

Prefrontal Neurons Coding Suppression of Specific Saccades

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Summary

The prefrontal cortex has been implicated in the suppression of unwanted behavior, based upon observations of humans and monkeys with prefrontal lesions. Despite this, there has been little direct neurophysiological evidence for a mechanism that suppresses specific behavior. In this study, we used an oculomotor delayed match/nonmatch-to-sample task in which monkeys had to remember a stimulus location either as a marker of where to look or as a marker of where not to look. We found a group of neurons in both the frontal eye field and the caudal prefrontal cortex that carried signals selective for the forbidden stimulus. The activity of these “don’t look” neurons correlated with the monkeys’ success or failure on the task. These results demonstrate a frontal signal that is related to the active suppression of one action while the subject performs another.

Introduction

The inability to suppress unwanted or inappropriate behavior, such as stimulus bound action, is the hallmark of humans who, by virtue of immaturity or disease, have poorly functioning frontal lobes (Fukushima et al., 1988; Guitton et al., 1985; Lhermitte, 1983; Munoz et al., 1998). This has been known since Harlow’s original description of Phineas Gage, whose frontal lobes were damaged by an iron bar passing through his head (Harlow, 1848), and confirmed by many subsequent descriptions of pa-

tients with frontal lobe damage. Despite the clinical importance of suppression, most studies of the frontal lobe (e.g., Hasegawa et al., 1998, 2000a, 2004) in monkeys have dealt with the generation of movement rather than its suppression.

The saccadic system provides an excellent model for the suppression of unwanted behavior. Monkeys as well as humans can voluntarily move their eyes not only to look at something but also to avoid looking at something. In social situations, the inability to avert our gaze may result in socially unacceptable or offensive behavior. Thus, monkeys avoid making eye contact with a dominant monkey, because such eye contact is an aggressive act (Mendelson et al., 1982; Van Hooff, 1972). Two mechanisms have been described for the suppression of saccadic eye movements. One is a fixation signal. Fixation neurons in the frontal eye field (FEF) (Bizzi, 1967; Segraves and Goldberg, 1987), superior colliculus (Munoz and Wurtz, 1993), pons (Gandhi and Keller, 1999), and substantia nigra (Hikosaka and Wurtz, 1983) discharge tonically except in the interval around the saccade. Fixation is an active process. When monkeys actively fixate, the threshold for evoking saccades by electrical stimulation from the FEF (Goldberg et al., 1986) and superior colliculus (Schiller and Sandell, 1983) increases, suggesting an inhibition by the fixation system on the generation of saccades. A second mechanism for the suppression of saccades can be seen in go/no-go tasks. In these tasks, a stimulus can be the target of a saccade unless a no-go or cancellation stimulus appears, in which case the monkey must not make the saccade. Some neurons in the FEF are activated specifically for stimuli under no-go conditions (Sommer and Wurtz, 2001). Both of these mechanisms can be considered aspects of global suppression: the monkey is instructed not to make any saccade at all.

However, in the real world most choices are not between making a saccade and not making one but rather between which saccade to make. This requires suppressing one saccade and generating another at the same time. In order to study activity that is related to the suppression of an unwanted saccade in the prefrontal cortex, we used delayed spatial match and nonmatch saccade tasks. In the *match* task, a green fixation point signaled that the monkey had to remember the location of the sample cue and eventually make a saccade to that location. In the *nonmatch* task, a red fixation point signaled that the monkey had to remember the location of the sample in order to avoid making a saccade to it. We found evidence for three different signals: a visual or working memory signal that did not distinguish between the two trials, a saccade-planning signal that predicted the eye movement that the monkey would make in the match task, and a response suppression signal that was selective for the one saccade that the monkey would not make in the nonmatch task. These signals were present both as an on response to the sample and as activity during the delay period, during which the monkey had to remember the stimulus. Preliminary reports of this study have been presented elsewhere (Ha-

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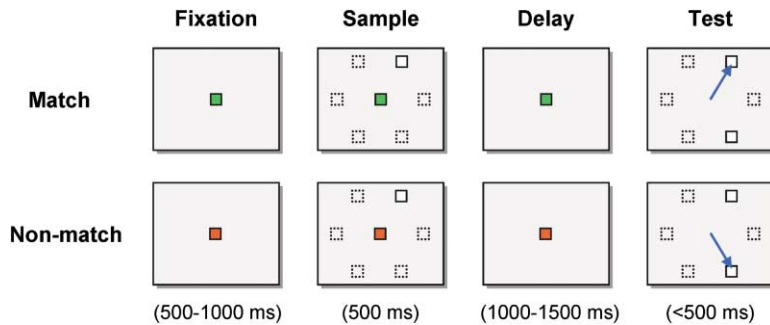


Figure 1. Delayed Spatial Match and Non-match Tasks

Each task has four periods: fixation, sample, delay, and test. During the fixation period, a fixation point appears, and the monkey fixates it for 500–1000 ms. During the sample period, a sample then appears for 500 ms at one of six possible locations, pseudorandomly intermixed. During the delay period, the sample disappears, and the monkey continues to fixate for 1000–1500 ms. During the test period, the fixation point disappears, and two identical stimuli appear, one at the original site of the sample and the other at one of

five other possible positions. In the match task (upper row), the fixation point is green, and in the test period the monkey must make a saccade to the stimulus at the original sample site within 500 ms to receive a reward. In the nonmatch task (lower row), the fixation point is red, and in the test period the monkey must make a saccade to the stimulus that is not at the sample site.

segawa et al., 2001, Soc. Neurosci., abstract; Hasegawa et al., 2002, Soc. Neurosci., abstract).

