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Temporal Evolution of a Decision-Making Process in Medial Premotor Cortex

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Summary

The events linking sensory discrimination to motor action remain unclear. It is not known, for example, whether the motor areas of the frontal lobe receive the result of the discrimination process from other areas or whether they actively participate in it. To investigate this, we trained monkeys to discriminate between two mechanical vibrations applied sequentially to the fingertips; here subjects had to recall the first vibration, compare it to the second one, and indicate with a hand/arm movement which of the two vibrations had the higher frequency. We recorded the activity of single neurons in medial premotor cortex (MPC) and found that their responses correlate with the diverse stages of the discrimination process. Thus, activity in MPC reflects the temporal evolution of the decision-making process leading to action selection during this perceptual task.

Introduction

Most perceptual tasks require several sequential steps to be carried out. This must be the case, for example, when subjects discriminate the difference in frequency between two mechanical vibrations applied sequentially to their fingertips (Mountcastle et al., 1990; Hernández et al., 1997). This perceptual task can be understood as a chain of neural operations that include encoding the two consecutive stimulus frequencies, maintaining the first stimulus in working memory, comparing the second stimulus to the memory trace left by the first stimulus, and then communicating the result of the comparison to the motor apparatus. Studying this chain of neural operations in different brain areas may lead to an understanding of how the brain accomplishes such sensory discrimination tasks (Romo and Salinas, 2001).

Recent studies have shown that neurons in the primary somatosensory cortex (S1) generate a neural representation of vibrotactile stimuli that correlates closely with psychophysical performance (Hernández et al., 2000; Salinas et al., 2000). Discrimination based on microstimulation patterns injected into clusters of S1 neurons is indistinguishable from that produced by natural stimuli (Romo et al., 1998, 2000). These findings thus establish a strong link between the neuronal activity of S1 and the sensory component of this task. However, where and in what form this sensory representation is transformed into a motor response that indicates discrimination is still unclear.

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Anatomical studies in monkeys have shown that S1 and the second somatosensory cortex (S2) are serially connected (Pons et al., 1987, 1992; Burton and Fabri, 1995; Burton et al., 1995; Krubitzer et al., 1995) and that one of the major outputs from S2 leads to the motor areas of the frontal lobe (Jones and Powell, 1969; Pandya and Kuypers, 1969; Jones et al., 1978; Jürgens, 1984; Luppino et al., 1993; Cipolloni and Pandya, 1999). Thus, in principle, S2 could process the S1 representation of vibrotactile stimuli and transmit its output to the motor cortices (Luppino et al., 1993). S2 neurons show a transformation of the S1 vibrotactile representation (Salinas et al., 2000) and appear to reflect activity associated with the comparison between the two stimuli (R.R., A.Z., and A.H., unpublished data). The question that arises then is whether there is a truly clear distinction between those areas presumably dedicated to sensory processing and those traditionally viewed as motor. There are two possibilities. First, the motor areas could process a fully formed decision signal in order to generate an appropriate set of motor commands. In this case, information and processes used before reaching a decision should be mostly absent from motor cortical activity. Second, the motor areas could participate more actively in the decision process; in which case, they should reflect details about the sensory inputs regardless of the motor outcome.

We tested these alternatives by recording from single neurons in two motor areas (the presupplementary motor area [pre-SMA] and the supplementary motor area-proper [SMA-proper]) of the medial premotor cortex (MPC) while the monkeys performed the vibrotactile discrimination task. These two subdivisions of the MPC show motor-related responses, but their activity also reflects cognitive components of various tasks (Chen et al., 1995; Thaler et al., 1995; Tanji, 1996; Shen and Alexander, 1997; Shima and Tanji, 1998, 2000). We show here that MPC contains neurons that signal the different components of the discrimination task in a manner that is conjectured to be a chain of neural operations leading to the selection of a motor action. At one extreme, MPC neurons signal the base stimulus frequency, while at the other, they generate a neural signal that correlates with the output of the animal's decision. Remarkably, in the middle of this chain, MPC neurons represent the memorized base stimulus frequency and the result of the comparison process; that is, during the comparison period, MPC neurons indicate the recall of the base stimulus, the current comparison stimulus, and the difference between the two stimuli. We suggest that the neuronal events recorded in MPC are evidence that the motor areas of the frontal lobe combine past and current sensory information for the selection of a voluntary motor action.

Results

Four monkeys (*Macaca mulatta*) were trained to perform the vibrotactile discrimination task up to their psychophysical thresholds (Figures 1A and 1D) (Hernández et

