implanted under aseptic conditions while the animal was anesthetized with isofluorane anesthesia. A prophylactic regime of antibiotics and analgesics was administered postoperatively.

Recording techniques

The recording techniques were the same as previously described (Miller et al. 1993). Briefly, a 23-gauge guide tube containing a parylene-coated tungsten microelectrode was advanced to ~10–15 mm above the ventral surface of the entorhinal cortex with the use of coordinates derived from the magnetic resonance imaging scans. The electrode was then slowly advanced out of the guide tube to the level of the entorhinal cortex until the activity of one or two single neurons could be isolated. During the recording ses-

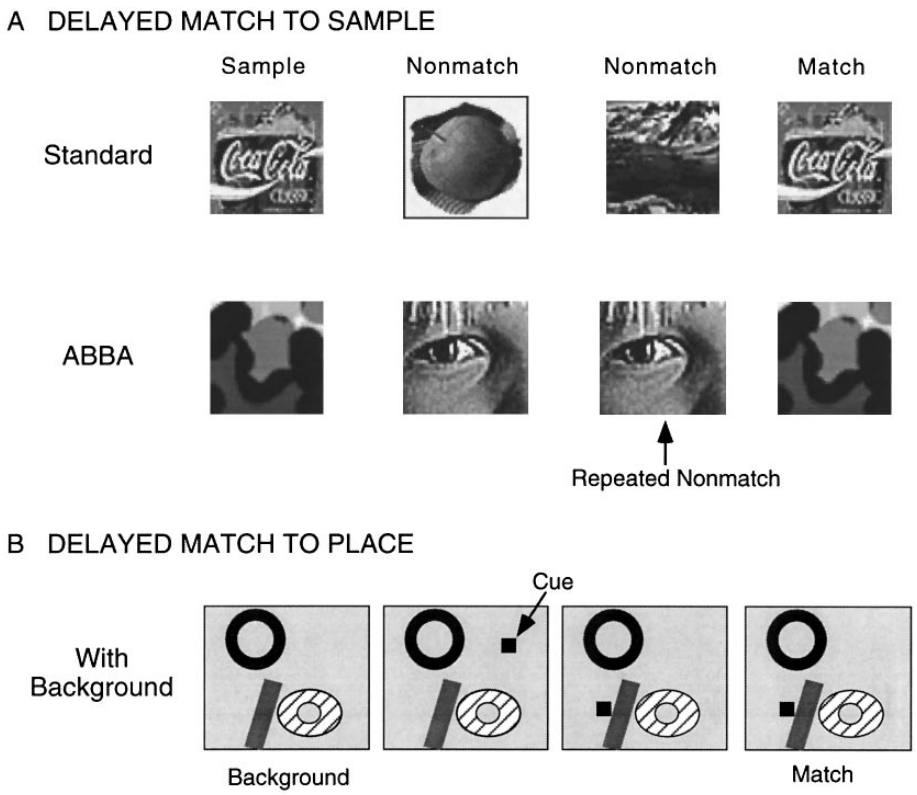

FIG. 1. *A*: schematic diagram of the delayed match to sample (DMS) task. Stimuli shown are gray scale representations of typical complex color stimuli used in the task. Each stimulus in the sequence was presented for 500 ms, except that the match stimulus was terminated as soon as the animal made a behavioral response. Delay intervals: 1,000 ms (*animal M1*); 700 ms (*animal M2*). Animal was rewarded for releasing a bar when the stimulus matching the sample appeared. See text for detailed description of standard and ABBA trial types. *B*: schematic diagram of the delayed match to place (DMP) task with background stimulus. A cue stimulus (■) was shown sequentially at several different locations on the screen. Background consisted of several geometric patterns that remained on screen for the duration of the trial. A cue stimulus was presented for 500 ms at each location, separated by delay intervals of 1,000 ms. Animal was rewarded for releasing the bar when any cue location was repeated in the sequence.

sions for both the object and place tasks, the responsiveness of the isolated neurons was assessed through the use of an audio monitor. If a neuron appeared to respond differentially during any phase of the task (i.e., during stimulus presentation or during the delay intervals), data collection was initiated. If the neuron did not appear to be responsive on the basis of auditory monitoring, it was noted as a nonresponsive cell and the electrode was advanced until another neuron was isolated.

Behavioral tasks

DMS TASK. *Animal M1* performed a modified version of the DMS task previously described in detail by Miller et al. (1993, 1996). The task is outlined in Fig. 1*A*. Briefly, the trial began with the monkey grasping a metal bar and fixating a small target in the center of the screen. Trials were aborted if the monkeys' gaze left a fixation window of 2.5° at any time during the remainder of the trial. Three hundred milliseconds after the animal achieved fixation, a sample stimulus was presented in the center of the screen, followed by a sequence of between zero and four nonmatching test items, also presented at the center of the screen. All sequences ended with the presentation of a test stimulus that matched the sample (i.e., a match). Animals were rewarded with fruit juice for releasing the bar within 500 ms of the match stimulus onset.

All visual stimuli were presented for 500 ms, except that the match stimulus was extinguished as soon as the monkey made its behavioral response. Delay intervals between stimuli were 1,000 ms in duration. Two different kinds of DMS trials were presented in a randomly intermixed fashion. One kind of trial has been referred to as ''standard'' (Miller and Desimone 1994; Miller et al. 1996). For these trial types, each of the nonmatching test items in the sequence was unique (Fig. 1*A*, Standard). Thus a sample stimulus A might be followed by the presentation of B. . .C. . .D. . .A. The correct response was a bar release to the second presentation of stimulus A. In the second type of trial, termed ''ABBA,'' one of the nonmatching test items was repeated (Fig. 1*A*, ABBA). In this case, sample stimulus A might be followed by the presentation of B. . .B. . .C. . .A. In this case, the correct response was to ignore the repetition of stimulus B (i.e., the repeated intervening test item) and respond to the second presentation of the sample stimulus A.

As previously described (Miller et al. 1993), the stimuli used for the task were multicolored pictures digitized from magazine photographs ranging in size from 1 to 3°. These are the type of stimuli that have previously been used to elicit stimulus-selective responses from perirhinal and prefrontal neurons (Miller et al. 1993, 1996). Gray scale representations of the type of complex stimuli used in the task are illustrated in Fig. 1*A*. Each cell was tested with between 6 and 18 stimuli, randomly chosen from a larger set of >300 stimuli. From that set of stimuli, which typically included stimuli that were both novel and familiar to the animal, a final set of six stimuli was chosen. We did not attempt to determine the ''optimal'' stimulus for any cell. Rather, the purpose of the initial screening was to find a set of stimuli that elicited a range of responses. This final set of six stimuli was then used in the formal testing of the cell such that each of the stimuli was shown in a counterbalanced fashion, sometimes as sample/match combinations and sometimes as nonmatches. Thus, in contrast to the versions of DMS typically used in neurobehavioral studies, this version of the task was not ''trial unique.''

Although most of the details of the DMS task performed by *animals M1* and *M2* were the same, there were also some notable differences. For example, *animal M2* performed a version of the DMS task in which only standard trials were given. In addition, the delay interval between intervening test items for *animal M2* was 700 ms in duration instead of 1,000 ms. Finally, *animal M1* had a great deal of difficulty performing trials with more than three nonmatching items in the sequence. Thus, in most sessions, this was the longest sequence used. *Animal M2* performed somewhat better on the longest sequence (see BEHAVIORAL PERFORMANCE),

and therefore sequences with up to four nonmatching items were used in all sessions in this animal.

DMP TASK. *Monkey M3* was trained on a place memory task in which cue stimuli were presented in a variable sequence of different locations or places on a computer screen. The task is outlined in Fig. 1*B*. The computer screen subtended ~12.5 and 9.5° of visual angle in the horizontal and vertical planes, respectively, and the cue stimuli appeared within a square region of ~7 × 7° (see below). The animal was required to remember all the cue locations in a sequence and to respond when any one of the locations was repeated in the sequence.

The animal initiated each trial by grasping a metal bar. A background stimulus made up of multiple geometric elements that covered a large extent of the computer screen was then presented and remained on the screen for the duration of the trial. A cue stimulus consisting of a dark green 1 × 1° square was then presented, superimposed on the background stimulus, in a variable sequence of up to four unique locations plus one repeated location on the screen. Each of the cue presentations was 500 ms in duration, separated by delay intervals of 1,000 ms. The background stimulus remained on the screen for the entire trial. The sequence ended when one of the cue locations was repeated (i.e., a match). If the animal released the bar within 500 ms of the onset of the matching cue location, it was rewarded with a drop of fruit juice. Each day, cue locations were chosen in a psudorandom fashion such that one cue appeared somewhere within each of the four quadrants of the screen (i.e., top left, top right, bottom left, bottom right). Generally, the cue locations were separated by ~3–8° of visual angle on the screen.

Despite a lengthy training protocol, we were unable to train the animal to maintain fixation on a central fixation target throughout the trial. As a consequence, eye position was not controlled for the majority of cells tested on the DMP task. Instead, the effect of eye movements on neuronal responses was tested in a separate control experiment (see *Fixation control experiment*). In addition, eye position was recorded with the use of the magnetic search coil technique and stored for later analysis.

Notably, the matching rule used on the DMP task (i.e., respond to the cue appearing in any of the previously shown locations) differed from the matching rule used in the DMS task (i.e., respond to the repetition of the sample stimulus shown at the beginning of the trial). There were two major reasons for using a different rule. First, if the animal had to remember only a single sample cue location presented at the start of the trial, we were concerned that the animal would simply attend to or even simply look at that location on the screen for the duration of the trial and respond whenever a second stimulus appeared there. With this strategy, the animal would not have to process any of the nonmatching stimuli, unlike in the DMS task. Second, many of the place memory tasks known to be sensitive to medial temporal lobe damage in humans require memory for multiple spatial locations (Cave and Squire 1991; Smith and Milner 1981; Warrington and Baddeley 1974). The version of the DMP task in which up to four locations were held in memory was more similar to this kind of task.

Changing backgrounds experiment. A subset of the neurons recorded in the DMP task was tested with the standard background stimulus as well as one to two different background stimuli. For these cells, the four tested cue locations remained constant across all of the different backgrounds.

A number of different testing protocols was used for the changing background experiments. For the majority of cells, responses were first recorded in the first part of the recording session with the use of the standard background stimulus. Responses were then recorded when the background was removed and the cues were shown on a homogeneous gray screen (''no-background'' trials). For some cells, the no-background conditions were tested first, followed by the standard background trials. For a smaller number of cells, three unique background conditions were tested.

Fixation control experiment. For these experiments, *animal M3* was retrained on a version of the task that required fixation on a central fixation target from the beginning of the trial through the time of the first cue stimulus presentation. Following the first cue, however, the fixation target was extinguished and the animal was free to move the eyes. This version of the task proved very difficult for *animal M3* to learn. To facilitate performance, the delay intervals for these experiments were decreased from 1,000 to 500 ms. All other aspects of the task were the same as described above.

Data analysis

Responses to stimuli were calculated over a 200-ms time interval beginning 75 ms after stimulus onset. The start point of the time interval was chosen to correspond with the shortest average response latency of entorhinal neurons, and the endpoint was chosen to occur well before the time of the behavioral response. The delay period firing rate was calculated over the last 500 ms of the delay interval. The first portion of the delay intervals was not included so as to exclude any changes of response related to the offset of the preceding stimulus. Baseline activity was calculated over the 100-ms interval preceding either the sample presentation for the DMS task or the first cue presentation for the DMP task.