Results

We recorded the activity of 310 single neurons in the caudal part of the dorsolateral prefrontal cortex that corresponded to areas 46 and 8a and the FEF in two rhesus monkeys (157 in monkey 1 and 153 in monkey 2) while they performed the delayed spatial match/non-match tasks (Figure 1; see the Experimental Procedures). In both tasks, the monkey looked at a fixation spot (fixation period), and 500–1000 ms later a small spot (sample cue) appeared for 500 ms at one of six peripheral locations on the screen (sample period). The monkey continued fixating for another 1000–1500 ms (delay period), after which the central fixation spot disappeared, and two stimuli appeared (test period), one at the same location as the sample, the other at another unpredictable location (one of five locations other than the sample cue location). Depending upon the color of the fixation spot, the monkey had to make a saccade either to the stimulus at the sample location (the match task) or to the other stimulus (the nonmatch task). We pseudorandomly intermixed trial types (match and non-match) and stimulus locations. Of 310 recorded neurons, 235 (132 in monkey 1 and 103 in monkey 2) showed spatially selective activity during at least one epoch of the task. However, different neurons were tuned during different epochs: 141 were tuned in the early sample period, 152 in the late sample period, 130 in the early delay period, and 128 in the late delay period. Eighty-four neurons were tuned in the both the early cue and late delay periods (see the Experimental Procedures for the definitions of these epochs).

Sample Period Activity

Because the color of the fixation point signaled the nature of the task, when the sample appeared the monkey already knew its behavioral significance. This foreknowledge was reflected in the activity of neurons. We found three different kinds of on responses. “Look” neurons (Figure 2A) had an enhanced response to a sample stimulus that the monkey knew a priori was a saccade target. “Don’t look” neurons (Figure 2B) had an enhanced response to a stimulus that the monkey knew a priori

was *not* a saccade target. “Pure visual” neurons did not distinguish between the tasks during the sample period (Figure 2C). Of 141 neurons that exhibited spatially tuned activity during the early sample period, the majority of neurons were pure visual (80%, 113/141), and only some of the neurons (look, 14/141, 10%; don’t look, 14/141, 10%) started discriminating the sample cue between match and nonmatch from the beginning of the early cue period. We found similar results in the late sample period (see Figure 5C for summary).

Delay Period Activity

In the late delay period (final 400 ms of the delay period), 128 neurons (80 neurons in monkey 1 and 48 neurons in monkey 2) exhibited spatially tuned activity. We also found the three different patterns of neuronal activity during this period. Sixty-eight (53%) were look neurons, which exhibited greater activity when the stimulus in their response fields was the saccade goal. Twenty-four (19%) were don’t look neurons, which exhibited greater activity when the stimulus in the response field was the stimulus to which the monkeys were forbidden to look. Thirty-six (28%) were “memory” neurons, which responded equally in both cases, holding a working memory of an object without indicating the behavioral significance of that object.

The neuron in Figure 3A is an example of a look neuron. The neuron exhibited increasing activity during the delay period in the match task when the sample cue appeared at the lower right location (“preferred location”). The minimum activity in this task occurred when the sample cue appeared at the upper left location (“nonpreferred location”). In contrast, there was just a slight buildup of activity for these two locations in the nonmatch task. Spatial tuning for sample cue location was much stronger in the match task than in the nonmatch task (Figure 3B). A two-way ANOVA (task × location—see the Experimental Procedures) indicated a significant ($p < 0.001$) interaction between these factors; the effect of location was significant ($p < 0.001$) in the match task but not ($p > 0.05$) in the nonmatch task. If this were a purely spatial working memory signal, the activity should be equal in both cases. Instead, the enhancement in the match task suggests that the delay period activity is related to some aspect of movement generation. It is also possible that the monkey solved the

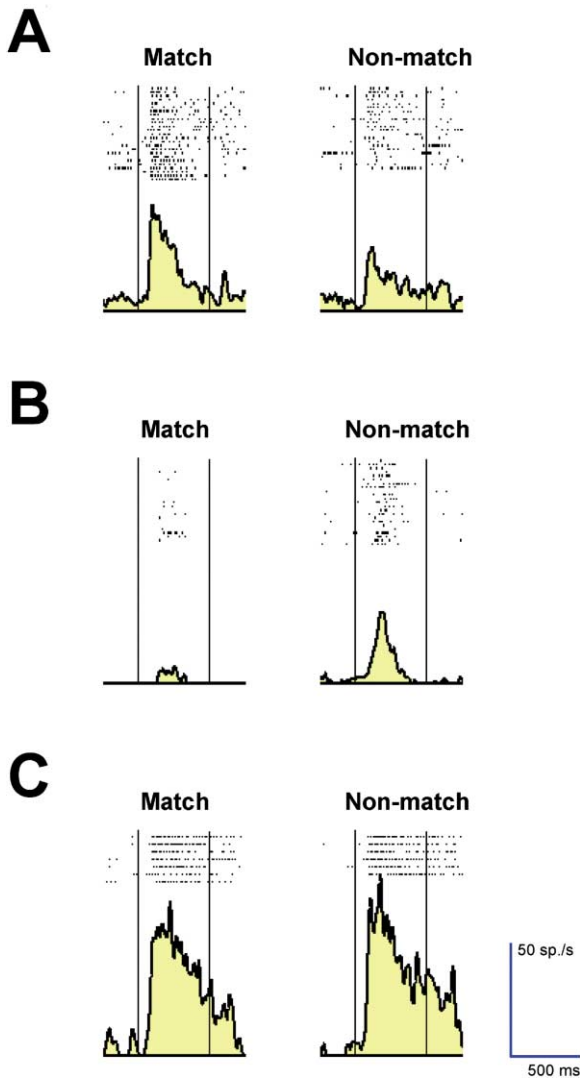


Figure 2. Visual Response of Three Cortical Neurons in the Match and Nonmatch Tasks

(A) Neuron that exhibited greater sample period activity in the match task. (B) Neuron that exhibited greater sample period activity in the nonmatch task. (C) Neuron that exhibited similar sample period activity in both tasks. In each of the six panels, the two vertical lines indicate the onset and offset of the sample stimulus. Neural responses are shown as raster diagrams; each dot represents an action potential of the neuron; each row represents a trial; successive trials are synchronized on the appearance of the sample stimulus. A yellow-filled spike density trace at the bottom of each panel displays the raster data converted to an instantaneous firing rate (see the Experimental Procedures).

nonmatch task by actively planning another saccade. Although the neuron is selective for the match case, it is not a simple presaccadic visuomovement neuron such as those found in the FEFs (Bruce and Goldberg, 1985). The neuron was tuned for saccade direction during the delay and presaccadic periods in the match task, but it did not respond before the saccade in the nonmatch task, suggesting that it was more involved in the delay process than the generation of the saccade itself (Figure 3B, bottom).