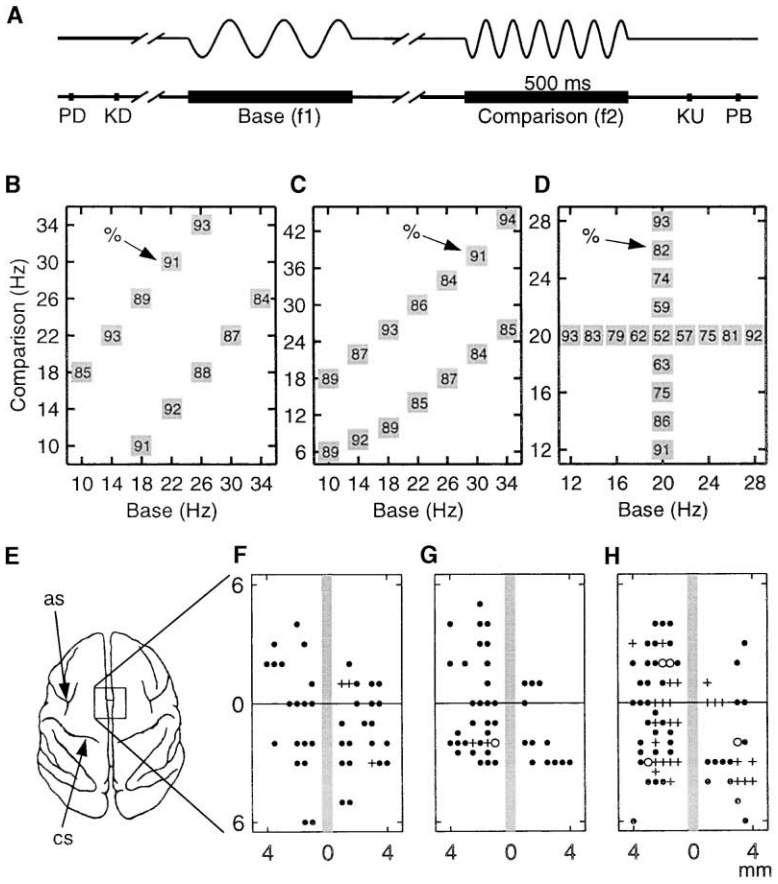

Figure 1. Discrimination Task

(A) Sequence of events during discrimination trials. The mechanical probe is lowered, indenting the glabrous skin of one digit of the restrained hand (PD); the monkey places his free hand on an immovable key (KD); the probe oscillates vertically, at the base stimulus frequency; after a delay, a second mechanical vibration is delivered at the comparison frequency; the monkey releases the key (KU) and presses either a laterally placed or a medially placed push button (PB) to indicate whether the comparison frequency was higher or lower than the base. (B–D) Stimulus sets used during recordings. Each box indicates a base frequency/comparison frequency stimulus pair used; the number inside the box indicates overall percent correct trials for that base/comparison pair. (E) Top view of the medial premotor cortex (MPC). MPC was subdivided by a line passing from the midline to the posterior edge of the arcuate sulcus (AS): rostral to this line is the presupplementary motor area (pre-SMA), and posterior to this line is the SMA-proper. Symbols in the insets indicate microelectrode penetrations for the four animals in which stimulus (F), delay (G), and differential responses (H) were recorded. Closed circles indicate 1–4 neurons recorded in that location; plus signs indicate 5–8 neurons recorded in that location; open circles indicate 9–12 neurons recorded in that location. CS, central sulcus.

al., 1997). To avoid variations in task difficulty, two of the stimulus sets (Figures 1B and 1C) had large differences between base (f1) and comparison (f2), compared with the monkey's psychophysical threshold. After training, neurophysiological recordings were made in MPC, which comprises the pre-SMA and the SMA-proper (Matsuzaka et al., 1992), while the monkeys performed the task. Based on off-line statistical tests, we identified 803 neurons that had task-related responses. Neurons from the pre-SMA and the SMA-proper of the two hemispheres were considered together because of similar activity during the vibrotactile discrimination task (Table 1). The total number of responsive neurons is exceeded because a neuron may participate in more than one period of the task.

Responses to Base Stimuli

During the vibrotactile discrimination task (Figures 1A–1D), monkeys first pay attention to f1. Based on this information, they must then elaborate the subsequent component of the discrimination process. We found 61 MPC neurons (53%, of 115 that responded to f1) that modulated their firing rate as a function of f1; Figure 1F shows their locations. Figure 2A shows an example. This neuron varied its firing rate as a positive monotonic function of f1 (Figure 2B). Forty two neurons (69%) varied their firing rate as a positive monotonic function of the increasing f1, while 19 others (31%) varied their firing rate as a negative monotonic function of the increasing f1 (Figure 2C). The response latency of the neuron shown in Figure 2A after the onset of f1 was 60 ms; for the

Table 1. Database of Medial Premotor Cortex (MPC)

	Responsive	f1	Delay f1-f2	f2	Rt	Mt
R. SMA-proper	237	31 (13%)	77 (32%)	167 (70%)	59 (25%)	51 (21%)
L. SMA-proper	332	37 (11%)	109 (33%)	153 (45%)	115 (34%)	64 (19%)
R. pre-SMA	76	18 (24%)	13 (17%)	36 (47%)	27 (36%)	7 (09%)
L. pre-SMA	158	29 (18%)	26 (16%)	71 (44%)	33 (21%)	16 (10%)
Totals	803	115 (14%)	225 (28%)	427 (53%)	234 (29%)	138 (17%)

f1, first stimulus; delay f1-f2, delay between the stimuli; f2, second stimulus; Rt, reaction time; Mt, movement time; R. SMA-proper, right supplementary motor area proper; L. SMA-proper, left supplementary motor area proper; R. pre-SMA, right presupplementary motor area; L. pre-SMA, left presupplementary motor area.

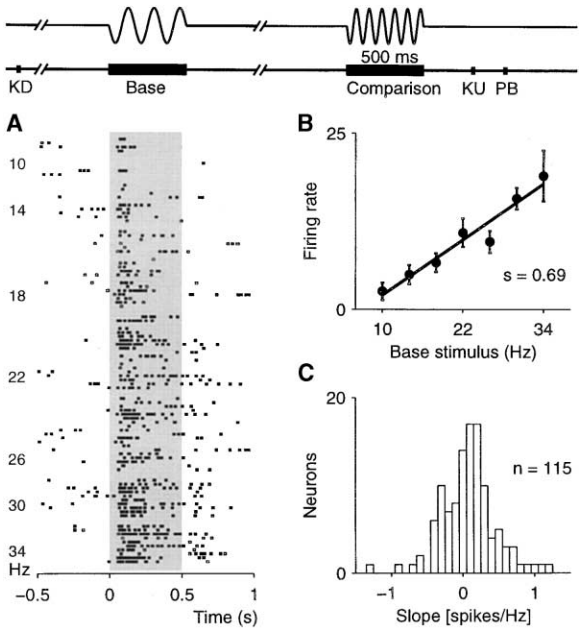

Figure 2. Firing Rate Modulation as a Function of the Base Stimulus Frequency

(A) Raster plots of a MPC neuron during base stimuli. Each row of ticks represents a trial, and each tick represents an action potential. Trials were delivered in random order and displayed as a function of the increasing base stimuli. Gray box indicates the timing of base stimulus, which lasted 500 ms. The vibration frequencies of the base stimuli are indicated by the numeric labels.

(B) Mean firing rate (± SD) as a function of the base stimulus frequency.