Analysis of variance (ANOVA) and *t*-tests were used to evaluate responses of individual cells to visual stimuli as well as their firing rate in delay intervals. A criterion level of $P < 0.05$ was used in these analyses. Some statistical analyses were conducted on the distribution of responses across the population of cells, such that each cell contributed a mean response for each condition examined. Other tests examined responses from individual cells comparing neuronal responses on individual trials in different behavioral conditions. For *animal M1*, the DMS data sets were composed of an average of 117 correct trials (range 72–243) made up of approximately equal numbers of trials with between zero and three intervening stimuli interposed between the sample and the match. In a typical data set there were ~270 correct responses to stimuli shown as nonmatches and 117 correct responses to stimuli shown as matches that were available for analysis. Each of the six stimuli used for that particular data set was shown an average of 45 times as a nonmatch and 18 times as a match. For *animal M2*, data sets were composed of an average of 269 correct trials (range 118–460). The total number of correct trials was approximately equal for sequence lengths including up to three intervening items (range 18–26% of total), with somewhat fewer correct trials at the longest sequence length (12%). In a typical data set, each of the six stimuli used was shown an average of 80 times as a nonmatch and 49 times as a match. For *animal M3*, the DMP data sets were composed of an average of 102 correct trials (range 80–112). There was an approximately equal number of correct trials in which the match occurred following 1, 2, or 3 cue presentations. In this animal, an average of 137 correct responses to nonmatching cue locations and 84 correct responses to matching cue locations were available for analysis. Each of the four cue locations was shown an average of 34 times as a nonmatch and 21 times as a match.

Localization of recording sites within the entorhinal cortex

All three animals were euthanized with the use of a lethal injection of Nembutal. They were then perfused transcardially first with ~4 l of saline solution, then with 3 l of a 5% formaldehyde solution. The brains were cryoprotected in graded glycerol solutions with 5% formaldehyde. Sections were cut on a freezing microtome and a sequential series of sections through the level of the recording

sites was mounted on glass slides and stained with thionin for further microscopic examination.

For *animal M2,* the location of the entorhinal recording site was situated just medial to the perirhinal recording sites, as illustrated in Fig. 2 of Miller et al. (1993). For *animals M1* and *M3,* unfolded two-dimensional reconstructions of the entorhinal cortex were made as described in Suzuki and Amaral (1994b). Briefly, line drawings of a series of 1-in-10 50-μm-thick sections through the entorhinal cortex were made with the use of a stereomicroscope with a camera lucida attachment. The cytoarchitectonic subdivisions of the entorhinal cortex were confirmed with a higher-power microscope and indicated on the line drawings. The location and extent of the recording sites was estimated from the guide tube penetrations visible dorsally in the cortex and projected onto the two-dimensional unfolded representations. To examine the topography of physiological responses during the performance of the object and place memory tasks, the location of the recording sites on the basis of the histological examination was correlated with the incidence of selective and responsive cells in the entorhinal cortex. The recordings in *animal M2* were limited to a small anterior-posterior distance in the entorhinal cortex, and, apart from localizing the major recording site, no further analysis was performed.

RESULTS

Localization of recording sites

For all three animals, the recording sites were limited primarily in the lateral portions of entorhinal cortex. The recording sites in *animals M1* and *M3* are illustrated in Fig. 2. The recording site in *animal M2* was localized to the posterior portions of the lateral entorhinal cortex, including the posterior portions of cytoarchitectonic area E_L (lateral subdivision of the entorhinal cortex) as well as lateral portions of E_C (caudal subdivision of the entorhinal cortex) and E_{CL} (caudal limiting subdivision of the entorhinal cortex) (see Fig. 2 of Miller et al. 1993). In *animal M1,* the recordings were situated in the anterior and lateral 4 mm of the entorhinal cortex and included cytoarchitectonic area E_L as well as lateral portions of area E_R (rostral subdivision of the entorhinal cortex) (Fig. 2). Because the recording sites in *animals M1* and *M2* often extended laterally to the fundus of the rhinal sulcus, we cannot rule out the possibility that some of the penetrations may have crossed into the immediately adjacent perirhinal cortex. Unfortunately, the distribution of recording sites in *animals M1* and *M2* was not wide enough to test for topographic differences in neuronal properties.

The recording sites in *animal M3,* in contrast, extended over a larger anterior-posterior extent of the entorhinal cortex, including cytoarchitectonic area E_L as well as lateral portions of area E_R, E_I (intermediate subdivision of the entorhinal cortex), and E_C. To test for topographic differences in the distribution of cell properties in this animal, we divided the entorhinal cortex into anterior and posterior divisions. Recordings in the midportions of E_L, medial E_I, and posterior-medial E_R were considered ''anterior'' and those in posterior portions of E_L and E_C were considered posterior. The topography of cell properties in these divisions is described in a later section of RESULTS.

DMS task

BEHAVIORAL PERFORMANCE. For both animals, ~30% of the trials were terminated because of eye movements. Excluding these trials, the average behavioral performance was 76% correct. Most errors were made on trials with the longest sequence lengths, and false alarms (18% of all trials) were more common than misses (6%). As described in METHODS, *animal M1* was not able to consistently perform trials with four intervening items, and therefore these longest trials were excluded from most session in this animal. *Animal M2* performed somewhat better on the longest sequences, but the performance of this animal dropped from 98% correct on sequences with no intervening items to 47% correct on sequences with four intervening items.

RESPONSES TO VISUAL STIMULI. A total of 203 cells was isolated (140 cells from *animal M1* and 63 cells from *animal M2;* Table 1). Cells that were classified as unresponsive on the basis of an initial auditory and visual assessment of responses during performance of the task or that exhibited extremely low firing rates (<1 spike/s) were not studied further ($n = 102$). The remaining 101 neurons were analyzed in detail (71 from *animal M1* and 30 from *animal M2*). Because the pattern and time course of the responses observed in *animals M1* and *M2* were similar, except where otherwise noted, the data from these two animals were combined.

To quantitatively assess whether a cell had a visual response, we used a paired *t*-test ($P < 0.05$) to compare the firing rate during the presample baseline period with the presentation of the sample stimulus. On the basis of this criterion, 51 cells, or 25% of the total number of isolated neurons, had a significant visual response (Table 1). The majority of these (45 of 51, 88%) gave excitatory responses, whereas the remaining neurons (6 of 51, 12%) gave inhibitory responses.

The latency of visual response was determined with the use of a paired *t*-test ($P < 0.05$) to compare the average firing rate in the 100 ms preceding presentation of the sample stimulus (i.e., baseline activity) with the firing rate in successive 20-ms bins following sample stimulus onset. Response latency was defined as the earliest time point when at least three consecutive bins differed significantly from baseline. Response duration was defined as the time following the onset of response until the time when the firing rate in two or more sequential bins was not significantly different from the baseline activity. Figure 3 illustrates the distribution of response latencies and durations for 36 of the 45 excitatory visually responsive cells. The responses of the remaining nine cells were too weak for a reliable latency and duration to be determined. There was substantial variability in both the latencies (mean onset latency 181 ms; range 100–300 ms) and duration (mean duration 293 ms; range 100–420 ms). Figure 4 illustrates several examples of excitatory visually responsive cells.

SELECTIVE RESPONSES. To determine whether a responsive neuron was stimulus selective, a one-way ANOVA was performed on the responses to the six different sample stimuli. The ANOVA revealed that about half of the visually responsive neurons (24 of 51, 47%) were stimulus selective (Table 1). An example is shown in Fig. 5.

ACTIVITY IN THE DELAY INTERVALS. During the delay intervals of the task, the monkeys viewed a blank screen while maintaining a memory of the sample stimulus. A relatively large proportion of entorhinal neurons exhibited prominent

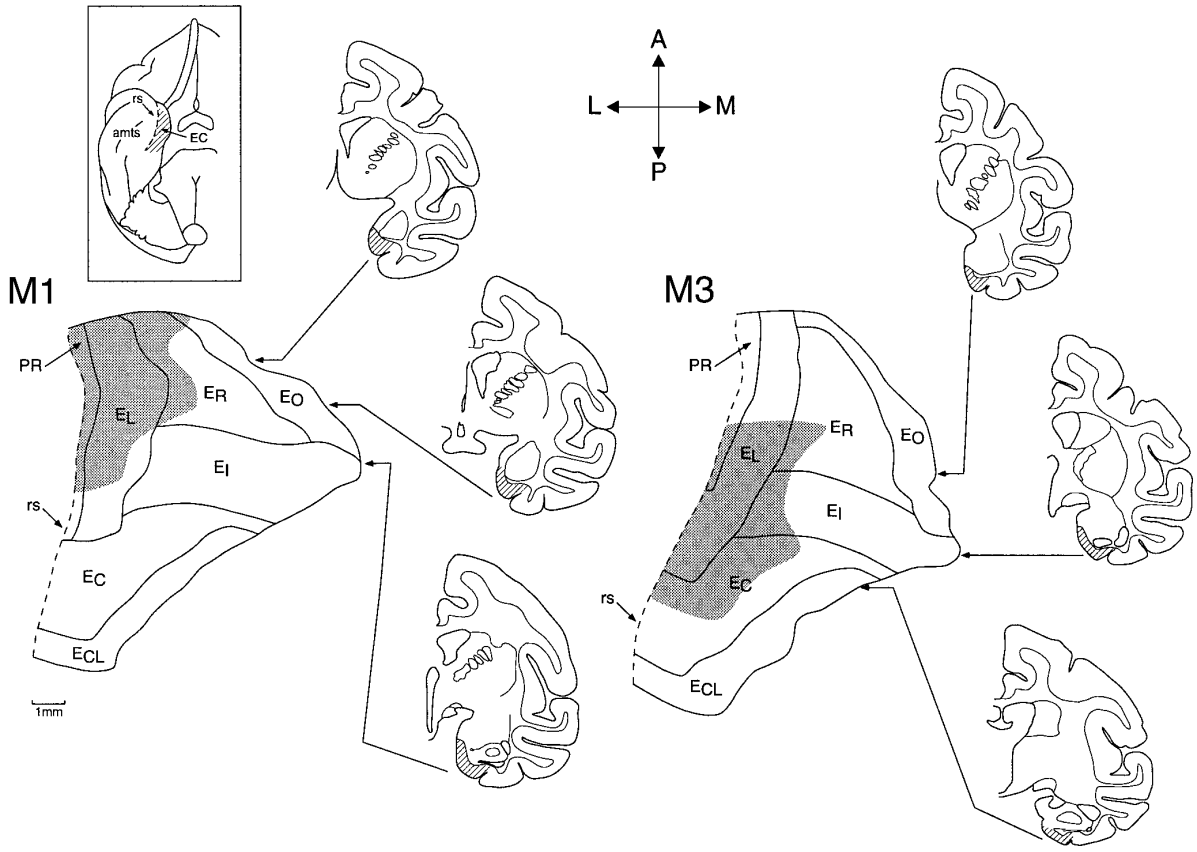

FIG. 2. *Top left*: ventral surface of the monkey brain. Hatched pattern: location of the entorhinal cortex, which has been unfolded for *animals M1* and *M3*. Orientation of the unfolded representation of entorhinal cortex corresponds to the orientation shown in the ventral view of the brain. Shaded areas on the unfolded maps: location of recording sites in each animal. Cytoarchitectonic subdivisions of the entorhinal cortex as described by Amaral et al. (1987) are also illustrated. To *right* of unfolded maps are line drawings of coronal sections from *animals M1* and *M3* at 3 different levels through the entorhinal cortex. Location of the entorhinal cortex in the sections is also indicated by hatched pattern. Scale bar applies only to unfolded maps. amts, Anterior middle temporal sulcus; EC, entorhinal cortex; E_C, caudal subdivision of entorhinal cortex; E_{CL}, caudal limiting subdivision of entorhinal cortex; E_I, intermediate subdivision of entorhinal cortex; E_L, lateral subdivision of entorhinal cortex; E_O, olfactory subdivision of entorhinal cortex; E_R, rostral subdivision of the entorhinal cortex; PR, perirhinal cortex; rs, rhinal sulcus; A, anterior; P, posterior; M, medial; L, lateral.

activity during the delay intervals of the task. An example of one cell is shown in Fig. 6. Two analyses were performed to identify cells with significant delay activity. First, we compared the mean firing rate during the delay intervals with the baseline activity preceding the first cue with the use of a paired *t*-test. This identified cells in which the overall amount of activity during the delay differed from the baseline. Second, an ANOVA was performed on the responses during the delays with the use of delay interval (i.e., 1st delay interval, 2nd delay interval, etc.) as a main factor. On the basis of these criteria, 35% of the total cells isolated (71 of 203) exhibited delay activity. For about half (35 of 71, 49%) the cells, the delay activity was above the baseline firing rate, with an average baseline firing rate of 12.02 ± 1.34 (SE) spikes/s and average delay activity of 13.92 ± 1.44 (SE) spikes/s. For the other half (36 of 51, 51%), the delay activity was below the baseline rate, with an average baseline activity of 12.45 ± 1.27 (SE) spikes/s and an average delay activity of 10.54 ± 1.09 (SE) spikes/s.