The neuron in Figure 3C is an example of a don't look neuron. Like the neuron in Figure 3A, the activity of this neuron was selective for both the sample cue location and the task. However, the neuron's delay period activity was spatially tuned for sample cue location only in the nonmatch task (Figure 3D, top). A two-way ANOVA indicated a significant ($p < 0.001$) interaction between location and task; the effect of location was significant ($p < 0.001$) in the nonmatch task but not ($p > 0.05$) in the match task. One possibility is that activity in the nonmatch task actually represented covert planning of a saccade in a direction away from the nonmatch sample. If the neuron merely represented planning of a tentative saccade in some nonmatch direction, it should have discharged in that same direction in the match task. The neuron was not tuned at all in the match task (Figure 3C, left). Similarly, it should have been tuned for a specific saccade direction in the nonmatch task. It was not (Figure 3C, right, and Figure 3D, bottom). Just as the neuron in Figure 3A was tuned only for trials in which the saccade was planned across the delay period and not for saccades that were generated de novo during the test period, this neuron was tuned only for trials in which the saccade had to be inhibited across the delay period and did not participate in a mechanism that inhibited saccades to its response field that were generated de novo during the test period.

The activity in the nonmatch task could have been related to some nonspecific attentional or arousal effect (Hasegawa et al., 2000b) rather than the inhibition of a saccade to a specific target maintained throughout the delay period. If that were the case, one would expect arousal parameters, such as task performance, saccade latency, and velocity, to differ between the two tasks. They did not. In the successful trials from which neuronal data were collected, mean saccade latency was 202 ± 2 ms (SEM) for match and 199 ± 2 ms for nonmatch. Mean peak velocity was $442^\circ/\text{s} \pm 7^\circ/\text{s}$ for match and $443^\circ/\text{s} \pm 7^\circ/\text{s}$ for nonmatch. In experiments from which neuronal data were collected, monkey 1 performed the match task at a rate of 84% and the nonmatch task at a rate of 87%. Monkey 2 performed the match task at 77% and the nonmatch task at 78%. There was no correlation of neuronal discharge with performance. To see if any component of neuronal discharge arose from saccade parameters, we performed a multiple linear regression analysis (see also Hasegawa et al., 2004) on late delay period activity at the preferred location, using the following model:

$$\text{activity} = w1 \times (\text{task}) + w2 \times (\text{latency}) + w3 \times (\text{velocity}) + c$$

where *activity* is neuronal activity on each trial, *task* is set to 1 on match or 0 on nonmatch task, *latency* is saccade latency, *velocity* is peak saccade velocity, $w1$ – $w3$ are partial regression coefficients, and c is a constant term. Most look and don't look neurons showed a significant coefficient only for task. In the population, the effect of task was much greater than that of saccade latency or velocity (Figure 4). These data suggest that any difference in activity between match and nonmatch tasks was not merely a result of differ-