(C) Distribution of slopes from linear fits to the rate-versus-frequency curves of all neurons that responded to base stimuli.

population, the latency was 67 ± 13 ms (mean ± SD). Thus, during the vibrotactile discrimination task, f1 is encoded directly in the firing rates of MPC neurons in a smoothly graded fashion.

Representation of the Base Stimulus during the Delay Period

The comparison of f2 is made against the memory trace left by f1. During the vibrotactile discrimination task (Figures 1A and 1C), we recorded 89 MPC neurons (39.5% of 225 that had delay activity) whose discharge rates varied during the delay period between f1 and f2 as a monotonic function of f1; Figure 1G shows their locations. Some of these MPC neurons discharged most weakly after stimulation with the lowest f1 and increased their firing rates steadily for increasing f1 (positive monotonic encoding, n = 57, 64%). Two examples are in Figures 3A and 3B; Figures 3E and 3F show the respective firing rates during the delay period as a function of f1. Others had discharge rates that varied in the opposite direction (negative monotonic encoding, n = 32, 36%). An example is shown in Figure 3C, with the firing rate during the delay period as a function of f1 shown in Figure 3G. Sixty-two percent of the time the firing rates of these MPC neurons were smooth functions (linear or soft sigmoid; see Experimental Procedures) of f1 (Figure 3H). Some of the neurons that displayed monotonic encoding of f1 during the delay period also responded in a similar fashion during the f1 period (n = 16). Thus, f1 is encoded directly in the neurons' firing rate in a smoothly graded fashion during the delay period between f1 and f2.

The monotonic encoding of f1 during the delay period between f1 and f2 was not static. We studied 43 of the 89 neurons that had fixed delays of 3 s, and 46 with fixed delays of 1 s, while the monkeys worked with the stimulus set shown in Figure 1C. In these two fixed interstimulus delay periods, monkeys could anticipate the timing of f2, and the MPC neurons often reflected this fact. For each neuron, we determined the times during the delay period in which their firing rates encoded a significant monotonic signal of f1. Most neurons could be described as falling into three main groups. "Early" neurons carried a signal about f1 during the first third, but not during the last third, of the delay period. "Persistent" neurons (Figure 3A) carried a signal about f1 during the entire delay period. "Late" neurons carried a signal about f1 during the last third, but not during the first third, of the delay period (Figures 3B and 3C). Figure 3D shows that most neurons studied that had fixed delay periods of 3 s manifested monotonic encoding of f1 just at the end of the delay period (31 of 43, 72%), whereas few manifested this property during the early component of the delay period (7 of 43, 16%) or during the entire delay period (5 of 43, 12%). Numbers were similar for the 46 neurons that encoded f1 during the fixed delay period of 1 s: most neurons showed monotonic encoding of f1 just at the end of the delay period (25 of 46, 54%), and few did during the early component (12 of 46, 26%) or during the entire delay period (9 of 46, 20%). Thus, regardless of the length of the delay period between f1 and f2, most MPC neurons manifested information about f1 at the end of the delay period. These results suggest that this anticipatory activity carries information about f1. This activity could also indicate the animal's motor plan, but this is unlikely given the design of the stimulus set used to study these MPC neurons (Figure 1C). This set was such that the correct motor plan could only be implemented after comparison of f2 against f1. The stimulus by itself could not give rise to a probability of correct discrimination higher than chance (50%), whereas the monkey's actual performance was between 84% and 94% correct discriminations.

Responses during the Comparison Period

To solve the vibrotactile discrimination task, the monkey had to compare f2 against the memory trace left by f1, decide whether f2 is higher or lower than f1, and then indicate its decision by pressing one of two push-buttons with its free hand. We recorded neurons in MPC that responded differentially during the comparison f2 period; for some neurons, this activity was prolonged to the reaction and movement time periods. By "differential" we mean that the activity is selective either for the comparison f2 > f1 or for f2 < f1 during correct discriminations. We wondered whether the responses quantified during f2 depended on f1, even though f1 had been applied 3 s earlier, or whether they simply reflected their association with the motor responses.

We examined f1 dependence during f2 as follows. In the stimulus set illustrated in Figure 1B, three f2 compar-

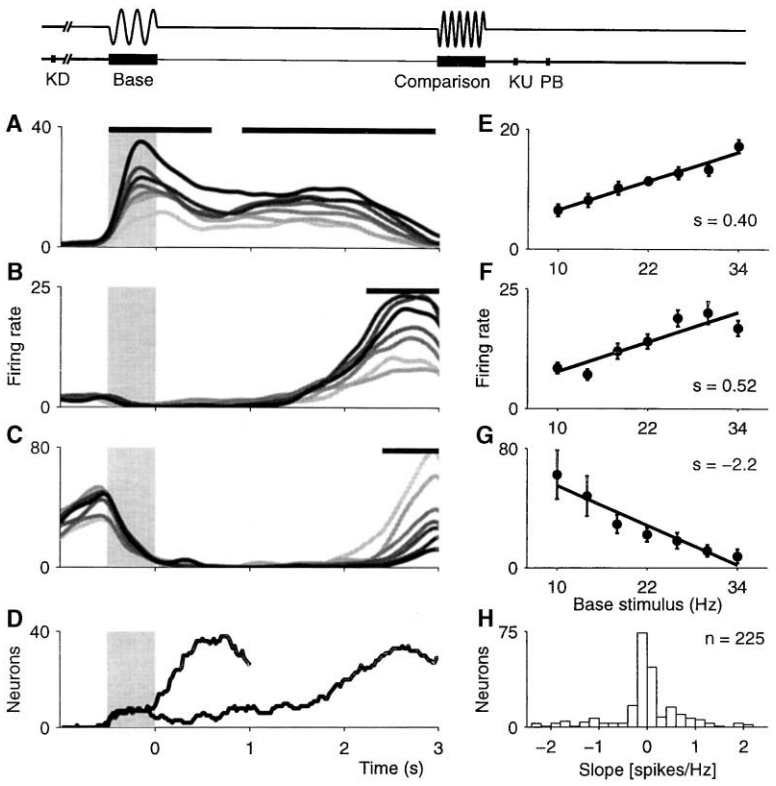

Figure 3. Monotonic Responses during the Delay between Base and Comparison Stimuli

(A–C) Time-dependent spike densities for each base frequency stimulus condition in three MPC neurons. Neurons in (A) and (B) are positive monotonic encoding of the increasing base stimulus. Neuron in (C) is negative monotonic encoding of the increasing base stimulus. Gray boxes in (A–D) indicate the base stimulus periods: the lightest grey line corresponds to 10 Hz, and the darkest line corresponds to 34 Hz. The dark horizontal bars above each plot indicate times during which a neuron's firing rate carried significant monotonic encoding.