TRENDS ACROSS DELAY INTERVALS. For many cells, the magnitude of delay activity varied across the different delay intervals. We compared the activity in the different delays with the use of a one-way ANOVA with the order of the delay as the factor (i.e., the delay after the sample, the delay after the 1st test stimulus, etc.). For 20% of the cells (41 of 203), the activity varied significantly as a function of the delay interval. This variation took several forms. Some cells, for example, showed the lowest activity in the first delay, with substantially higher levels of activity in subsequent delays (Fig. 6), whereas other cells showed the exact opposite pattern. Another pattern was low activity in the first delay and the highest activity in the second delay, followed by decreasing activity across the remaining two delays.

SAMPLE-SELECTIVE DELAY ACTIVITY. In previous studies of perirhinal and prefrontal cortices, the magnitude of delay activity varied depending on which stimulus was used as a sample at the start of the trial (Miller et al. 1996). Entorhinal cells also showed this sample-selective delay activity. We assessed this for each cell by performing an ANOVA on the delay activity averaged across all the intervals. The sample stimulus used on each trial was the factor in the ANOVA. For one monkey (*M1*), we collected data from enough trials to compute a two-way ANOVA with the order of the delay interval in the trial as the second factor. Across both animals,

TABLE 1. *Incidence of selective and responsive neurons in entorhinal, prefrontal, and perirhinal cortex from animals performing the ABBA version of the delayed match to sample task*

	Entorhinal (M1 and M2)		Prefrontal		Perirhinal	
	n	Percent	*n*	Percent	*n*	Percent
Total cells sampled	203		264		193	
VR	51	25	76	29	135	70
	n	Percent VR	*n*	Percent VR	*n*	Percent VR
Visually selective	24	47	29	38	127	94
Total cells with MNM effect	30	59	37	49	68	50
Selective MNM	18	35	19	25	60	44
Nonselective MNM	12	24	18	24	8	6

Data from prefrontal and perirhinal cortex are from a single animal previously described in detail in Miller et al. (1996). The incidence of visually responsive (VR) and visually selective responses differed significantly between entorhinal and perirhinal cortices (χ^2: responsive, $P < 0.001$; selective, $P < 0.001$) as well as between prefrontal and perirhinal cortices (χ^2: responsive, $P < 0.001$; selective, $P < 0.001$). The incidence of visually responsive, selective, or delay active cells did not differ between entorhinal and prefrontal cortices. The three areas did not differ in the incidence of total match-nonmatch (MNM) effects (χ^2, entorhinal vs. prefrontal, $P = 0.26$; entorhinal vs. perirhinal, $P = 0.3$; prefrontal vs. perirhinal, $P = 0.81$); however, both entorhinal and prefrontal cortex tended to have a larger proportion of nonselective MNM responses compared with perirhinal cortex.

the average delay activity of 12 cells (of 203 total isolated cells, 6%) varied significantly with the sample stimulus.

The preceding analysis identified cells whose average activity across all delay intervals showed sample-selectivity. However, this test was not sufficient to establish that selectivity was maintained during each of the delay intervals, i.e., across each intervening nonmatching test stimuli. Previous studies showed that sample-selective delay activity was maintained across intervening stimuli in prefrontal cortex but not perirhinal cortex (Miller et al. 1996). There were too few data for a single given stimulus to perform a statistical test on the activity in each delay interval separately for each cell. Therefore we addressed this question at the population level. The sample stimulus that elicited the highest overall (''best'') or lowest (''worst'') level of average delay activity was determined for each of the 12 cells with sample-selective delay activity. Figure 7 shows the firing rates for this population in each of the delay intervals. A paired *t*-test showed that the differences in activity following the best and worst samples were significant for all the delay intervals (delay 1, $P < 0.05$; delay 2, $P < 0.01$; delay 3, $P < 0.01$; delay 4, $P < 0.05$). These results indicate that sample-selectivity was maintained across, or ''bridged,'' the delays. Similar results were found when we recomputed the best and worst samples on the basis of activity in just the second delay interval.

COMPARISON OF SAMPLE-SELECTIVE DELAY ACTIVITY AND STIMULUS RESPONSES. We noted that a cell's preference for a particular sample stimulus during the delay interval was not necessarily the same as its preference during the sample presentation. Of the 12 cells with sample-selective delay activity, about half (5 of 12, 42%) did not respond selectively to the sample stimuli. For the remaining seven neurons that did exhibit sample-selective responses, we compared the ranking of stimulus preference during the delay intervals with that during the stimulus presentation. For all seven cells, there was good agreement between the selectivity during the delay intervals and during the stimulus presentation. The stimuli that elicited the best visual response also tended to elicit the highest activity during the delay intervals, whereas the stimuli that elicited the worst visual responses also tended to elicit the lowest delay activity.

EFFECTS OF MEMORY ON RESPONSES TO STIMULI. Previous studies in perirhinal and prefrontal cortices showed that some cells responded differentially to test stimuli depending on whether or not they matched the sample. For some cells, responses to matching stimuli were suppressed relative to nonmatching stimuli (match suppression), whereas the responses of other cells were enhanced (match enhancement) (Miller and Desimone 1994; Miller et al. 1991b, 1993). To test for match suppression or enhancement in the entorhinal cortex, we performed a two-way ANOVA on each of the visually responsive cell's activity to the different test stimuli. The factors were the identity and match/nonmatch status of the test stimulus. Only test positions at which both matches and nonmatches occurred were included in the analysis. Thus the initial sample presentation and the final match were excluded. This analysis revealed that 59% (30) of the visually responsive neurons showed an overall difference in response

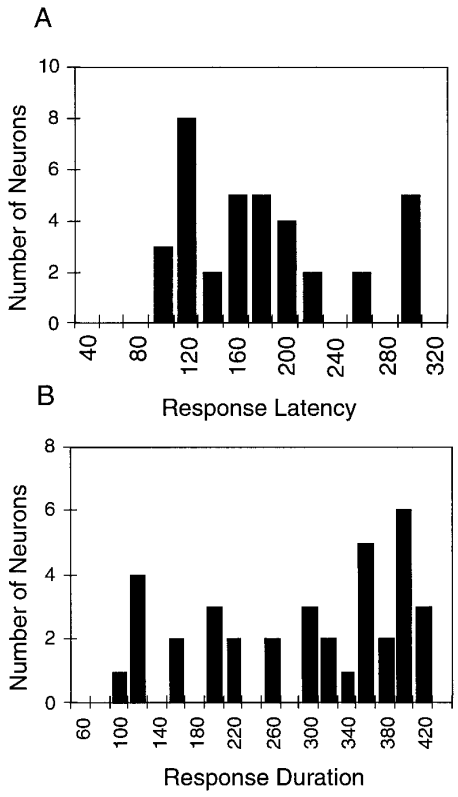

FIG. 3. Frequency histograms illustrating the distribution of response latencies (*A*) and response durations (*B*) for the population of 36 entorhinal neurons with excitatory visual responses in the DMS task.

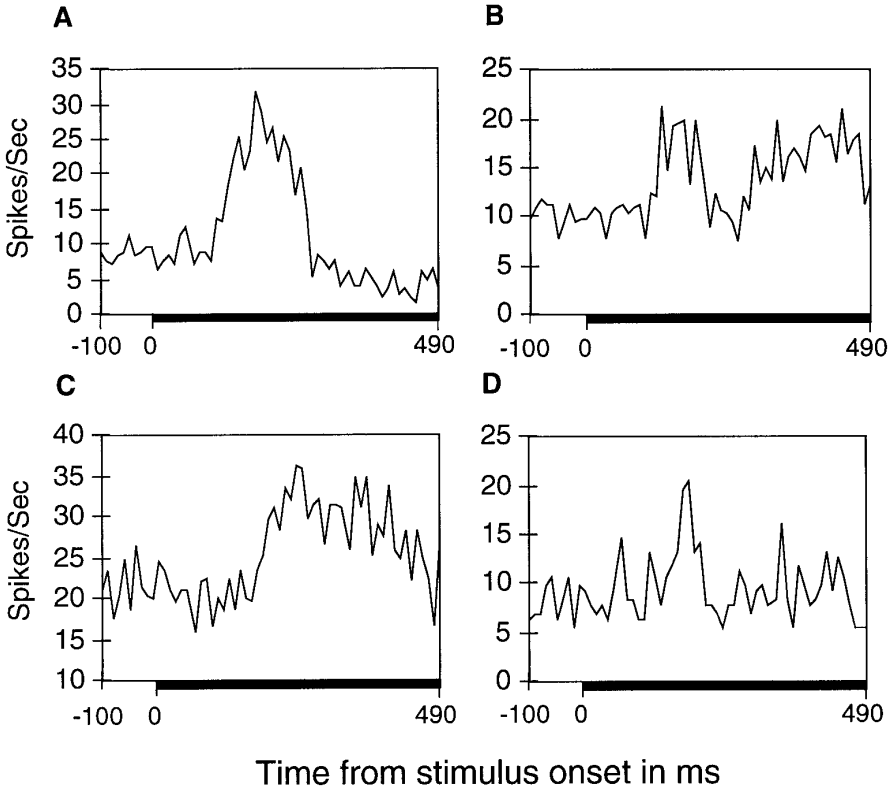

FIG. 4. Response histograms for 4 cells (*A–D*) to all of the 6 sample stimuli used. Thick horizontal bar: time the stimulus was on. Binwidth: 20 ms.