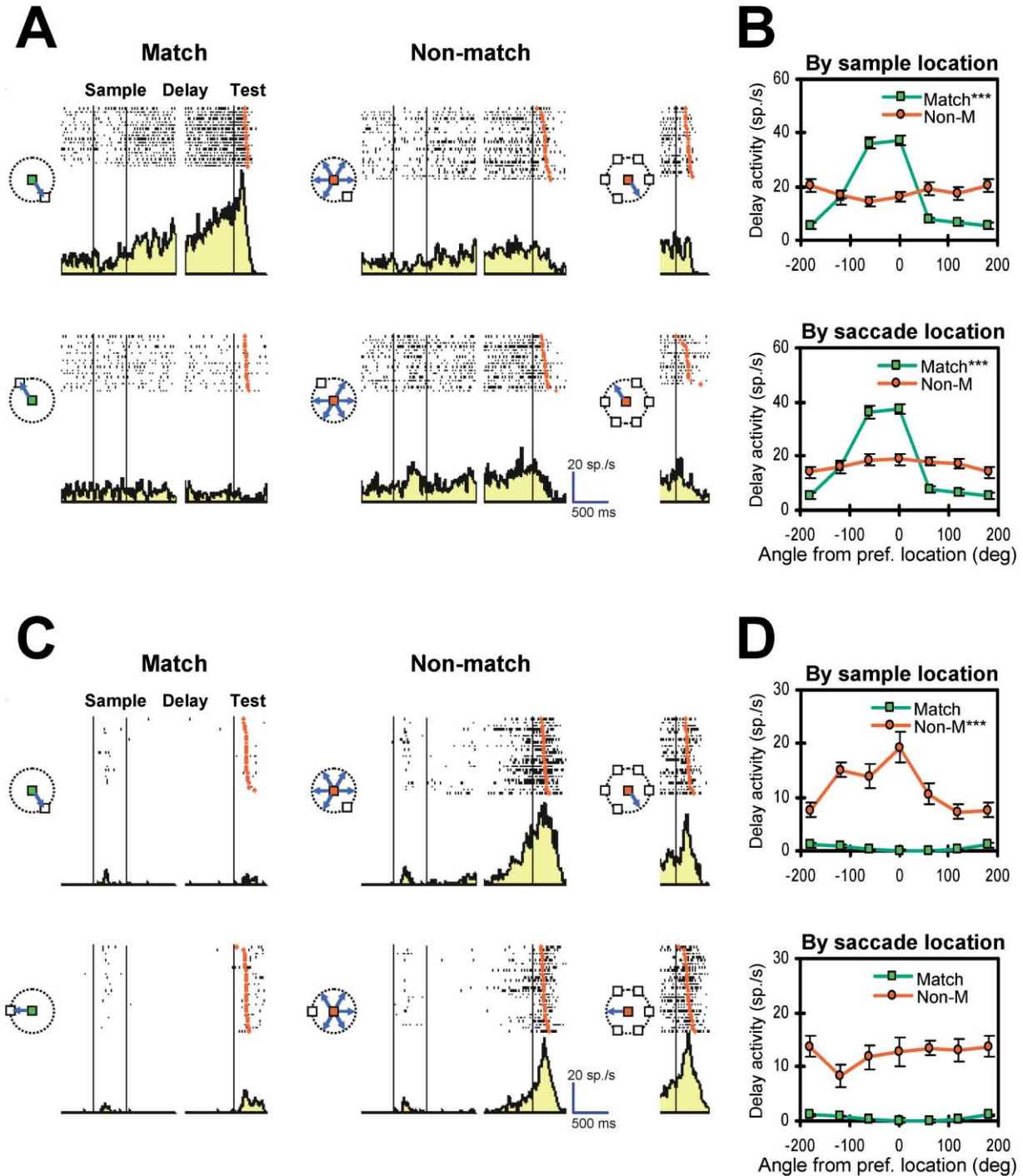


Figure 3. Response of Two Cortical Neurons in the Match and Nonmatch Tasks

(A) A look neuron, found in the frontal eye field, that was strongly activated during the delay period of the match task when the sample stimulus was presented below and to the right of the fixation point (upper left panel). No response was observed in match trials where the sample stimulus appeared to the upper left (lower left panel). In nonmatch trials, there was a small increase in activity during the delay period that did not depend on stimulus location (center panels). Neural responses, selected by the sample cue location, are shown as raster diagrams and spike density plots, same as in Figure 2. Trials are synchronized on the appearance of the sample (left part of histogram) or the test stimuli (right part). The red vertical line in each trial signifies the beginning of the saccade. Cartoons to the left of each panel show the fixation point (green or red square), sample location (white square), and saccade(s) made by the monkey (blue arrows). In the match task, the saccade was to the sample location. In the nonmatch task, it was to one of the other five locations. Far right panels show responses in the nonmatch task selected by saccade location. The top panel shows data for nonmatch trials where the monkey made a saccade to the preferred location during the match task (below and to the right). The bottom panel shows data for nonmatch trials with saccades to the nonpreferred (upper left) direction. Note that activity is similar to that in the nonmatch records selected by sample: no increased activity was observed for saccades to the preferred location.

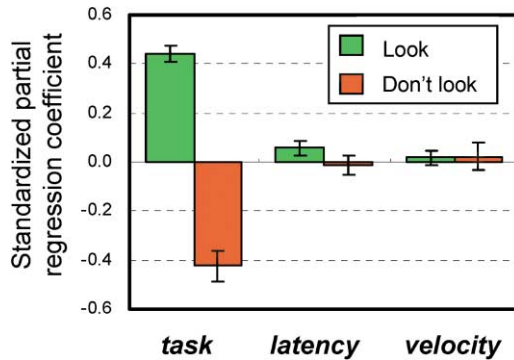


Figure 4. Multiple Regression Analysis of Late Delay Period Activity of Neurons with Task-Specific Spatial Tuning

Averages and SEM of standardized partial regression coefficients were plotted for 68 look and 24 don't look neurons. "Task" indicates the kind of task (match = 1; nonmatch = 0). "Latency" and "velocity," respectively, represent saccade latency and saccade peak velocity.

ences in attention or arousal between the two tasks. In particular, the increased activity that was present even in nonpreferred stimulus locations in the nonmatch task in the neuron that is illustrated in Figures 3C and 3D must have arisen from some factor specific to the nonmatch task rather than from a nonspecific attention or arousal effect.

The Temporal Progression of Look and Don't Look Activity

As the trial progressed, neurons frequently shifted their type. The neuron in Figures 5A and 5B showed pure visual activity in the sample period but developed look activity during the delay period. Across the sample of 128 neurons that were spatially tuned in the late delay period, there was a gradual transition from pure visual or "visual-memory" activity to look activity as the trial progressed (Figure 5C). The time courses of activity of these late delay look and don't look populations were quite different (Figure 6). Neurons that were to develop look activity typically responded to the onset of the sample, and this initial visual response decayed (Figure 6A). In match trials, activity gradually increased during the delay, and there was a presaccadic burst. In the nonmatch trials, there was no buildup of activity, but there was a second onset response to the appearance of the test stimulus. In contrast, neurons that were to develop don't look activity had little or no response to the onset of the sample; they gradually increased their activity in the nonmatch task. These neurons responded

before the saccade in both the match and nonmatch task, but their activity was greater before the saccade in the nonmatch task, and they then gradually increased their activity in the match task above the baseline maintained in the nonmatch task as the trial progressed. Don't look neurons typically responded only weakly, if at all, to sample onset and gradually developed nonmatch-specific activity during the delay period, like the neuron in Figures 3C and 3D (Figure 6B).

Activity in Error Trials

The population activity predicted the accuracy of the monkey's response for both look and don't look neurons. This could even be seen in the activity of single neurons. Figure 7A compares the activity in correct and error trials for the same neurons that are shown in Figure 3. This was also true across the sample as a whole. We compared the activity on error trials for 33 look and 11 don't look neurons, for which the monkeys made three or more errors on trials for the preferred location in the preferred task (Figure 7B). Delay activity during error trials was significantly lower than the activity during correct trials for both types of neurons (Wilcoxon sign rank test; $p < 0.001$ for look and $p < 0.01$ for don't look neurons).

Distribution within the Cortex

To examine the regional distribution of neuron types, we divided the recording areas into two subareas (Figure 8A): the FEF, where electrical stimulation (50 μ A) elicited saccadic eye movements, and the pre-FEF, the area surrounding the FEF anteriorly (mostly area 8a and a part of area 46 around caudal edge of the principal sulcus), where electrical stimulation (50 μ A) failed to elicit saccadic eye movements. Although look neurons predominated in both areas, don't look neurons were more prevalent in the pre-FEF (Figure 8B). This bias was significant in each monkey individually (χ^2 test; $p < 0.05$).

Discussion

In this study, we probed the frontal mechanisms underlying response suppression and response planning. We used a task that required a monkey to remember the location of a stimulus during a delay period and, when it reappeared along with a new stimulus, either to make a saccade to the original sample or to plan a saccade to the new stimulus. During the delay period, the monkey had to remember the spatial location of the sample for one of two very different purposes: to plan a saccade to it or not to make a saccade to it when it reappeared.

(B) Spatial tuning of the look neuron shown in (A). Average activity in the final 400 ms of the delay period in the match (green) and nonmatch (red) tasks is plotted for each of the sample cue locations (top) or each of the saccade locations (bottom). Error bars are SEMs. Abscissa indicates angular position of sample stimulus or saccade relative to the preferred sample location in degrees.