(D) Total number of recorded neurons (during fixed 1 or 3 s delay period runs) carrying a significant signal about the base stimulus, as a function of time. Zero indicates to the beginning of the delay period. Individual neurons may participate in more than one bin.

(E–G) Mean firing rates as a function of base stimulus averaged across the entire delay periods, where slopes were significant for neurons in (A–C), respectively. Small vertical bars in (E–G) are ± SEM.

(H) Distribution of the neurons that had delay periods in which the slopes were significant.

ison frequencies (18, 22, and 26 Hz) are preceded by f1 frequencies such that in some trials, f1 is 8 Hz higher, and in some trials, it is 8 Hz lower than f2. For each of these f2 frequencies, we computed the area under the receiver-operating characteristic (ROC) curve (Green and Sweets, 1966), which quantifies how discriminable the distributions of responses to high and low f1 values were. According to their responses during f2, we classified the neurons into two groups: those with higher firing rates for f2 > f1 trials than for f2 < f1 trials, and those with higher rates for f2 < f1 trials than for f2 > f1 trials. We then used ROC analysis to determine how well each neuron could discriminate between these two conditions. A value of 1 indicates, for one of the groups, that all the responses during f2 for f2 > f1 trials had more spikes than any of the responses for f2 < f1 trials. For the other group, it indicates that all the responses during f2 for f2 < f1 trials had more spikes than any of the responses for f2 > f1 trials. A value of 0.5 indicates that the two sets of responses were similar. For each neuron, we took the average of the area under the ROC curve for each of the relevant f2 frequencies and designated this as the neuron's "ROC index" (Britten et al., 1992; Kim and Shadlen, 1999; Dodd et al., 2001). We found 264 MPC neurons (62% of 427 that responded during the comparison period) that had ROC indices significantly different from 0.5, thus indicating significant f1 dependence (permutation test, n = 1000 shuffles for each neuron, $p < 0.01$) (Siegel and Castellan, 1998); Figure 1H shows their locations. To study the temporal dynamics of the 264 neurons, we computed the ROC index in each neuron's response using a sliding window of 100 ms duration in steps of 20 ms increments from a period beginning 1000 ms before and ending 1000 ms after the comparison period. A total of 146 neurons (out of 264, 55%) deviated their ROC indices above 0.5 at some point during the comparison period or during the reaction and movement time periods due to the strongest activity for f2 > f1 correct discriminations (Figure 4A), whereas others (n = 118, 45%) deviated their ROC indices above 0.5 due to the strongest activity for f2 < f1 correct discriminations (Figure 4B).

A crucial question, as indicated above, is whether these differential responses indicate the comparison between f1 and f2, or the differential motor response that is implemented to indicate discrimination. We ruled out the presence of a simple differential motor activity associated with the push-button presses by testing these MPC neurons in a control task where the same vibrotactile stimuli were used (Figure 1A), but animals had to follow a visual cue to produce the motor response. In this condition, all neurons reduced the deviation of their ROC indices from 0.5 (Figure 4C represents the analysis of a subpopulation of neurons from Figure 4A; Figure 4D represents the analysis of a subpopulation of neurons from Figure 4B). Thus, when a comparison between f1 and f2 was not needed in order to determine the appropriate motor response, most of the differential activity disappeared. These results suggest that the differential activity observed during the comparison period depends on the actual computation between f1 and f2 and do not reflect a purely motor response aimed to press one of the two push-buttons.

An important question is whether the MPC neurons reflect the estimation of which of two motor outputs is the more likely on the basis of the sensory inputs re-

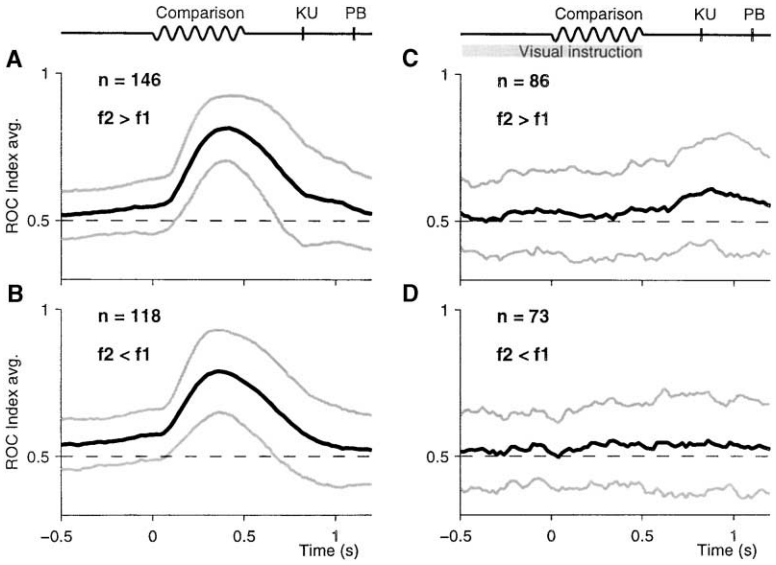

Figure 4. Differential Responses (ROC Indices) of MPC Neurons during the Comparison Process

(A) Population average ROC index for neurons that discharged more strongly during f2 when f2 > f1, and (B) for neurons that discharged more strongly during f2 when f2 < f1. (C and D) Population average ROC index for some of the neurons shown in (A) and (B) but tested during the control task in which identical motor responses were triggered by visual cues. Continuous dark and gray lines are mean ± SD of ROC indices as functions of time.

ceived during the f2 period, and not to the comparison between f1 and f2. If MPC neurons show in their activity a predictive motor signal, neurons that increase their firing rate during the f1 period as a function of the highest f1 would indicate that the monkey knows in advance that f2 will be lower than f1 and, so, the corresponding motor response. If this were the case, the MPC neurons would increase their firing rate during the comparison period when f2 < f1 (selective for lower frequencies). The 61 neurons that had monotonic responses during the f1 period are quite appropriate for determining whether their activities predict the f2 response and the corresponding push-button press. A total of 43 of the 61 neurons responded differentially during the f2 period, but for 28 (65%) neurons, the f2 and motor responses could not be predicted on the basis of f1 responses. For example, the neurons that increased their firing rate during the f1 period as a positive monotonic function of the increasing f1 also increased their firing rate during the f2 period when f2 > f1: in other words, in the opposite direction according to a motor prediction signal. Thus, these neuronal correlates suggest that monkeys do not anticipate their motor reactions based only upon sensory inputs, but rather, need to compare the two stimuli.