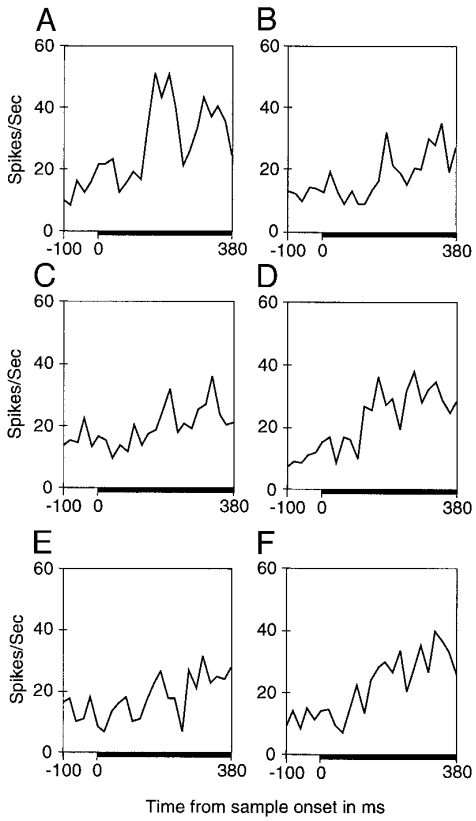

FIG. 5. Average responses to 6 different sample stimuli (*A–F*) used for a typical sample-selective entorhinal cell. Each graph shows the average of ~40 trials. Thick horizontal bar: time the stimulus was on. Binwidth: 20 ms.

to matching compared with nonmatching test stimuli (match/nonmatch effects; Table 1). Thirty-seven percent (11 of 30) of these cells showed match enhancement. The median enhancement effect was a 24% increase in response to the match stimulus compared with the nonmatch with the baseline activity included, or a 99% increase in response with the baseline activity subtracted from the responses. The remaining 63% (19 of 30) of the cells showed match sup-

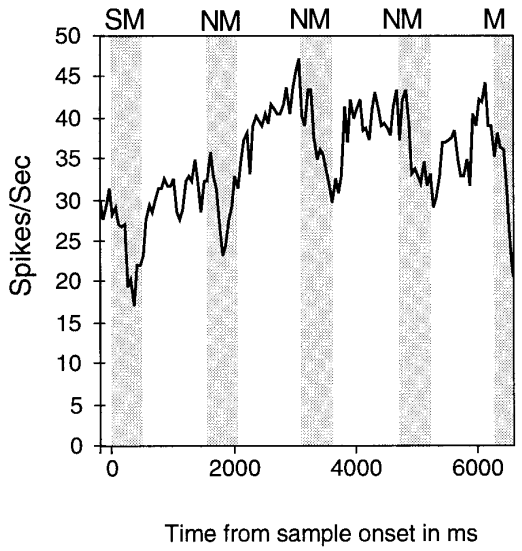

FIG. 6. Example of a neuron that exhibited increasing delay activity across delay intervals. Gray areas: time when stimuli were presented. Only responses from trials in which the sample stimulus was followed by 3 intervening stimuli are shown. M, matching stimulus presentation; NM, nonmatching stimulus presentation; SM, sample presentation. Binwidth: 50 ms.

pression. For these cells, the median suppression effect was a 20% increase in response to the nonmatch stimulus compared with the match with the baseline activity included, or a 74% increase in response with the baseline activity subtracted from the responses.

For most (18 of 30, 60%) of the cells with match/nonmatch effects, these effects varied depending on the stimulus (significant stimulus factor). The remaining cells had approximately equal match/nonmatch effects for all stimuli tested. Of the cells with stimulus-selective effects, most (11 of 18, 61%) were of the match suppression type, whereas the remaining cells (7 of 18, 39%) showed match enhancement.

We examined the ''memory span'' of the match suppression and enhancement effects by testing whether these effects were maintained when multiple stimuli intervened between the sample and the match stimulus. To do this, we first identified the individual stimuli that elicited significant match/nonmatch effects with the use of a *t*-test on the responses of all visually responsive cells ($n = 51$) to all six stimuli. Significant match suppression and enhancement effects were found for 35 and 30 stimuli, respectively. This is well above the number of stimuli that would be expected by chance (binomial theorem, $P < 0.001$).

Figure 8*A* shows the average responses to the 35 stimuli with match suppression, plotted separately for each test interval. This graph shows that the match suppression effects were maintained even when multiple nonmatching stimuli intervened between the sample and match. As described above, *animal M1* performed trials with up to three intervening stimuli, whereas *animal M2* performed trials with up to four intervening stimuli. Thus, in Fig. 8*A*, the responses to sample presentations as well as the match/nonmatch responses for zero, one, and two intervening stimuli includes data from both *animals M1* and *M2*, whereas the match/nonmatch responses for three and four intervening stimuli include data only from *animal M2* (22 stimuli). A paired *t*-test applied to the population responses revealed significant suppression following up to two intervening nonmatch stimuli ($P < 0.001$). The difference was not significant, however, with three intervening test items ($P = 0.3$). As described previously, the performance of *animal M2* dropped to 47% correct on the longest sequence. Thus one possible explanation for the waning of the match suppression effect at the longest delay interval was that *animal M2* was not paying close attention to the stimuli on these trials.

Figure 8*B* shows a population response histogram for the same 35 stimuli illustrated in Fig. 8*A*, and Fig. 8*C* illustrates the response of one representative neuron with match sup-

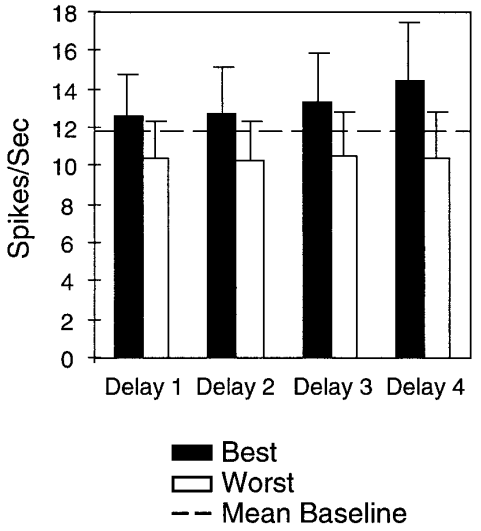

FIG. 7. Average firing rates in delay intervals for 12 cells with sample-selective delay activity. Shown are averaged responses for sample stimuli that elicited the highest (''Best'') and lowest (''Worst'') activity averaged over all delay intervals. Error bars: means ± SE.

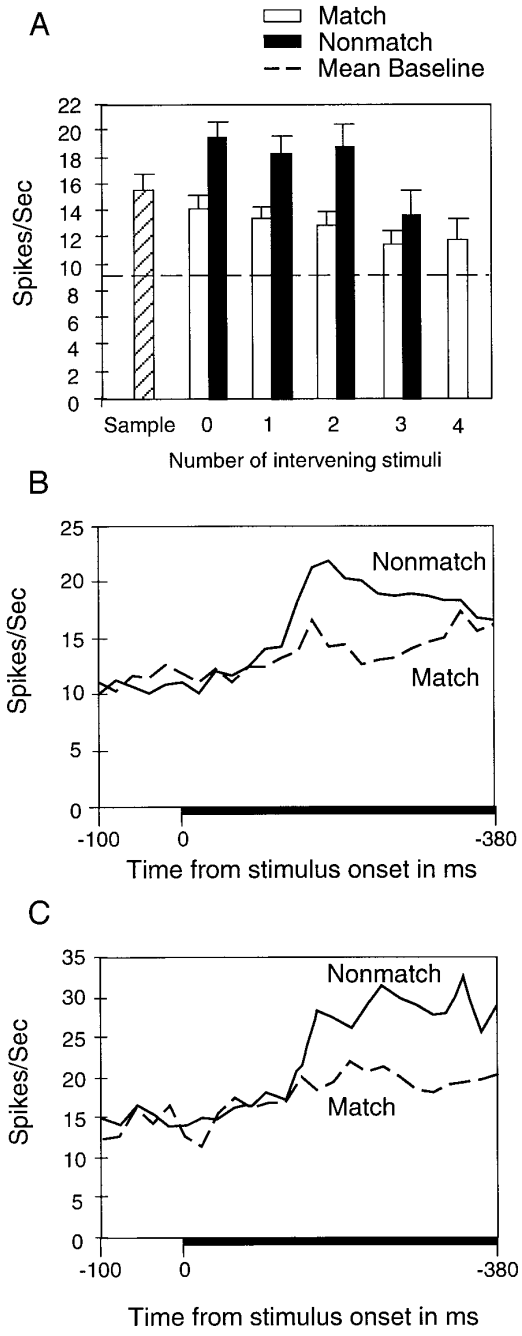

FIG. 8. *A*: average firing rates for 35 individual stimuli that exhibited significant match suppression. Error bars: means ± SE. *B*: average population response histogram for the same 35 significant test items shown in *A*. *C*: response histogram from a single entorhinal neuron that exhibited match suppression. Thick horizontal bar: time the stimulus was shown. Binwidth: 20 ms.

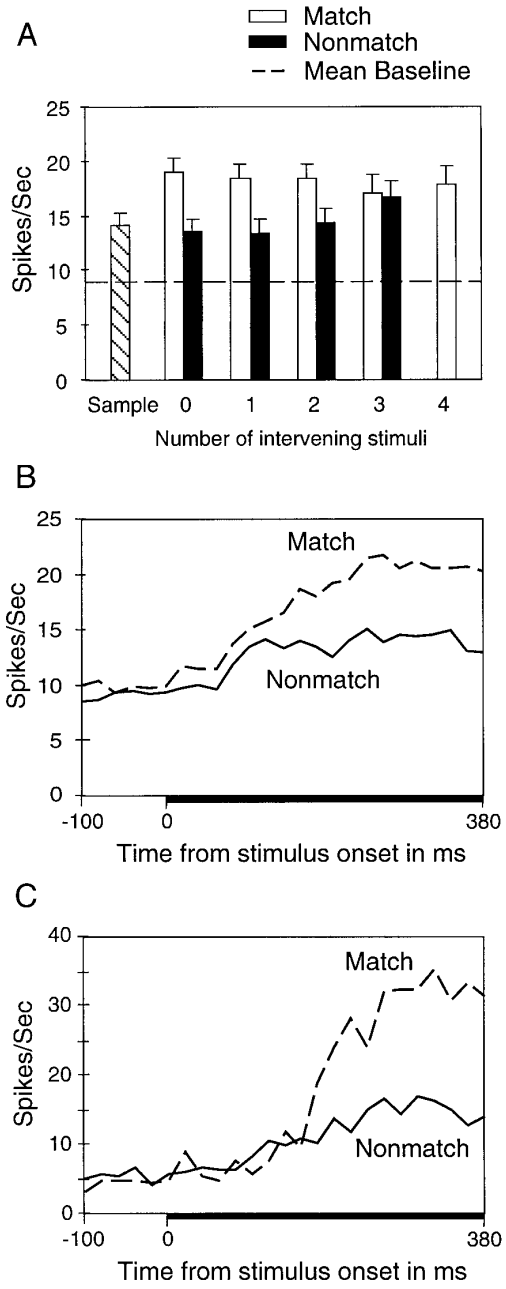

FIG. 9. *A*: average response for 30 test items that showed a significant match enhancement effect. Error bars: means ± SE. *B*: average population response histogram for the same 30 significant test items shown in *A*. *C*: example of a single entorhinal neuron that exhibited significant match enhancement. Thick horizontal bar: time the stimulus was shown. Binwidth: 20 ms.

pression. In both cases, the responses to the match and nonmatch stimuli diverged well before the behavioral response, which occurred 368 ms after stimulus onset, on average.

Largely parallel results were found for match enhancement. The average responses to the 30 test items with significant match enhancement are shown in Fig. 9*A*. The difference in response to the match and nonmatch stimuli was significant following up to two intervening items (paired *t*-test applied to the population response, $P < 0.001$). As with match suppression, the enhancement effect in *animal M2* was not significant ($P = 0.6$) following three intervening test items. Figure 9*B* shows the average population response histogram for the same 30 stimuli shown in Fig. 9*A*, and Fig. 9*C* shows an example of a representative neuron with exhibiting match enhancement. The time course of the match enhancement effect was similar to that observed for match suppression.