(C) A don't look neuron, found in the frontal eye field, which fired rapidly at the end of the delay period in the nonmatch task but not in the match task. (Upper center panel) Response in the nonmatch task where sample stimulus was presented in the preferred (bottom right) location. (Lower center panel) Response in the nonmatch task where sample stimulus was presented in the nonpreferred (straight left) location. (Upper and lower left panels) Response in the match task where sample was presented at same locations as in center panels. (Upper and lower right panels) Response in nonmatch trials where the monkey made a saccade to the preferred (upper right panel) or nonpreferred (lower right panel) locations as determined from the center panels.

(D) Spatial tuning of the don't look neuron shown in (C). Average activity in the final 400 ms of the delay period in the match (green) and nonmatch (red) tasks are plotted for each of the sample cue locations (top) or each of the saccade locations (bottom). Conventions as in (B).

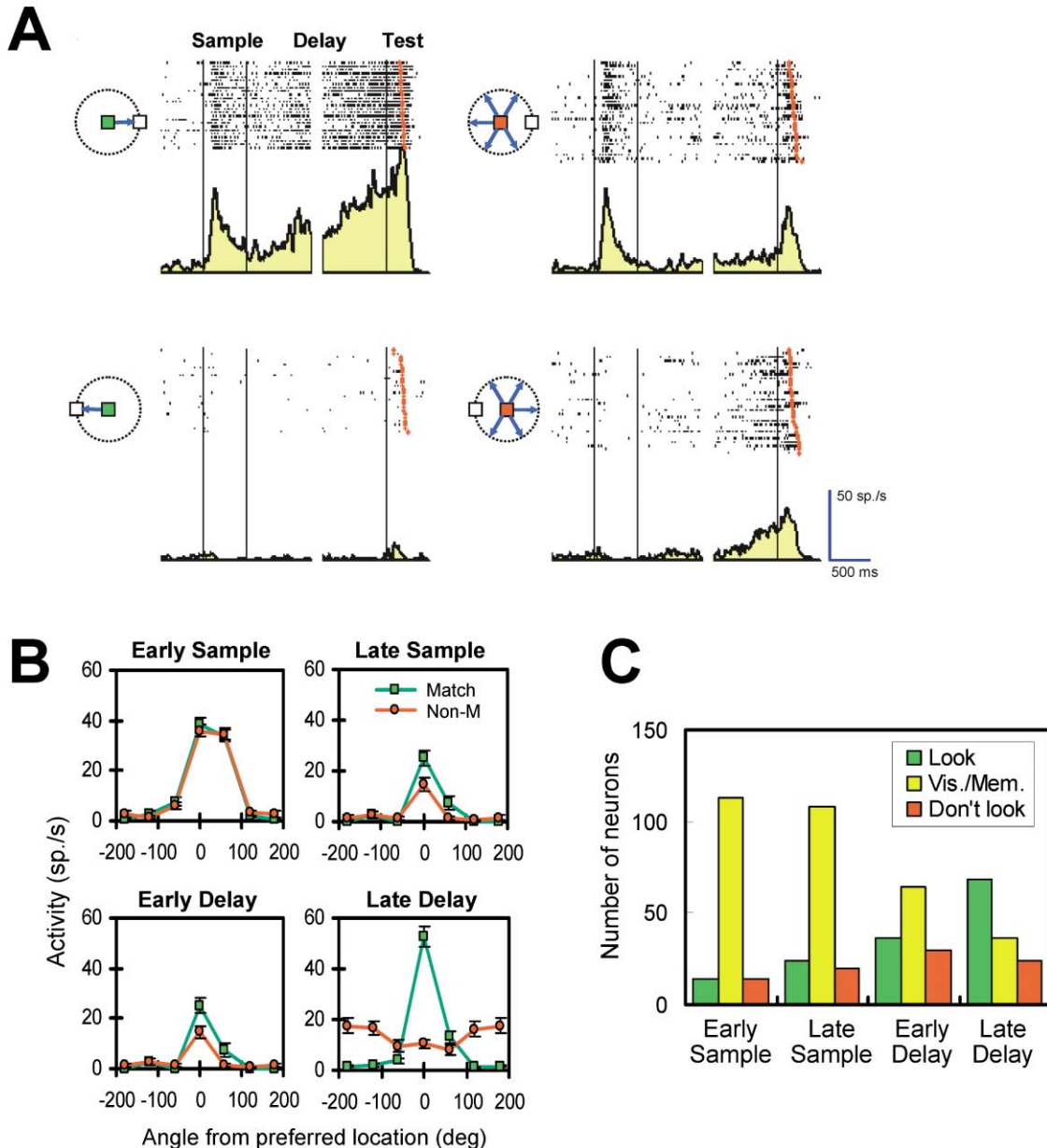


Figure 5. Neuron that Exhibited Different Relative Activation in Match versus Nonmatch Task during Different Task Epochs

(A) Rasters and spike density histograms of responses in match task (left panels) and nonmatch task (right panels) when sample stimulus was presented in preferred (top panels) and nonpreferred (bottom panels) locations. Format of data is the same as in Figures 3A and 3C except that records selected by saccade direction are omitted.

(B) Average activity in the match (green) and nonmatch (red) tasks are plotted for each of the sample cue locations during four task epochs. The layout is the same as in Figures 3B and 3D. Identical spatial tuning observed in the early sample period shifts to match activity as time progresses.

(C) Number of neurons that exhibited look (green), visual or memory (yellow), and don't look (red) activity as determined by ANOVA in each of the four task epochs. As the trial proceeds, the preponderance of visual or memory activity seen in early sample period shifts to a preponderance of look activity.

We found that there are separate neural mechanisms in the frontal cortex for response suppression and response planning. We will discuss this finding in terms of previous studies of response suppression, working memory, and current concepts of frontal function.