Dynamics of the Comparison Process

Assuming that the discharges during the comparison period depend on the information of f1 and f2, then the trace of f1 and the current f2 could be observed during the comparison period before the discharges indicated the motor responses. The neuron shown in Figure 5A illustrates these processes. This neuron discharges more strongly during the comparison period when the monkey judges that f2 > f1, than in trials where f2 < f1 (middle panel of Figure 5B). The responses are a function of the interaction between f1 and f2. For example, when f2 is equal to 18, 22, and 26 Hz it can be judged higher or lower, depending on f1 (middle panel of Figure 5B), and the response reflects this. Notice also that this neuron carries information of f1 during the delay period preceding f2 (Figure 5A and left panel of Figure 5B). Responses as functions of both f1 and f2 disappeared for this neuron during the second half of the comparison period (right panel of Figure 5B). The examples in Figures 6A and 7A indicate that these differential responses can be observed also in the second half of the comparison period (middle panel of Figure 6B) and during the comparison, reaction, and movement time periods (middle and right panels of Figure 7B).

To further quantify the interaction between f1 and f2 during the comparison period and beyond it, we used a multivariate regression analysis (Draper and Smith, 1981). We fit the activity of each differential response over the periods before, during, and after the comparison period as a linear function of both f1 and f2. The responses, which in principle could be an arbitrary function of both f1 and f2, were reasonably well approximated by a general linear fit to both f1 and f2:

$$\text{firing rate} = a1 \times f1 + a2 \times f2 + a3. \qquad (1)$$

In this formulation, the coefficients a1 and a2 serve as direct measurements of firing rate dependence on f1 and a2, respectively. To illustrate this analysis, the resulting coefficients a1 and a2 for the neuron in Figure 5A are plotted in Figure 5C. Three lines are of particular importance in these fits. Points that fall on the a2 = 0 axis represent responses that are a function of f1 (the memory trace of f1; represented by the open circle in panel left of Figure 5C). Points that fall on the a1 = 0 axis represent responses that are a function of f2 (the sensory evidence of f2). And points that fall on the a1 = −a2 line represent responses that are functions of the difference between f1 and f2 (open circle in middle panel of Figure 5C). This last consideration is of particular importance because in this task, correct behavior depends on the sign of the difference between f1 and f2.

Based on this analysis, 139 of the 264 neurons whose strongest responses occurred during the f2 period (Figure 6A) fall always on the diagonal (Figure 6D); 63 neurons had similar responses but showed the highest discharges during the reaction and movement time periods

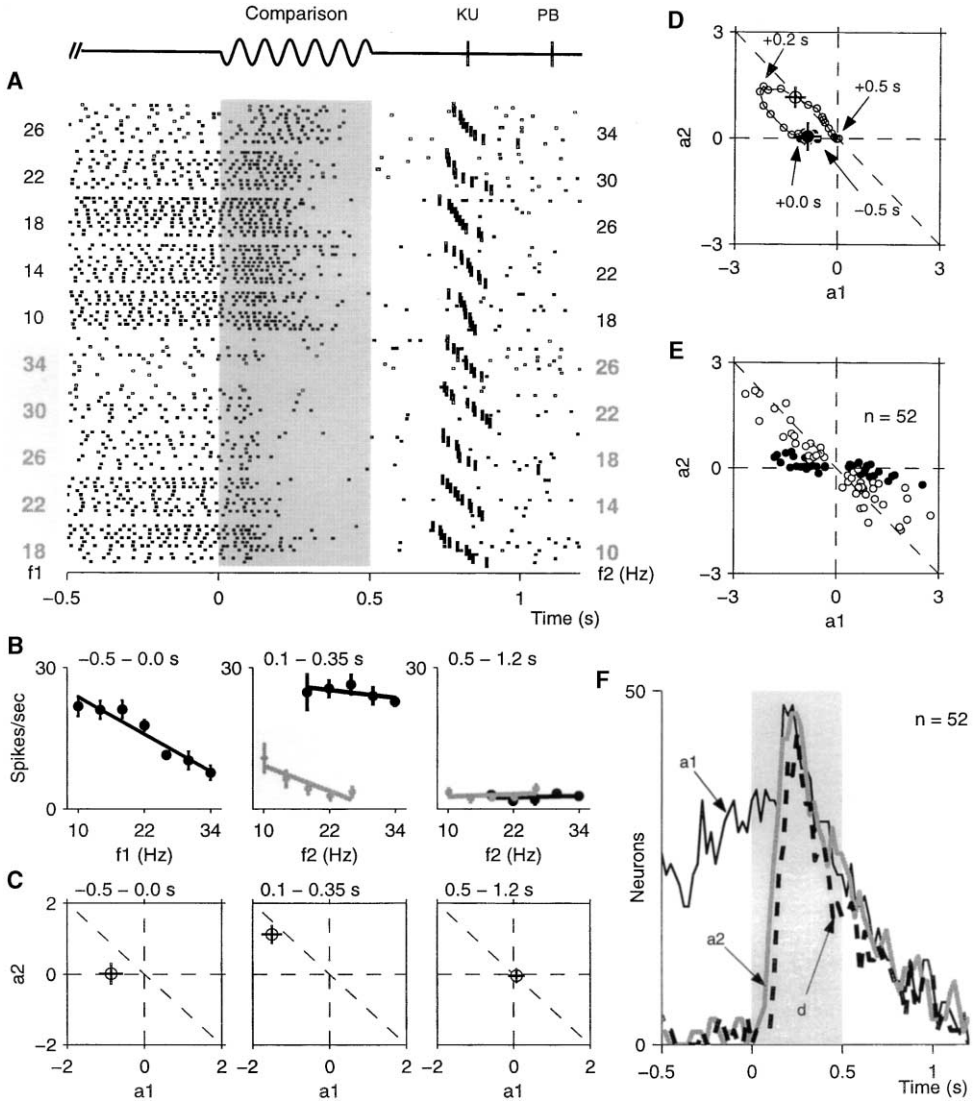

Figure 5. Differential Responses during the Comparison Period Preceded by Delay Activity