Previous studies in prefrontal and perirhinal cortex showed that cells with match suppression or match enhancement differed in how they responded to the repeated nonmatching stimulus in the ABBA version of the DMS task (Miller and Desimone 1994). Specifically, cells exhibiting match suppression also had suppressed responses to the behaviorally irrelevant repeated nonmatch (e.g., the repeated B stimulus in an ABBA trial). In contrast, the cells exhibiting match enhancement gave enhanced responses only to the matching stimulus, that is, the stimulus that matched the sample actively held in working memory. We were able to examine the responses of entorhinal neurons to repeated nonmatches in the animal that performed the ABBA version of the task (*animal M1*). A total of 14 individual stimuli with significant match/nonmatch effects was found in this animal, and almost all of these (13 of 14) exhibited suppression. Figure 10*A* shows the average responses for these 13 stimuli in the match, nonmatch, and repeated nonmatch conditions. Similar to what was found in perirhinal and prefrontal cortex, the responses to the match and repeated nonmatch stimuli were equally suppressed. On the basis of a paired *t*-test on the population, the responses to nonmatches were significantly greater than either responses to the matches ($P < 0.01$) or repeated nonmatches ($P < 0.05$). Moreover, the responses to matches and repeated nonmatches did not differ ($P = 0.8$ with 1 intervening stimulus and $P = 0.9$ with 2 intervening stimuli). Thus the suppressive effect occurs automatically for any type of stimulus repetition. Figure 10*B* shows an example of a cell that differentiated between matching and nonmatching stimuli at ~110–120 ms after stimulus onset, well before the animal's mean response latency of 375 ms.

RELATIONSHIP OF PROPERTIES WITHIN CELLS. Cells with stimulus-selective responses were also more likely to also exhibit other forms of selective activity compared with nonstimulus-selective cells. A relatively large proportion of stimulus-selective cells exhibited match/nonmatch effects (13 of 24, 54%), sample-selective delay activity (5 of 24, 21%), and delay activity selective for the previously shown stimulus (6 of 24, 25%). In contrast, nonselective visually responsive cells were less likely to exhibit match/nonmatch effects (9 of 27, 33%), sample-selective delay activity (3 of 27, 11%), or delay activity selective for the previously shown stimulus (4 of 27, 15%). A similar trend was found in prefrontal cortex (Miller et al. 1996).

DMP task

BEHAVIORAL PERFORMANCE. In general, the DMP task proved to be more difficult than the DMS task. *Animal M3* responded correctly on an average of 68% of the trials. The error trials were made up of equal proportions of false alarms (16%) and misses (16%). As for the DMP task, the most errors tended to be made on the longest trials with the largest number of stimuli in the sequence.

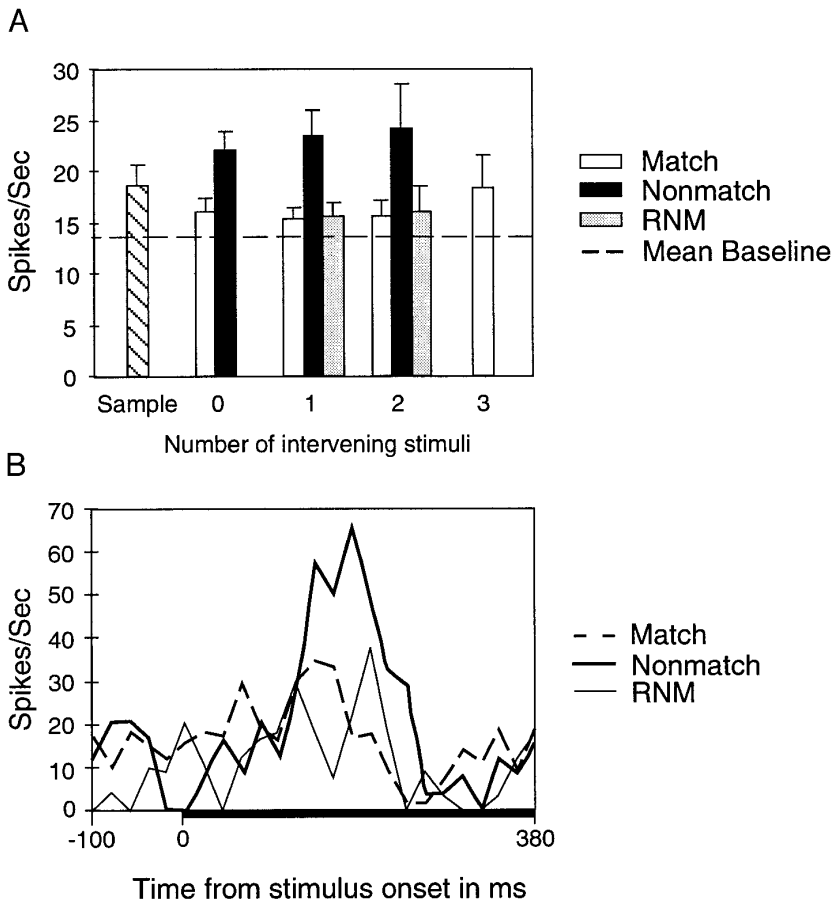

FIG. 10. *A*: average response to 13 individual stimuli that exhibited significant match suppression in the animal that performed the ABBA version of the DMS task (*M1*). RNM, response to repeated nonmatch. Error bars: means ± SE. *B*: response histogram of a single entorhinal neuron to its preferred stimulus shown as match, nonmatch, and repeated nonmatch. Thick horizontal bar: time the stimulus was shown. Binwidth: 20 ms.

RESPONSES TO VISUAL STIMULI. The results in the DMP task closely paralleled those described in the DMS task. A total of 291 cells was isolated in *animal M3* (Table 2). Of these 291 cells, 172 either lacked a clear visual response during auditory assessment or exhibited extremely low firing rates (<1 spike/s) and were excluded from analysis. A detailed statistical analysis was conducted on the remaining 119 neurons.

As in the DMS task, we assessed visual responsivity on the DMP task with the use of a paired *t*-test ($P < 0.05$) to compare the responses during the precue baseline period with the average response to all cue presentations. On the basis of this test, 40 cells showed a significant visual response. A large majority of these responses (31 of 40, 78%) was excitatory and the remaining responses (9 of 40, 23%) were inhibitory. We noted that few cells without significant overall excitatory or inhibitory responses to all cue locations nonetheless appeared to respond highly selectively to a single location. To better identify these selective cells, we performed a one-way ANOVA ($P < 0.05$) on the responses to the four cue locations for all 79 cells that did not exhibit a significant response according to the paired *t*-test. An additional 11 visually responsive cells were identified, which is significantly greater than what would be expected by chance (binomial theorem, $P = 0.001$). Taken together, a total of 51 visually responsive cells was identified in the DMP task (Table 2).

TABLE 2. *DMP task*

	Totals		Anterior EC		Posterior EC	
	n	Percent	*n*	Percent	*n*	Percent
Total cells sampled	291		105		186	
VR	51	18	26	25	25	13
Delay neurons	32	11	14	13	18	10
	n	Percent VR	*n*	Percent VR	*n*	Percent VR
Place selective	28	55	16	62	12	48
Match-nonmatch effect	11	22	5	19	6	24

DMP, delayed match to place. EC, entorhinal cortex. For remaining abbreviations, see Table 1.

SELECTIVE RESPONSES. As in the DMS task, we asked whether the responses were selective for different stimuli. To assess this quantitatively, a one-way ANOVA was performed on the responses of all responsive cells to the cues at the four different locations. The ANOVA revealed that the majority of the visually selective cells (28 of 51, 55%) were also location selective (Table 2). As mentioned above, some of these cells were highly selective, giving a significant response to a cue at only one location. The preferred cue locations for each cell were approximately evenly distributed across the contralateral, ipsilateral, and central portions of the screen. Figure 11*A* illustrates the average population response to the cue location that elicited the highest (best) and lowest (worst) firing rate for the 28 location-selective cells. The response to the best cue location appeared to

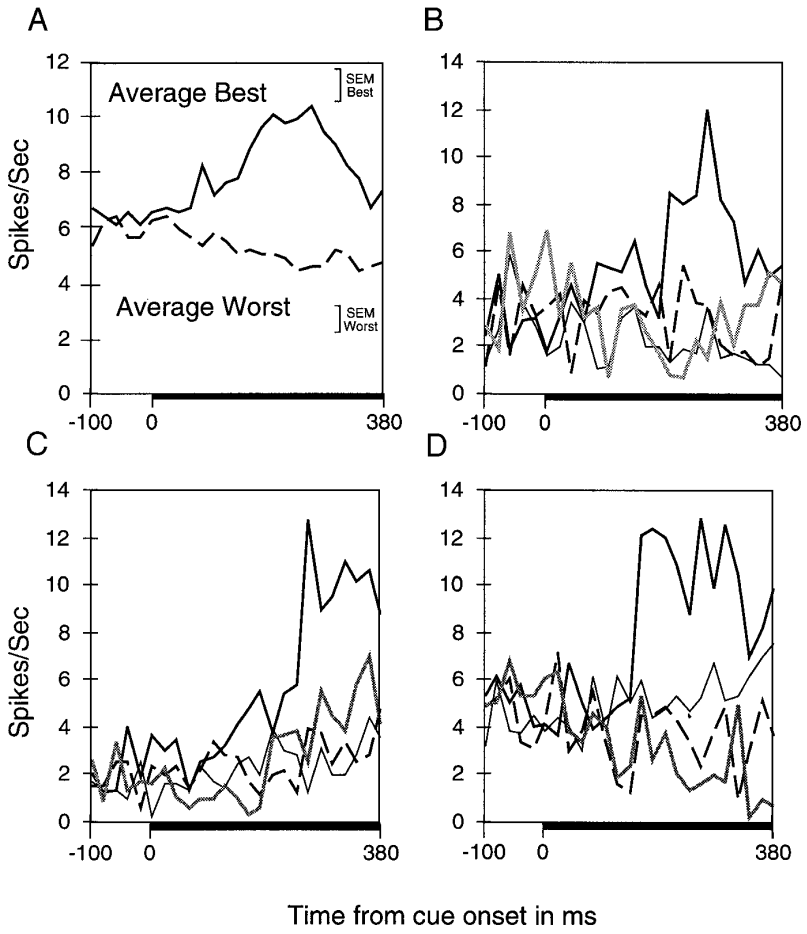

FIG. 11. *A*: response histograms averaged from 28 location-selective cells to the cue location that elicited the highest (''Average Best'') and lowest (''Average Worst'') firing rate for each cell. Shown on *right of graph* is the averaged mean ± SE for responses to the best and worst locations. *B* and *C*: examples of responses of individual location-selective neurons to the 4 cue locations tested, each represented by a different line format. Thick horizontal bar: time the stimulus was shown. Binwidth: 20 ms.

differentiate from the response to the worst cue locations ~80–100 ms after cue onset. Examples of individual location-selective cells are shown in Fig. 11, *B–D*.

EFFECT OF EYE POSITION ON SELECTIVE RESPONSES. Because we were unable to train the animals to fixate throughout the trial, it is possible that the location-selective responses were influenced or determined by the animal's eye position during the time of the cue presentations. If the firing rate of entorhinal cells varied according to the position of the eye in the orbit, for example, systematic differences in eye position could lead to apparently location-selective responses. The influence of eye position was therefore examined in two ways.

First, for the cells that exhibited significant location-selective responses, we computed the average horizontal and vertical components of the eye position in the time window used for the analysis of neuronal responses to the cues. We then computed separate one-way ANOVAs on the horizontal and vertical components as a function of cue location on each location-selective cell. Eye position data were available for 21 of the 28 place-selective cells. We found no significant difference in the average eye position for the different cue locations for the vast majority (20 of 21) of cells. We then recomputed the ANOVAs with the use of an even smaller time window corresponding to the cell's maximal cue response (i.e., 180–280 ms after stimulus onset). This also corresponds to a time point in which the animal's eye position might be most different for the different cue locations. This analysis revealed similar results. Thus systematic differences in at least the average eye position are unlikely to account for the results.