Because the fixation point that started the trial also signaled the type of the trial, the monkeys knew the significance of the stimulus when it appeared. In keeping

with this foreknowledge, some neurons reflected saccade planning or response suppression immediately upon the appearance of the sample. Others developed it during the delay. Presaccadic onset enhancement has been previously described in the FEF (Bruce et al., 1985; Wurtz and Mohler, 1976) and prefrontal cortex (Boch and Goldberg, 1989), but FEF neurons do not show no-go onset enhancement (Sommer and Wurtz, 2001). In

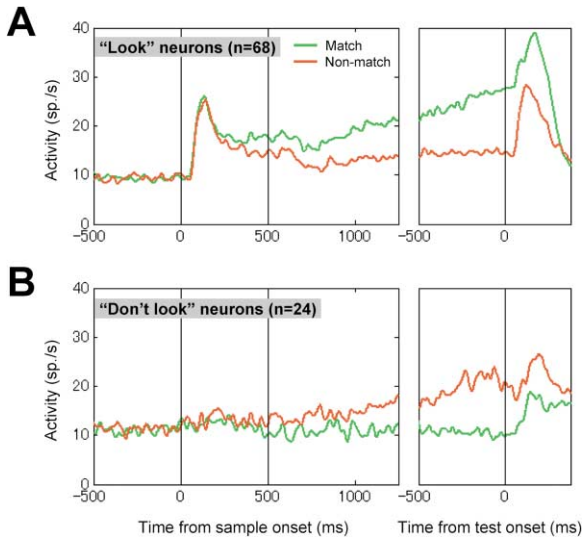


Figure 6. Population Time Course
Responses of 68 look neurons (top) and 24 don't look neurons (bottom), which were classified by the late delay period activity, were averaged. (A) plots the time course of this average activity for the look neurons during those match and nonmatch trials in which the sample stimulus appeared in the neuron's preferred location (determined from match trials). (B) plots the time course of average activity for the don't look neurons during those match and nonmatch trials in which the sample stimulus appeared in the neuron's preferred location (determined from nonmatch trials). Activity is synchronized on the appearance of the sample (left column) or the test stimuli (right column).

our study, we used the fixation point color to determine the meaning of the sample stimulus. The neurons could, therefore, have been responding to the color rather than to the necessity of making or inhibiting a saccade. This is unlikely for several reasons. The first is that neurons

did not respond to the appearance of the fixation point, which was therefore outside their response fields. The sample and test stimuli that were in the receptive field were white, so visual color selectivity could not have been operational when these stimuli appeared. The second is that many cells developed selectivity late in the delay period. It is unlikely that neurons making a chromatic decision would take so long to make a decision. Certainly, the latencies of color-selective neurons in V4 (Schein and Desimone, 1990) and inferior temporal cortex (Komatsu and Ideura, 1993) are far shorter. Third, many of the neurons were in the low-threshold FEF, in which neurons have been shown not to have stimulus color specificity (Thompson et al., 1997). Finally, we were recording from dorsolateral prefrontal cortex. There is an increasing amount of evidence that there is a segregation of visual input to prefrontal cortex, with pattern (and color) input from the ventral stream projecting to ventrolateral prefrontal cortex and motion and spatial activity projecting to dorsolateral prefrontal cortex (Goldman-Rakic, 1988). Using a multidimensional attention task with a go/no-go procedure, Sakagami and his colleagues (Sakagami et al., 2001) recently reported finding color-selective go/no-go neurons in ventrolateral prefrontal cortex, but these neurons changed their color selectivity when the no-go color changed. Furthermore, these neurons carried no information about go/no-go when motion and not color was the discriminated dimension. In their study, unlike ours, the stimuli in the neurons' receptive fields bore the information for the response (the fixation point in our case) but had no relationship to the spatial aspect of the response (the sample location in our case), nor did the neurons distinguish color when color was not the discriminated dimension. For these reasons, it is extremely unlikely that the look and don't look neurons in our study were responding primarily to the color, rather than to the task mandated by the color.

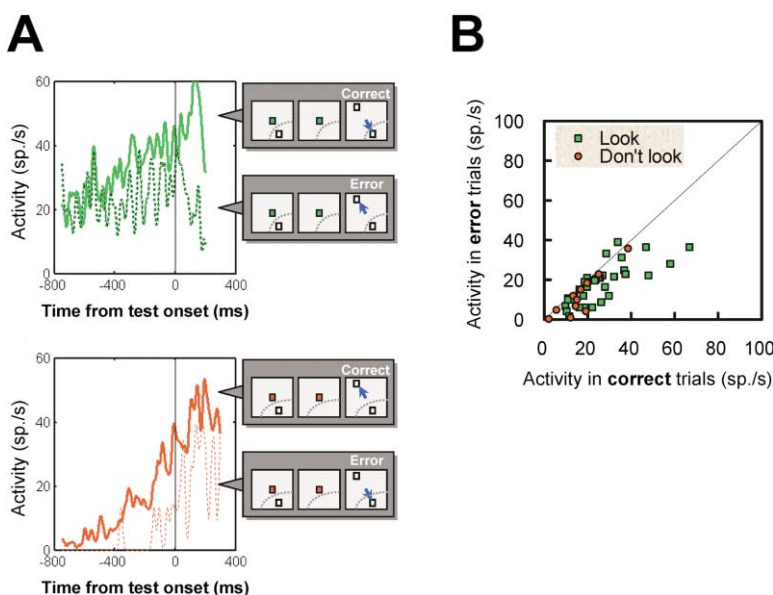


Figure 7. Analysis of Error Trials
(A) Examples of error analysis in single neurons. (Top) Green records plot activity of the look neuron that was shown in Figure 3A during the late delay period in trials where the monkey made the correct saccade to the match test stimulus (solid green trace) and in those where he made an incorrect saccade to the nonmatch test stimulus (dotted green trace). Insets indicate this behavior. (Bottom) Red records plot activity of the don't look neuron that was shown in Figure 3C during the late delay period in trials where the monkey made the correct saccade to the nonmatch test stimulus (solid red trace) and in those where he made an incorrect saccade to the match test stimulus (dotted red trace). Insets indicate this behavior. Traces are aligned on onset of the test stimuli. (B) Population analysis. Late delay period activity of 33 look (green symbols) and 11 don't look neurons (red symbols) on error trials (ordinate) is plotted against activity of the same neurons on correct trials (abscissa). Only those neurons that were recorded in sessions in which the monkey produced errors on three or more trials at the preferred locations were used for the population analysis.