For this figure, data from 52 neurons with significant activity and differential responses during the comparison period were used.

(A) Raster plot for a single neuron showing responses around the comparison period. Comparison period lasts 500 ms (gray box). Base (f1) and comparison (f2) frequencies are indicated by the numeric labels at the left and right of each block. Blocks with f2 $>$ f1 are labeled in black, blocks when f2 $<$ f1 are labeled in gray. Data from f1 periods are not shown.

(B) Mean firing rates before (left), during (middle), and after (right) f2 period for the neuron in (A). In the left panel, data were fit separately as a function of f1 during the delay period, while in middle and right panels, they were fit separately as a function of f2 when f2 $>$ f1 (black circles and lines) and f2 $<$ f1 (gray dots and lines).

(C) Coefficients from f1 and f2 responses plotted as a function of f1 and f2 before (left), during (middle), and after (right) the f2 period. In the left panel the open circle falls on the a2 = 0 axis, indicating a response that is a function of f1 only; this corresponds to the memory trace of the base stimulus. In the middle panel, the open circle falls on the a1 = $-$a2, indicating a response that is a function of f1 and f2; coefficients for f1 and f2 contribute equally but with opposite signs, resulting in a differential response that is a function of f2-f1. This signal is lost after the comparison period (panel right of [C]).

(D) Dynamical change in coefficients a1 and a2 for the neuron in (A). The neuron carries information about f1 (closed circles) before and during the beginning of the comparison period, and later becomes differential and falls in the diagonal (a function of f2-f1).

(E) Coefficients a1 and a2 for the 52 neurons with delay activity. Black circles indicate values computed during the delay period; open circles indicate values computed during the comparison period. Each circle corresponds to one single neuron.

(F) Number of neurons with significant coefficients a1 and a2 values as a function of time; "d" indicates cases where coefficients a1 and a2 are of almost similar magnitude, but of opposite signs (falling on the diagonal as shown in [E]).

(Figure 7A) and fall on the diagonal (Figure 7D). However, not all neurons indicated the difference between frequencies equally clearly. During the comparison period, we found 81 neurons whose activities indicated information of f1 and shifted later to the diagonal. This corresponds to a memory recall of the base stimulus during the early part of the comparison. Fifty-two of these neurons carried information of f1 during the delay period (Figure 5E; closed circles represent f1 values, and open circles represent the difference between f1 and f2), and

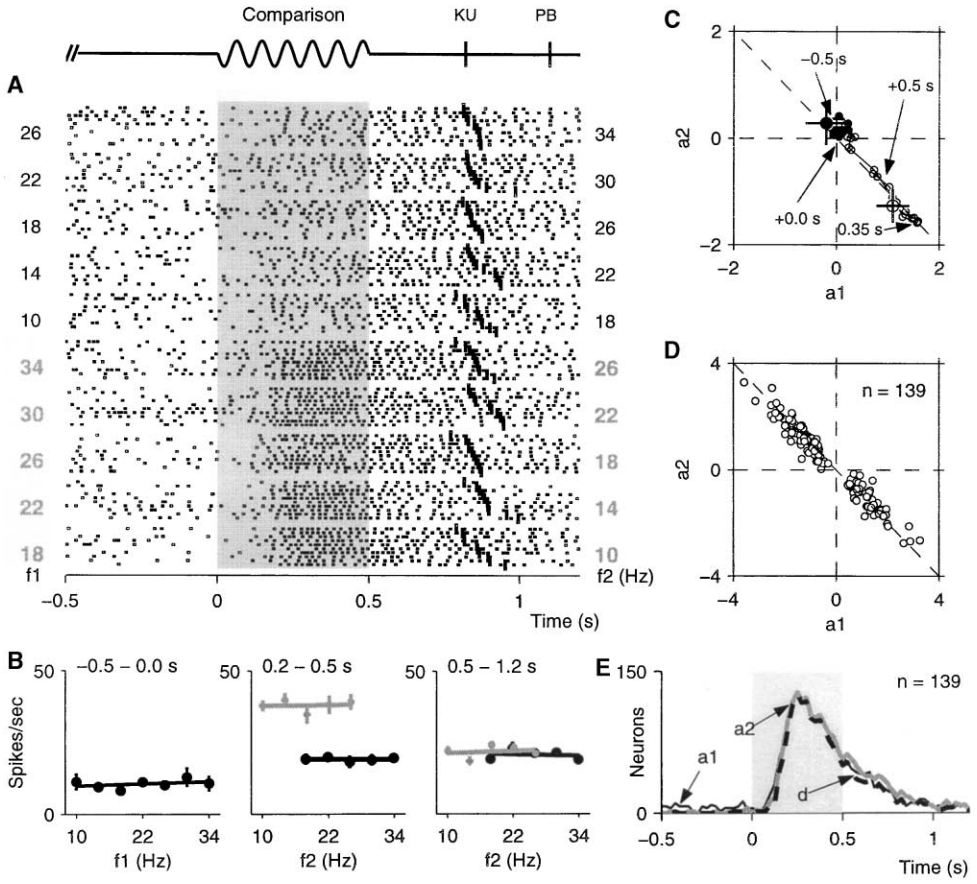

Figure 6. Differential Responses during the Comparison Period

Plots and axes as in Figure 5. For this figure, we used data from 139 neurons without delay activity and with differential responses that were strongest during the comparison period.