The second way in which we addressed this issue was to test an additional 28 cells in control experiments in which the animal was required to maintain fixation on a central fixation target during the presentation of the first cue in the sequence. Fixation was not required during the subsequent delay intervals or cue presentations. Cells with location-selective responses were first identified by comparing the responses to the different cue locations with the use of a one-way ANOVA. Both fixation-controlled and non-fixation-controlled cue presentations were included in this analysis. On the basis of this criterion, 5 of the 28 cells tested (18%) had significant location-selective responses. We then examined the responses to the first cue presentation for these five cells, during which fixation was controlled. For all five cells, the preferred cue location remained the same with fixation controlled. We also recomputed the ANOVA on responses to the different cue locations for these five cells, with the use of only the responses to the first cue presentation. Although the power of this test was weaker than the original test because far fewer responses were available, the location selectivity remained significant for two of the five cells. Thus, taken together, these findings suggest that the location-selective responses were not caused by variations in eye position.

EFFECT OF CHANGING THE BACKGROUND STIMULUS. The cue stimuli were presented against a background ''scene'' composed of large geometric elements (Fig. 1*B*). Thus the location-selective responses may have been due either to selectivity for the location of the cue or to an interaction between the cue location and the scene. To test the role of the background, an additional 25 cells were tested in conditions in which the four possible cue locations remained fixed but the background changed across trials (see *Changing backgrounds experiment* in METHODS). The majority of these cells (20 of 25) was tested with the standard background scene composed of large elements as well as in a blank (no-background) condition. For five neurons, three unique background configurations were tested.

Of the 25 cells tested with two or more backgrounds, 56% (14) had location-selective responses with at least one of the background stimuli tested according to an ANOVA computed on the responses to the different cue locations. Changing the background revealed two different patterns of response. One group of cells (5 of 14, 36%) maintained their location-selective responses irrespective of the background stimulus used. Figure 12 shows an example of a cell that maintained its location selectivity under three different background conditions. These results suggest that some entorhinal cells respond simply to the location of the cue stimulus on the screen.

A second group of cells (9 of 14, 64%) was strongly influenced by the particular background stimulus used. Typically, these cells responded selectively in one of the background conditions (''good'' background), but not in the other (''poor'' background). Three of these nine neurons were completely unresponsive to cues at any location in the poor background condition. The remaining six neurons continued to respond to cues on the poor background, but the responses were no longer selective. Figure 13 shows an example of a cell that had different location selectivity under the different background conditions.

ACTIVITY DURING THE DELAY INTERVALS. Given the large proportion of cells with delay activity in the DMS task, we asked whether the same were true in the DMP task. Cells with delay activity were identified in two ways. First, we compared the mean firing rate during the delay intervals with the baseline activity preceding the first cue with the use of a paired *t*-test. This identified cells in which the overall amount of activity during the delay differed from the baseline. Second, we computed a two-way ANOVA on the responses during the delay. One factor was the delay interval (i.e., 1st delay interval, 2nd delay interval, etc.), and the other factor was the location in which the cue was shown in the interval immediately preceding the delay. These two factors identified cells with different amounts of delay activity in different delay intervals as well as cells in which the overall amount of delay activity varied according to remembered location. On the basis of these criteria, 32 cells (11% of the total isolated) were considered to be delay active (Table 2).

The two-way ANOVA also showed that about a third of the delay active cells (10 of 35, 29%) had a significant effect of cue location. That is, the delay activity of these cells varied according to the location of the immediately preceding cue. To evaluate whether the immediately preceding cue location was differentiated equally well in each of the delay intervals throughout the trial, the cue locations that elicited the highest and lowest delay activity averaged over all the delay intervals were determined for each of the cells with location-selective delay activity. Figure 14 shows the average delay activity following the best and worst cue locations

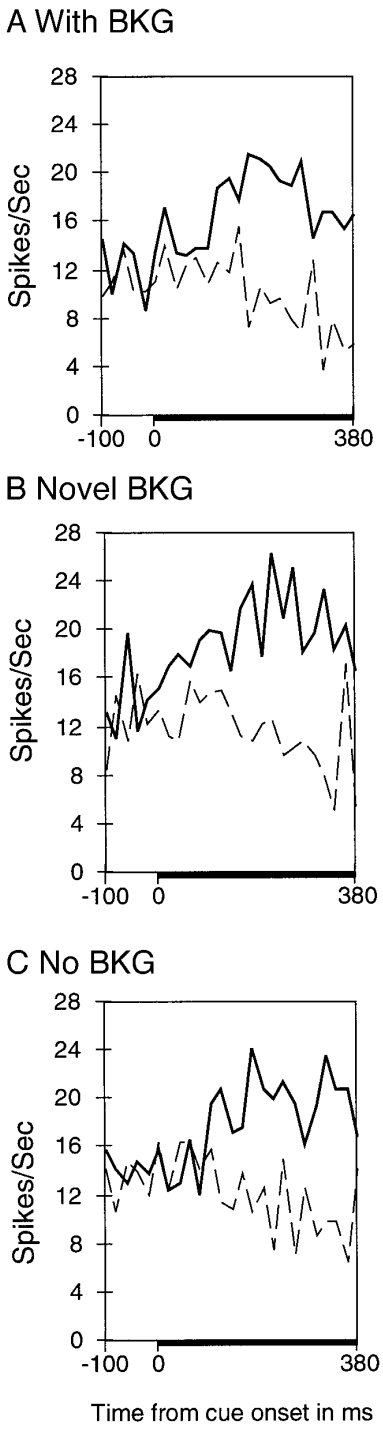

FIG. 12. Example of a cell that maintained its preference for 1 cue location in 3 different background conditions: standard background (*A*), novel background (*B*), and blank screen with no background (*C*). Thick horizontal bar: time the cue stimulus was presented (ms). Binwidth: 20 ms.

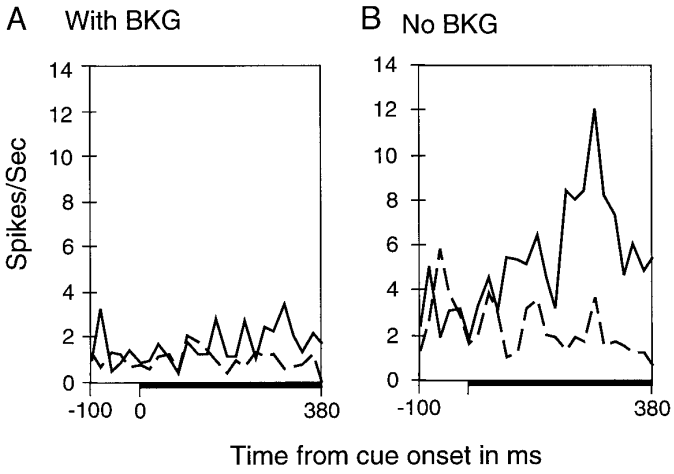

FIG. 13. Example of a cell whose location selectivity differed depending on the background stimulus used. *A*: response to cues presented at the best and worst places when the standard background was shown. *B*: response to the same cue locations when no background stimulus was used. Thick horizontal bar: time the stimulus was shown. Binwidth: 20 ms.

at each delay interval tested. A paired *t*-test applied to the population data indicated that the activity following the best and worst locations was significantly different in all of the four delay intervals. Similar results were obtained if the best and worst locations were determined on the basis of activity in the second delay activity only.

In the DMS task, the animal was required to remember only the sample stimulus, and the delay activity averaged over all delay intervals varied as a function of the sample stimulus shown for some cells. In the DMP task, the animal was required to remember all of the cue locations shown in a given trial and to respond when any of the cue locations was repeated. Therefore, for this task, we asked whether location-selective delay activity was maintained when averaged across all of the delay intervals following a given cue. To test this, a two-way ANOVA was performed on the delay activity with the use of cue location as one factor and interval following that cue presentation (i.e., 1st delay interval, 2nd delay interval, etc.) as the second factor. This analysis revealed no significant effects. Because the animal was required to remember up to three locations in a given delay interval, it is possible that the delay activity was influenced jointly by each of the remembered locations. If so, there may have been insufficient data to detect the influence of just a single location.

EFFECTS OF MEMORY ON RESPONSES TO CUES. As in the DMS task, we next asked whether holding a particular cue location in memory affected the responses to the subsequent cues. To test this, for each visually responsive neuron we computed a two-way ANOVA on the responses to the four cue locations for each cell individually. The two factors used were cue location and match status (i.e., whether the cue was presented in a location that matched or did not match the location of a previous cue in the trial). Only test positions at which both matches and nonmatches occurred were included in the analysis. Thus the initial cue presentation and the final match were excluded. A total of 22% (11) of the visually responsive cells showed a significant effect of match status, i.e., they responded differently to a cue depending on whether it was a match or nonmatch (Table 2). The responses of seven these cells were enhanced when the cue occurred at a matching location. For these cells, the mean enhancement effect was a 36% increase in response to the match stimulus with baseline activity included and a 219% increase in response with the baseline activity subtracted from all responses. The responses of the remaining cells to the matching cue (4 of 11) were suppressed. The mean suppression effect for these cells was a 41% increase in response to the nonmatch stimulus with the background activity included and a 364% increase in response with the baseline activity subtracted from all responses.

The majority (7 of 11, 64%) of the cells with match/nonmatch effects also showed a significant effect of cue location. Of the cells with stimulus-selective effects, most (6 of 7) were of the match enhancement type and the remaining one cell showed match suppression.

To test whether these match/nonmatch effects survived the presentation of intervening cues in the stimulus sequence, we first identified all of the cue locations that had significant match/nonmatch effects across the group of cells showing a significant visual response ($n = 51$). These cue locations were identified by comparing the response to each cue in the match and nonmatch condition with the use of a *t*-test ($P < 0.05$). A total of 26 cue locations was identified with significant match/nonmatch effects, with match enhancement about as common (11 of 26 locations) as match suppression (15 of 26 locations). This is well above the number of significant cue locations that would be expected by chance (binomial theorem, $P < 0.001$). The average match enhancement effect for these individual locations (with baseline included) was a 76 ± 24% (mean ± SE) increase in response to a cue when it was matching compared with the same cue when it was nonmatching (range 42–293%). The corresponding average match enhancement effect if the baseline was excluded was a 345% increase. The average match suppression effect was a 122 ± 16% (mean ± SE) increase in the response to the nonmatching cue location compared

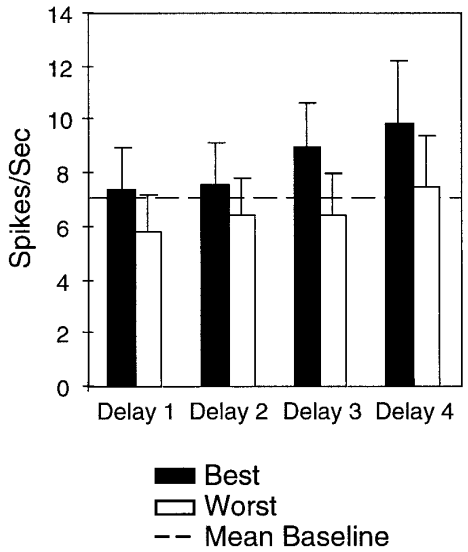

FIG. 14. Average firing rates and means ± SE for 11 cells that showed significant location-selective delay activity. Best and worst cue locations were determined from the average firing rates across all delay intervals.

with the same cue location shown as a match (range 48–271%). If the baseline firing rate was subtracted, there was a 254% average increase in firing to the nonmatch cue compared with the matching cue.

Figure 15*A* shows the average firing rates for the 11 cue locations that elicited match enhancement as a function of the number of intervening cue locations. The responses to matching cue locations were clearly larger than the responses to nonmatching cues, and this difference appears to be maintained despite intervening cue presentations. According to a paired *t*-test applied to the population data, the difference between the match and nonmatch responses was significant with both zero ($P < 0.001$) and one ($P < 0.05$) intervening cue locations.