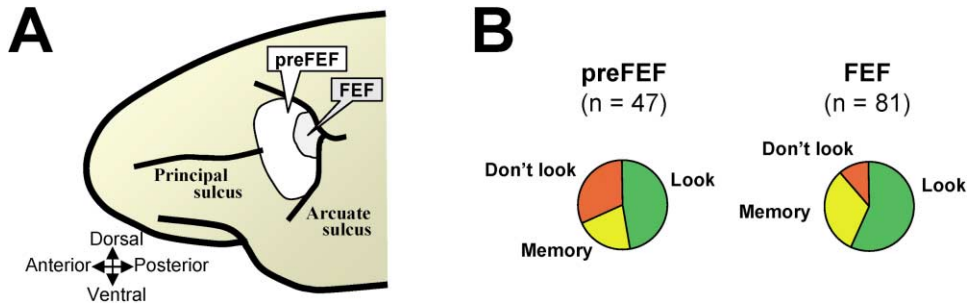


Figure 8. Recorded Area and Regional Differences of Neuron Type
(A) Schematic drawing of the recorded areas as reconstructed from MRI examinations.
(B) Pie charts showing the distribution of all look neurons (green), don't look neurons (red), and memory neurons (yellow) in the caudal prefrontal (pre-FEF; left) and the frontal eye field (FEF; right).

Physiological studies have demonstrated neurons that fire tonically and are associated with global suppression of all saccades in a number of brain areas: the nucleus of the dorsal raphe (Gandhi and Keller, 1999; Keller, 1974), rostral superior colliculus (Munoz and Wurtz, 1993), the substantia nigra pars reticulata (Hikosaka and Wurtz, 1983), and the FEF (Bizzi, 1967; Segraves and Goldberg, 1987). Electrical stimulation of fixation neurons in the colliculus (Munoz et al., 1996), FEF (Burman and Bruce, 1997), and nucleus of the dorsal raphe (Gandhi and Keller, 1999) suppresses all saccades.

The countermanding task is an example of a task that is performed by the activation of a global suppression mechanism. In this task, the subject is cued by the reappearance of the fixation point to continue fixating rather than making the saccade that it was generating. Hanes et al. (1998) studied FEF activity during this task and showed that during successfully canceled saccades the activity FEF visuomovement neurons declined significantly before the estimated stop signal reaction time occurred. They did not show any activity that was specifically excited by the saccade cancellation process. Recently, Pare and Hanes showed similar results for the superior colliculus—the visuomovement cells declined, and the fixation cells increased before the stop signal reaction (Pare and Hanes, 2003). Furthermore, the activity of the fixation neurons in the rostral superior colliculus predicted the success of the cancellation process. This suggests that the countermanding task is accomplished by shutting down the saccadic system rather than inhibiting a specific saccade.

Another task that requires the suppression of all behavior is the go/no-go task, which has also been used to study inhibitory processes in frontal cortex (Iversen and Mishkin, 1970). In these tasks, a visual cue instructs subjects either to respond (“go”) or not to respond (“no-go”). Imaging studies in humans have reported activation of prefrontal cortex in this task (Casey et al., 1997; Kawashima et al., 1996; Konishi et al., 1998; Tsujimoto et al., 1997). In monkeys, damage to the dorsolateral prefrontal cortex causes impairment on this task (Iversen and Mishkin, 1970). Neurons in this area respond selectively to the instructional cue (go or no-go) during the manual version (Iwabuchi and Kubota, 1998; Li and Kubota, 1998; Sakagami and Niki, 1994a, 1994b; Sakagami et al., 2001; Watanabe, 1986) as well as the oculo-

motor version (Sommer and Wurtz, 2001) of this task. In a no-go task, like the countermanding task, the subject is rewarded for not making any movement at all. It is therefore possible that activity that is preferential for the no-go case could be related to the suppression of all movements rather than an active suppression of a specific movement while another movement was being planned. Thus, a human imaging study suggests that the no-go signal is thought to activate a common inhibitory process that would suppress movement of either hand (Konishi et al., 1999) or in fact any unwanted movement. On the other hand, spatially selective no-go enhancement was also found in prefrontal neurons (Sakagami and Niki, 1994b) and in the FEF itself (Sommer and Wurtz, 2001). In the study by Sommer and Wurtz (2001), however, error trial analysis showed that the activity of the go/no-go selective neurons described the task but did not correlate with whether or not the monkey actually made the saccade. In contrast, in the delayed non-match-to-sample task, the activity of don't look neurons predicted success or failure on the task.

Another plausible model for response suppression is the antisaccade task. In this task, the subject must look directly opposite the stimulus. The stimulus location defines the saccade target location, not directly, as in a visually guided saccade, but through a process of stimulus-response association. Neurons describing such arbitrary stimulus-response association have been described in prefrontal cortex (White and Wise, 1999). Antisaccade-specific neurons have been described in the supplementary eye field (SEF) (Schlag-Rey et al., 1997). It is not clear whether this activity in the SEF is related to inhibiting the saccade or affirming the arbitrary stimulus-response association. Neurons in the FEF describe the actual movement (Everling and Munoz, 2000), and neurons in the lateral intraparietal cortex (LIP) describe first the stimulus and later, as the locus of attention switches to the saccade goal, both the stimulus and the response (Zhang and Barash, 2000; Gottlieb and Goldberg, 1999).

In contrast to the examples discussed above, the don't look mechanism that we have described does not disable the entire saccadic system or describe an arbitrary stimulus-response association but instead provides a spatially tuned signal to suppress a specific saccade while the monkey actively generates a different saccade. Mere activation of the tonic suppressive sys-

tem or specifying not to make a saccade as in the no-go task could not enable successful performance in the nonmatch task. In keeping with this specificity, activity in error trials correlates with the monkey's actual performance and not with the rule, for both look and don't look neurons.