(A) Raster plots; (B) mean firing rates; (C) dynamics of the coefficients a1 and a2 associated with f1 and f2; (D) diagonal responses; and (E) number of neurons with coefficients a1 and a2; "d" indicates cases where a1 and a2 are of almost similar magnitude, but of opposite signs.

29 neurons indicated the memory recall during the early component of the comparison period (data not shown). We found only 18 MPC neurons whose responses during the comparison period displayed information of f2 and shifted later to the diagonal (data not shown; coefficients values fall in the vertical axis). Thus, what is typically observed in MPC during the comparison is that initially some neurons encode f1 or f2, and later these and other units encode the differences between f1 and f2.

The comparison between f1 and f2 is not a static operation. We therefore analyzed it as a function of time. We measured the firing rate using a sliding window of 100 ms duration in 25 ms increments and then fit the responses as functions of both f1 and f2 with time-dependent coefficients. Figures 5D, 6C, and 7C show the time-dependent fits to the responses of the neurons shown in Figures 5A, 6A, and 7A, respectively. The neuron shown in Figure 5A carried information of f1 about 750 ms (we show only 500 ms) before the onset of f2 (Figure 5D) and maintained this information during the early component of the comparison period. Then, approximately 200 ms into the comparison period, the neuron's response shifted to the diagonal, to a purely differential response. The population response (Figure 5E) is replotted in a different format in Figure 5F. Here the number of neurons with significant coefficients of both f1 and f2 are plotted as a function of time. Clearly, these neurons carry information about f1 during the delay and comparison periods. The result of the comparison between f1 and f2 is evident only later in the comparison, beginning with a differential population response of 159 $\pm$ 81 ms ($\pm$ SD) after f2 onset.

Neurons that only indicated the difference between f1 and f2 were more abundant in the database ($n = 139$; Figure 6D). These cells had no delay activity and produced their strongest differential responses during the comparison period. Analysis of this population as a function of time shows that the differential signal occurs during the second half of the comparison period, beginning with a differential population response of 201 $\pm$ 66 ms (Figure 6E). The response decreases sharply at the beginning of the reaction time period. The initiation of the differential response was significantly delayed for this population compared with the neurons that carried information of f1 during the delay period (Wilcoxon-Mann-Whitney test, $p < 0.01$) (Siegel and Castellan, 1988).

We also looked at MPC neurons that carried information about the comparison between f1 and f2 during the motor reaction. We found 63 neurons with strongest

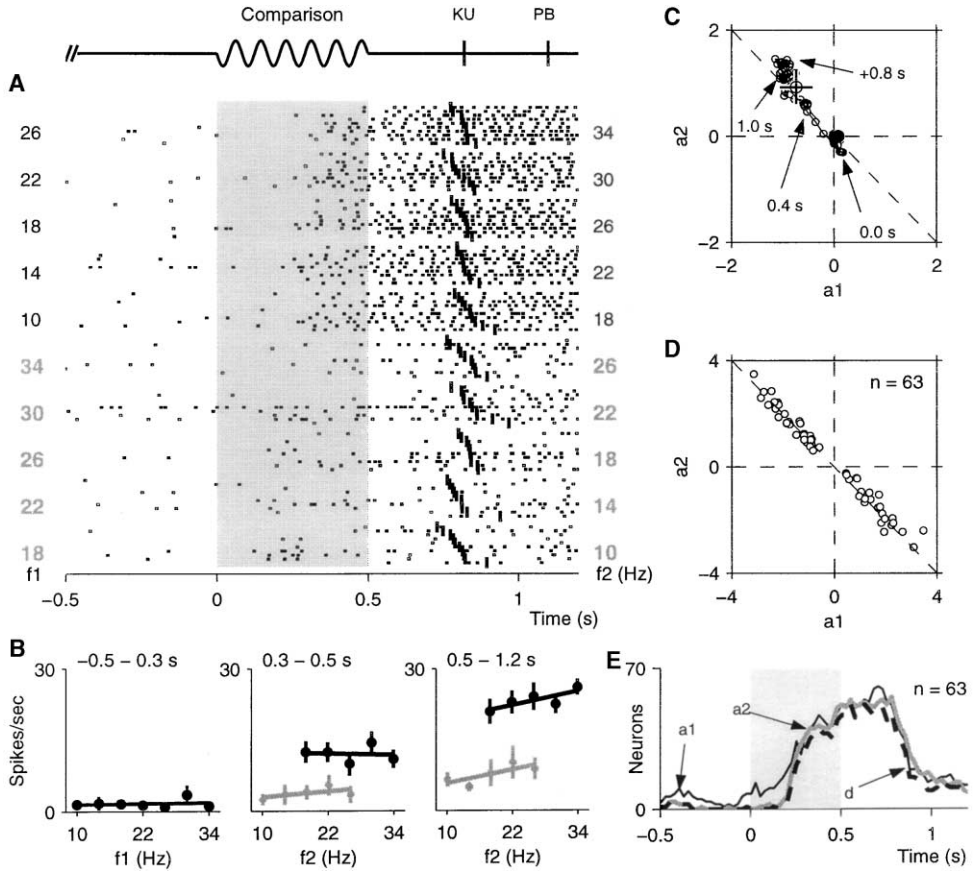

Figure 7. Differential Responses throughout the Reaction and Movement Time Periods

Plots and axes as in Figure 5. For this figure, we used data from 63 neurons that had no delay period and produced the strongest differential response signals during the reaction time period. These neurons initiated the differential response during the second half of the comparison period and extended this activity to the reaction and movement time periods.