The time course of the match enhancement effect is illustrated in Fig. 15*B*, which shows the average response to matching and nonmatching locations for a single entorhinal cell. Match responses appear to diverge from nonmatching responses at ~100 ms after stimulus onset. This corresponds with the earliest response latency of the entorhinal neurons and also occurs well before the animal's mean behavioral response latency of 373 ms.

Figure 16*A* shows the average firing rates for the 15 cue locations that elicited match suppression as a function of the number of intervening cue locations. Similar to the match enhancement effect, the match suppression effect survived at least one intervening cue location, according to a paired *t*-test computed on the responses (0 intervening cue locations, $P < 0.001$; 1 intervening cue location, $P < 0.01$). Figure 16*B* shows a single cell response. As with match enhancement, match suppression appears to begin well before the animal's mean behavioral response latency of 373 ms.

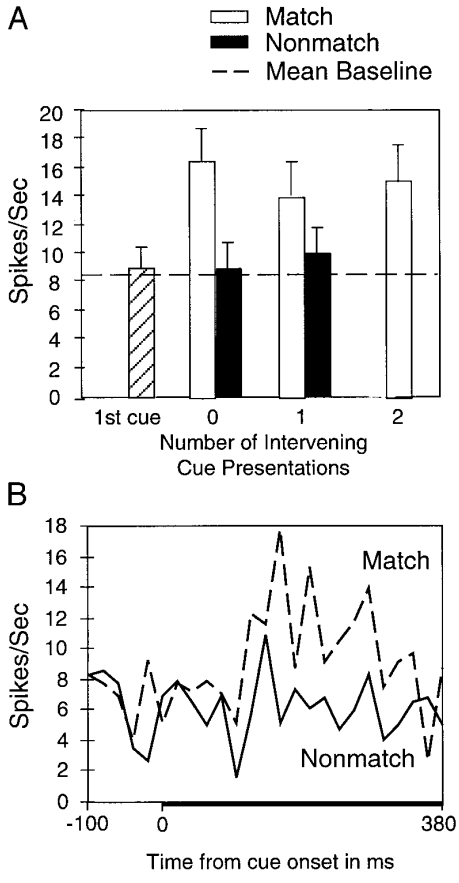

FIG. 15. *A*: average firing rates and means ± SE for 11 cue locations that elicited significant match enhancement. *B*: responses of a single cell that exhibited significant match enhancement. Thick horizontal bar: time the cue stimulus was shown. Binwidth: 20 ms.

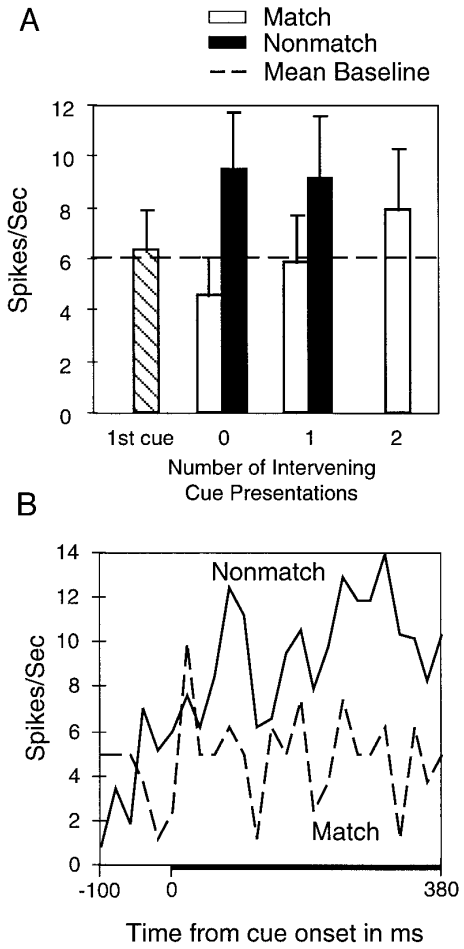

FIG. 16. *A*: average firing rates and means ± SE for 15 cue locations that elicited significant match suppression. *B*: responses of a single cell that exhibited significant match suppression. Thick horizontal bar: time the cue stimulus was shown. Binwidth: 20 ms.

RELATIONSHIP OF PROPERTIES WITHIN CELLS. We examined the relationship between cells with location-selective responses, delay activity, and match/nonmatch effects. The clearest trend appeared to be that cells with location-selective responses were more likely to show match/nonmatch effects (9 of 28, 32%) compared with visually responsive cells that did not exhibit location-selective responses (2 of 23, 9%).

TOPOGRAPHY OF CELL PROPERTIES IN THE DMP TASK. Table 2 shows the percentages of responsive and selective neurons found in anterior or posterior portions of the entorhinal cortex in *animal M3*. In general, responsive and selective cells were observed at all levels of the entorhinal cortex. In particular, there was no difference, on the basis of a χ^2 analysis, between the relative incidence of place-selective neurons in anterior compared with posterior entorhinal neurons ($P = 0.33$).

DISCUSSION

The entorhinal cortex has direct or indirect anatomic connections with many structures known to be important for object and spatial memory. It is also the dominant cortical source of input and output for the hippocampus. It receives inputs from ventral stream areas important for object recognition via the perirhinal cortex, and it receives inputs from dorsal stream areas important for spatial vision via the parahippocampal cortex (Insausti et al. 1987; Suzuki and Amaral 1994a; Van Hoesen and Pandya 1975). It is also reciprocally connected with prefrontal cortex (Barbas 1993; Insausti et al. 1987; Van Hoesen et al. 1973), which plays an important role in both object and spatial memory (Bachevalier and Mishkin 1986; di Pellegrino and Wise 1993; Funahashi et al. 1993; Fuster 1973; Mishkin 1957; Niki and Watanabe 1976). Consistent with the key position of the entorhinal cortex in the flow of sensory information from both dorsal and ventral stream pathways into the hippocampus, the present study demonstrates that entorhinal neurons encode information important for the performance of both object and place memory tasks.

Object memory in the entorhinal cortex

To solve the DMS task the monkey must, in principle, solve three interrelated problems. First, it must discriminate among the different stimuli. Second, it must retain the memory of the sample for the length of the trial. Third, it must make a decision about whether the current test stimulus matches the sample held in memory. Entorhinal cells have properties that suggest a role in all three of these operations. Consistent with the first requirement, some entorhinal cells show stimulus selectivity in that they respond to some objects better than others. Because the objects were highly complex, we made no attempt to plot ''tuning curves'' of entorhinal cells to individual features such as color or orientation. Previous studies have failed to explain the stimulus preferences of many cells in perirhinal cortex or area TE in terms of simple feature selectivity (Desimone et al. 1984; Fujita et al. 1992; Miller et al. 1993), and we suspect that the same is true of entorhinal cortex. The fact that entorhinal cells do respond differentially to different objects indicates that object information is retained in entorhinal cortex and is presumably passed on to subsequent structures, such as the hippocampus. Previous studies have shown that hippocampal neurons also exhibit various forms of object or object-place selectivity (Eifuku et al. 1995; Riches et al. 1991; Rolls et al. 1989; Young et al. 1995). Consistent with the second requirement for solving the DMS task, some entorhinal cells also show sample-selective activity in the delay intervals following the sample. This activity might mediate an explicit representation of the sample memory during the delay (see below). Finally, consistent with the third requirement for solving the DMS task, some entorhinal cells respond differentially to the test stimuli depending on whether or not they match the sample. For some cells responses to matching stimuli are suppressed relative to nonmatching stimuli, but for other cells the responses are enhanced. Because the enhancement and suppression effects occur well before the behavioral response, these effects may contribute to the animal's decision about whether a current test stimulus matches the sample held in memory.

COMPARISON WITH PERIRHINAL AND PREFRONTAL CORTEX. The sequential DMS task used in the current study was the same task used in previous studies of perirhinal and prefrontal cortex (Miller et al. 1996). This afforded us the opportunity to directly compare neuronal properties across the three areas, some of which are summarized in Table 1. This table includes all cells isolated in the three areas, including those that appeared to be unresponsive on initial testing and were therefore rejected for further study. The proportions of both visually responsive cells and stimulus-selective cells were substantially less in entorhinal cortex than in perirhinal cortex but were similar to what was found in prefrontal cortex. In fact, the difference between entorhinal cortex and perirhinal cortex is even more dramatic if one considers stimulus-selective cells as a proportion of the total population of isolated cells. Stimulus-selective cells constituted only 12% (24 of 203) of the total cells sampled in entorhinal cortex but 66% (127 of 193) of the total cells sampled in the perirhinal cortex. Eleven percent (29 of 264) of the total number of sampled cells in prefrontal cortex were selective. Thus the entorhinal cortex was more similar to prefrontal cortex in this respect. The relatively low incidence of stimulus selectivity suggests that both entorhinal cortex and prefrontal cortex are less involved in the analysis and coding of object features than is perirhinal cortex. This difference may be related to the fact that of the three areas, the perirhinal cortex receives the strongest direct input from unimodal visual area TE (Suzuki and Amaral 1994b).

In contrast to the differences in stimulus selectivity across areas, the responses of about half the visually responsive cells in all three areas varied according to whether the test stimulus matched the sample. In all areas, these match/nonmatch effects were maintained following the intervening stimuli in the sequential DMS task. The match/nonmatch effects were stimulus selective for some cells and nonselective for others in all three areas; however, the proportion of cells with selective match/nonmatch effects was somewhat higher in perirhinal cortex compared with entorhinal and prefrontal cortex, consistent with the greater incidence of stimulus-selective responses in this area. In all three areas, the responses to stimuli matching the sample were suppressed for some cells and enhanced for others.

We previously found in perirhinal and prefrontal cortex that cells exhibiting match suppression also exhibited suppression for repetitions of the intervening nonmatch stimuli in the ABBA task, e.g., the second B stimulus (Miller and Desimone 1994; Miller et al. 1996). We found the same to be true for cells exhibiting match suppression in entorhinal cortex. Thus responses appear to be suppressed automatically by any type of stimulus repetition, not just by stimuli matching an item actively held in memory. For this reason, we refer to this effect as ''repetition suppression.'' Repetition suppression appears to be a common phenomenon in area TE as well (Baylis and Rolls 1987; Brown et al. 1987; Fahy et al. 1993; Gross et al. 1979; Mikami and Kubota 1980; Miller et al. 1991a; Riches et al. 1991; Sobotka and Ringo 1996; Vogels and Orban 1994; but see Eskandar et al. 1992). Repetition suppression may be an intrinsic prop-

erty of cells in visual cortex that does not depend on feedback from higher areas (Desimone et al. 1995).

We previously found that perirhinal and prefrontal cells exhibiting match enhancement gave enhanced responses only to the test stimulus matching the sample held in memory and not to the irrelevant repetitions of the nonmatch items in the ABBA task (Miller and Desimone 1994; Miller et al. 1996). Thus, unlike repetition suppression, the enhancement effect appears to depend on active working memory. Unfortunately, nearly all of the cells exhibiting match enhancement in entorhinal cortex were recorded in the monkey tested in the standard DMS task rather than the ABBA task. We were therefore unable to determine whether the enhancement effect in entorhinal cortex was specific to the match stimulus, as it is in the other two areas.

In addition to the modulatory effects of the sample stimulus memory on responses to the subsequent test stimuli, the sample memory also influenced activity during the delay periods. Some cells in all three areas showed sample-selective delay activity, in that delay activity was higher following some sample stimuli than following others. An obvious function for this delay activity would be to actively maintain a representation of the sample stimulus when it is no longer present. However, we previously found in perirhinal cortex that the delay activity was not maintained following the first nonmatching test item in the stimulus sequence (Miller et al. 1993). Delay activity in prefrontal cortex, by contrast, bridged all of the nonmatching items in the sequence (Miller et al. 1996). Surprisingly, we found in the present study that entorhinal cortex is similar to prefrontal cortex and unlike perirhinal cortex in this respect.