In a more general theory of frontal cortical function, Miller and Cohen suggested that one function of frontal cortex is the association of stimuli with rules that govern how the subject will behave toward that stimulus (Miller and Cohen, 2001; Wallis and Miller, 2003). Both the look and don't look neurons could be described as associating a stimulus with a specific rule. However, as the look-type response has been widely accepted as the representation of saccade planning to a specific location (Snyder et al., 1997), it is reasonable that the don't look signal more naturally should be considered as activity selective for suppression of a saccade plan. This implies a close linkage between motor planning and response suppression. In fact, don't look neurons were found in the caudal part of prefrontal cortex, including the FEF, that are involved in the memory of a saccade goal and/or the generation of a saccade plan (Bruce and Goldberg, 1985; Funahashi et al., 1989; Hasegawa et al., 1998, 2000a).

A popular model of decision making is a race model, in which a decision occurs when a neural integrator reaches a preset threshold. This model has been used successfully to describe saccade countermanding (Hanes et al., 1998) and the decision in a two-alternative forced choice motion discrimination task (Mazurek et al., 2003; Roitman and Shadlen, 2002; Shadlen and Newsome, 2001). In the pure version of this model, no inhibitory process is necessary. Our demonstration of a robust inhibitory signal that corresponds with the monkey's successful rejection of the stimulus in its receptive field suggests either that the integrator model may not be valid for this particular decision or that inhibitory signals can affect the integration process, which then must be modeled synaptically as well as in a spike-counting manner.

The relationship between prefrontal cortex and working memory has been repeatedly described, especially in relation to the sensory aspects of visual stimuli (Constantinidis et al., 2001; Funahashi et al., 1993; Wilson et al., 1993). Indeed, we found memory neurons that coded spatial location of the sample cue regardless of its behavioral meaning. Working memory is not, however, monolithic. Look and don't look neurons specify how the animal must behave toward the objects whose memory trace they carry, as well as merely describing the spatial location of the object. In contrast, memory neurons code stimulus location independent of its meaning. The parallel representation of look and don't look or, more generally, response and response suppression in these prefrontal neurons must be important for the flexibility of context-dependent behaviors, allowing the brain not only to plan an appropriate movement but also to inhibit an inappropriate movement simultaneously.

Experimental Procedures

Animals

Two adult male rhesus monkeys (*Maccaca mulatta*; weighing 10–12 kg) were prepared, using standard sterile surgical techniques under

isoflurane/ketamine anesthesia, for head restraint, eye position recording with a magnetic search coil, and recording activity of cortical neurons. The National Eye Institute Animal Care and Use Committee approved all animal protocols, which were in compliance with the NIH Guide on the Care and Use of Laboratory Animals.

Tasks

A small red or green square (1° in diameter) served as a fixation spot. Another small white square (1° in diameter) was presented as a sample cue at one of six peripheral locations 7.5°–30° away from the fixation spot (usually 15°). After a delay, the fixation spot disappeared, and two peripheral spots that were identical in size, color, and luminance to the sample appeared as test stimuli, one at the same location as the sample, the other at any of the five remaining locations. In the match task (green fixation spot), the monkey had to move his eyes to the test spot that matched the location of the sample cue. In the nonmatch task (red fixation spot), he had to move his eyes to the nonmatching test spot. Therefore, the two test stimuli had different meanings (saccade target or distractor) depending on a color of the fixation point. We pseudorandomly intermixed all possible conditions (60 = 2 tasks × 6 sample locations × 5 additional locations), using a shuffle algorithm to ensure that there would be an equal number of correct trials for each condition. This ensured that the monkey could not predict, during the delay period, the distractor location in the match task or the target location in the nonmatch task. The monkey was rewarded with a drop of water on correct trials, but there was no punishment for incorrect trials. We used the REX system (Hays et al., 1982) running on a Dell Pentium II computer for behavioral control and eye position monitoring. A second PC, controlled by the REX machine, generated visual stimuli and back-projected them on a tangent screen 57 cm in front of the monkey.

Recording

We recorded the activity of single neurons using standard tungsten microelectrodes (FHC) and a Plexon data acquisition system that enabled us to do online spike discrimination and generate pulses marking the action potentials of up to eight single neurons, which were collected by the REX system. The recording sites were verified by MR imaging with an electrode in place. During the daily recording sessions, we regularly used the regular (delayed spatial match/nonmatch) task with the sample cue 15° away from the fixation spot in order to isolate neurons. In the isolated neurons, 12 trial types (combination of two tasks and six sample cue locations) were tested more than seven times. After this initial recording session, we often used a simple visual saccade task without delay, in which a small white spot (1° in diameter) was presented at 18 locations that were in six directions (60° spacing) at three eccentricities (7.5°, 15°, or 30° away from the fixation point). If we found a better eccentricity that elicited a stronger response than the original one (15°), we also tested the regular match/nonmatch task for that eccentricity and adopted the data for the following analyses. In this report, we concentrated on the neurons located between the caudal end of the principal sulcus and the arcuate sulcus (areas 46 and 8a). The FEF was then identified physiologically by recording from saccade-related neurons and by electrical stimulations that evoked saccades at <50 μA threshold, using 70 ms trains of biphasic pulses, 250 μs per phase, at a frequency of 300 Hz.

Data Analysis

We analyzed data offline using programs written in Matlab. We focused on neuronal activity in four distinct epochs during each trial. The early and late sample periods are 150 ms intervals spanning 50–200 ms or 250–400 ms, respectively, after the sample cue onset. The early and late delay periods are 400 ms intervals spanning 100–500 ms after sample cue offset or 400–0 ms before the onset of the test stimuli, respectively. We used a two-way ANOVA with respect to task and cue location to classify neurons, using responses on single trials for each task at each location. If there was a main effect for cue location and/or interaction between cue location and task, the activity was defined as “directional” (spatially tuned). Directional neurons were further divided into the following three groups. (1) “Memory” neurons (“visual” if during the sample cue period), with main effect only for sample cue location but neither

main effect for task nor interaction. (2) "Look" neurons, with main effects for both location and task or with interaction, in which the maximum average activity was observed at any of the sample locations in match task. (3) "Don't look" neurons, with the same ANOVA criteria as look neurons but with the maximum average activity occurring at any of the sample cue locations in the nonmatch task. For the display purpose, we calculated a spike density function by convolving the neuronal impulse function with a Gaussian kernel (Richmond et al., 1987) with a σ of 10 ms and averaging this function throughout a given epoch. We used the Matlab function regress to perform multiple linear regressions.

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