It has been suggested that prefrontal cortex is the primary source of stimulus-specific activity during the delay periods of working memory tasks (di Pellegrino and Wise 1993; Funahashi et al. 1993; Fuster 1973; Miller et al. 1996; Niki and Watanabe 1976). Maintained excitatory feedback from prefrontal cells may then be sent back to posterior visual areas, biasing responses in favor of behaviorally relevant stimuli. This feedback may cause the match enhancement effects found in perirhinal cortex during working memory tasks. The presence of bridging delay activity in entorhinal cortex suggests that its functions might parallel those of prefrontal cortex in working memory. Given the prominent feedback projections from entorhinal to perirhinal cortex (Suzuki and Amaral 1994a), entorhinal cortex would be in a good position to bias activity in perirhinal cortex. If entorhinal cortex does play such a role in working memory, it might explain why prefrontal lesions in humans typically impair but do not eliminate some forms of working memory (Milner 1995).

Taken together, the results indicate many similarities in short-term memory mechanisms across three anatomically interconnected cortical areas (see Fig. 17*A*). However, there are also differences that may suggest a crude functional hierarchy between perirhinal cortex on the one hand and entorhinal and prefrontal cortex on the other. Perirhinal cortex is distinguished primarily by its stimulus-selective responses. By contrast, entorhinal and prefrontal cortex are distinguished primarily by the presence of cells with delay activity that bridges intervening stimuli in the DMS task. Thus perirhinal cortex may be relatively specialized for ''bottom-up'' stimulus processing, whereas entorhinal and prefrontal cortex may be relatively specialized for ''top-down'' modulation of activity in visual processing areas in working memory tasks. This scheme is also consistent with the neuroanatomic hierarchy of these areas. From a neuroanatomic perspective, the perirhinal cortex appears to be the ''lowest''-order area, receiving the strongest direct projections from unimodal visual area TE (Jones and Powell 1970; Martin-Elkins and Horel 1992; Suzuki and Amaral 1994b; Van Hoesen and Pandya 1975; Webster et al. 1991) and providing visual information to entorhinal (Insausti et al. 1987; Suzuki and Amaral 1994a; Van Hoesen and Pandya 1975) and prefrontal cortices (Barbas 1993; Carmichael and Price 1995; Morecraft et al. 1992). Perirhinal cortex provides a feedforward laminar pattern of anatomic projections to entorhinal cortex and receives a feedback laminar pattern of projections in return (Suzuki and Amaral 1994a). The same may be true of the connections between perirhinal and prefrontal cortex, although the laminar patterns of these interconnections has not been fully described.

Place memory in the entorhinal cortex

To perform the DMP task, the animal must solve three problems analogous to the three problems of the DMS task. It must discriminate between the different spatial locations, it must retain a memory of the locations, and it must be able to make a decision about whether a current cue matches the location of a previous cue. As we found in the DMS task, entorhinal cells have properties consistent with a role in each of these three operations. Indeed, the properties of cells in the two tasks were remarkably parallel (Fig. 17).

Similar to cells in the hippocampus (Cahusac et al. 1989; Rolls et al. 1989), we found that entorhinal cells responded differentially depending on the location of the cue on the screen. When we tested spatial selectivity on different background scenes, we found one population of cells that retained the same location-selective response irrespective of the background stimulus used. Thus these cells appeared to be selective simply for the location of the cue on the screen.

In this regard, it is interesting that some entorhinal ''place cells'' in the rat respond when the rat enters a particular location in a maze, and the same spatial selectivity is maintained in other mazes as well (Quirk et al. 1992). Similar patterns of responses have been reported in the dorsal subiculum in the rat (Sharp and Green 1994). Of course, it is not known whether looking at or attending to a location on a screen is comparable in the monkey to moving the body to a location in the environment for a rat.

We found a different population of entorhinal cells with location-selective responses that were dependent on the background scene. These cells exhibited location-selective responses when a particular background was used but either did not respond at all or responded nonselectively for cue locations on other backgrounds. One possibility is that this apparent selectivity for place and background was due simply to the visual feature selectivity of the cells. For example, the cell might be selective for a particular feature that happened to be present in one location of one background scene but was not present in other scenes. An alternative possibility is that these cells respond selectively to the combination of

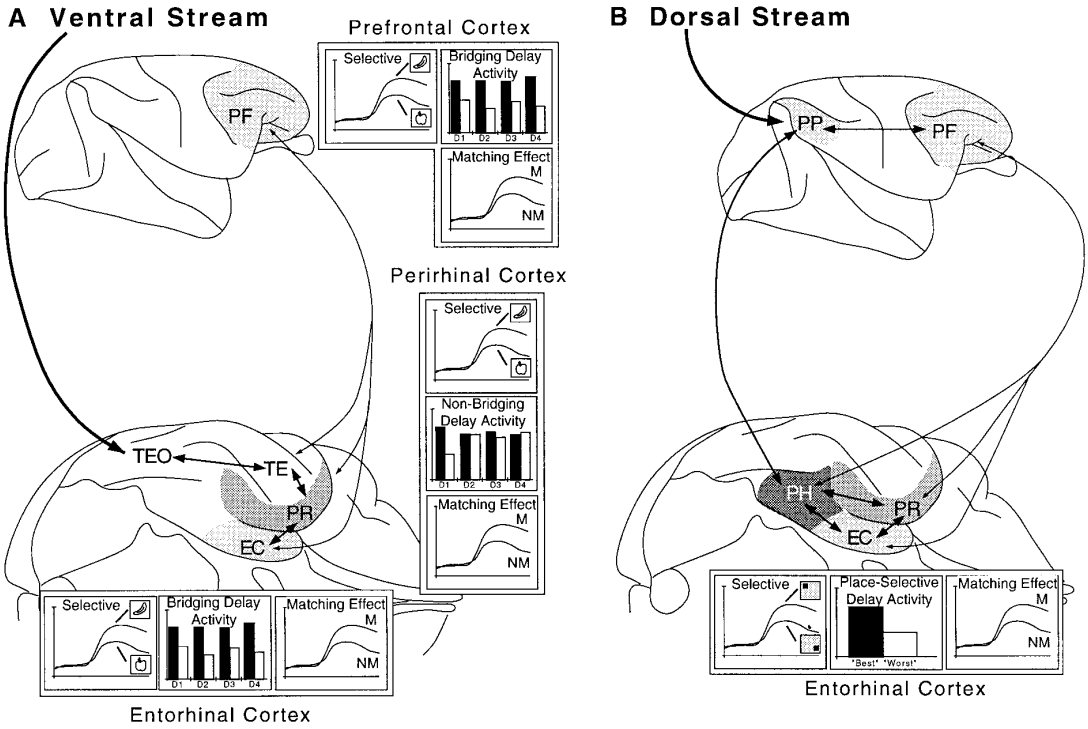

FIG. 17. Schematic diagram illustrating some of the ventral stream (*A*) and dorsal stream (*B*) areas involved in object and place memory tasks, respectively. Arrows: neuroanatomic projections. Icons: response properties typically observed in prefrontal (PF), perirhinal (PR), or entorhinal (ER) cortices. For *B*, because analogous tasks of place memory have not been studied in either prefrontal or posterior parietal cortices (but see Constantinidis and Steinmetz 1996), we could not include icons for these areas. PH, parahippocampal cortex; PP, posterior parietal cortex; TE, area TE; TEO, area TEO.

a particular location in the ''context'' of a preferred background. Again, it is difficult to relate this spatial selectivity to the properties of place field cells in rats. However, it is interesting that many place field cells in the hippocampus respond when the rat enters a particular location in one maze but will either not respond at all or respond to a completely different location if the shape of the maze is changed (Muller and Kubie 1987; Quirk et al. 1992). Lesion studies in the monkey also support the idea that the hippocampal system is important for learning the context in which a particular stimulus or location is important (Gaffan 1992, 1994).

RELATIONSHIP BETWEEN EYE POSITION AND PLACE-SELECTIVE RESPONSES. Entorhinal cells exhibited place-selective responses in conditions in which eye position was constant (fixation control experiment) as well as in conditions in which the animal was free to move the eyes. In the latter condition, we found no systematic relationship between the animals' average eye position at the time the cues were presented and the location of the cue itself. Because we did not directly manipulate both eye position and retinal stimulation, we cannot rule out the possibility that entorhinal cells have conventional visual receptive fields. However, the results are suggestive that the spatial receptive fields of entorhinal cells are at least partially independent of retinal location (i.e., they exhibit a nonretinocentric frame of reference). This would not be surprising considering that the receptive fields of cells in posterior parietal cortex are determined jointly by retinal location and eye position (Andersen et al. 1990b) and that posterior parietal cortex is an indirect source of spatial information to the entorhinal cortex (Andersen et al. 1990a; Suzuki and Amaral 1994b). Indeed, there are now several examples of neurons whose receptive fields are not coded in retinocentric coordinates. For example, neurons in area PO have visual receptive fields that remain anchored to the same absolute spatial location irrespective of the eye position (Galletti et al. 1995). Neurons in the ventral premotor cortex (Graziano et al. 1994) as well as the putamen (Graziano and Gross 1993) have receptive fields that code locations in a body-part-centered coordinate system. Similarly, there is some evidence that neurons in the monkey hippocampus represent space in an allocentric or world-centered coordinate frame (Feigenbaum and Rolls 1991).

MEMORY-MODULATED RESPONSES TO CUE LOCATIONS. The responses of some entorhinal cells were significantly suppressed when a cue location was repeated within the sequence, and the responses of other cells were enhanced. This is similar to the repetition suppression and match enhancement effects observed in entorhinal, perirhinal, and prefrontal cortices during performance of the DMS task. Interestingly, cells in posterior parietal cortex show strong match suppression for cues presented in repeated locations when animals perform a spatial DMS task (Steinmetz and Constantinidis 1995). Hippocampal cells also show repetition suppression when objects are repeated in a particular spatial location (Rolls et al. 1989).

DELAY ACTIVITY IN THE DMP TASK. Similar to the sample-selective delay activity found in the DMS task, some entorhinal cells exhibited spatially selective delay activity. Spatially selective delay activity in visuospatial memory tasks is a

common property of cells in dorsal stream areas, including area 46 in prefrontal cortex (di Pellegrino and Wise 1993; Funahashi et al. 1993; Fuster 1973; Niki and Watanabe 1976) and posterior parietal cortex (Constantinidis and Steinmetz 1996; Gnadt and Andersen 1988).

TOPOGRAPHY OF PLACE-SELECTIVE RESPONSES. Place-selective cells were about equally common in anterior and posterior portions of entorhinal cortex. The widespread distribution of location-selective cells is consistent with the corticocortical connectivity of the entorhinal cortex. As described above, the entorhinal cortex receives the bulk of visuospatial information from dorsal stream areas via projections from the parahippocampal cortex, which projects directly to posterior portions of the entorhinal cortex (Insausti et al. 1987; Suzuki and Amaral 1994a; Van Hoesen and Pandya 1975) and indirectly to anterior entorhinal regions via the perirhinal cortex (Suzuki and Amaral 1994b) (Fig. 17*B*). The indirect projection via the perirhinal cortex is a potential route by which place information from dorsal stream areas may be combined with detailed object information. This kind of visuospatial information may be used in our place memory tasks, in which cue locations are at least partially defined in the context of a complex visual background stimulus. Thus, although findings from neuroanatomic studies alone could not determine the relative importance of the direct and indirect pathways of parahippocampal input to the entorhinal cortex, physiological studies suggest that, at least in some instances, both pathways may be equally important.

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