(A) Raster plots; (B) mean firing rates; (C) Dynamics of the coefficients a1 and a2 associated with f1 and f2; (D) Diagonal responses; and (E) number of neurons with coefficients a1 and a2; "d" indicates cases where a1 and a2 are of almost similar magnitude, but of opposite signs.

differential activity during the reaction time period (Figures 7A and 7D). The differential response for these cells is typically initiated during the comparison period (364 ±104 ms; Figure 7E). These neurons started firing significantly later than the neurons with the strongest differential activity during the comparison period (Wilcoxon-Mann-Whitney test, $p < 0.01$) (Siegel and Castellan, 1988). Only 23 of these neurons initiated the differential response during the reaction time period, and 14 maintained it through the movement time period. None of the neurons that responded differentially during the reaction and movement times indicated any information of f1 or f2 only. Thus, their activity may be related to the comparison process or to the associated motor commands; in the present task, it is difficult to distinguish between these alternatives after the comparison stimulus.

Dynamics of the Discrimination Process

As mentioned above, the differential response of MPC neurons with significant delay activity developed earlier. We looked at this result more carefully through additional analysis. For this we used a stimulus set in which monkeys performed at psychophysical thresholds (Figure 1D). In half of the trials, f2 was held fixed and f1 varied from trial to trial, and in the other half of the trials, f2 varied and was compared against a fixed f1. The onset of the differential signal (the ROC index) was calculated separately for different combinations of f1 and f2. We studied 26 neurons that carried significant f1 information during the delay when f1 or f2 varied across trials. The results are shown in Figures 8A and 8B. The *y* axes in these plots show the ROC index regardless of whether the neuron fires more strongly when f2 > f1 or f2 < f1. Each curve represents the mean average of the temporal evolution of the ROC indices for differences of 0, 2, 4, and 8 Hz between f1 and f2. These were measured using a sliding window of 100 ms duration in 20 ms increments. Trials of 0 Hz of difference between f1 and f2 were grouped according to the push-button presses. The onset of the comparison signal for these neurons varied as a function of the difference between f1 and f2 (Figures 8A and 8B). For example, for f2 fixed at 20 Hz, when the difference between f1 and f2 was 8 Hz, the latency of the differential signal was 80 ms relative to the start of f2, whereas with 0 Hz difference, the onset of the differential response was 160 ms (Figure 8A). Intermediate response latencies between two values were ob-

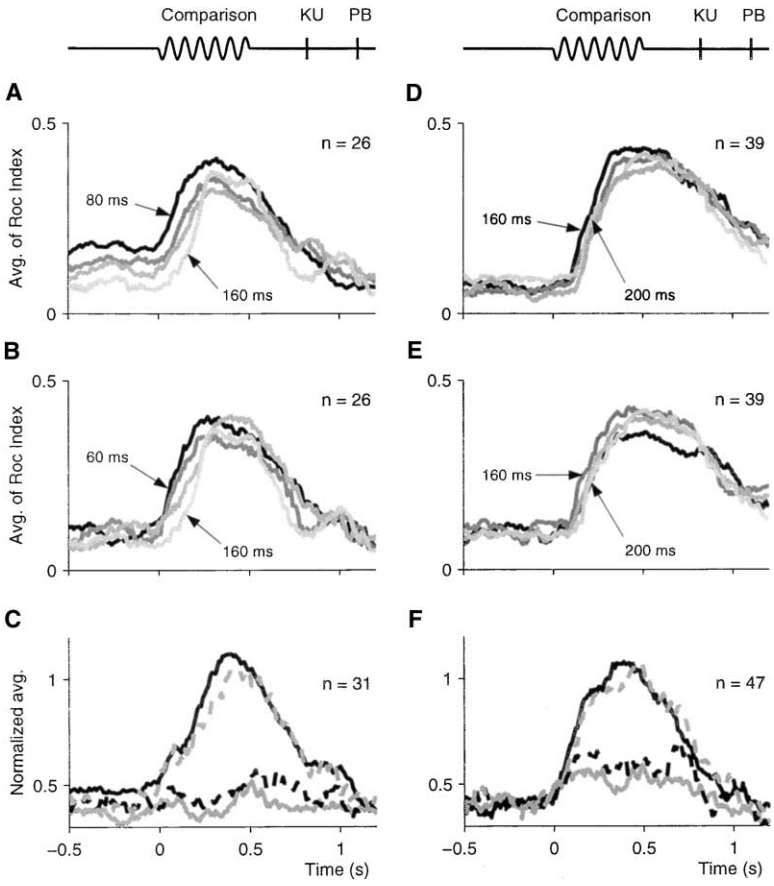

Figure 8. Discrimination Capacities of MPC Neurons

These neurons were tested with the stimulus set illustrated in Figure 1D.

(A and B) The vertical axes show the average across neurons of ROC index, which measures the average strength of the differential response regardless of whether it corresponds to f2 > f1 or f2 < f1. This quantity is shown as a function of time. Differences between base (f1) and comparison (f2) frequencies are indicated by gray level; differences were 0 (lightest), 2, 4, and 8 Hz (darkest). Traces in (A) were computed from trials in which f1 changed from trial to trial and were compared against a fixed f2. Traces in (B) were computed from trials in which f1 stayed fixed and f2 varied from trial to trial. Notice that neurons carrying information about f1 during the delay show stronger ROC indices during the delay. The differential activity increases during the comparison. (D and E) Strength of differential activity for MPC neurons that did not carry information about f1 during the delay. These neurons were tested with the same stimulus set (Figure 1D) as those in (A) and (B). These neurons do not show significant ROC indices during the delay period. Their differential responses during the comparison begin later than in (A) and (B). Arrows and numbers in (A), (B), (D), and (E) are the onsets (in milliseconds) of the discrimination process. These correspond to the initiation of the differential responses. (C and F) Normalized neuronal responses as a function of time for neurons with (C) and without (F) significant delay activity. Separate traces are shown for correct trials in the preferred condition (continuous, black line) and nonpreferred condition (continuous, gray line). Broken lines indicate incorrect trials. The preferred condition is either f2 > f1 or f2 < f1, whichever produces a stronger response for a given neuron. Traces were calculated from trials with differences of 4 Hz between f1 and f2. Activities were normalized with respect to the highest firing rates during correct trials.

tained when the difference between f1 and f2 was 2 (140 ms) and 4 Hz (120 ms), respectively. Similar latencies were obtained when f2 varied from trial to trial and f1 remained fixed at 20 Hz (Figure 8B).

We repeated the analysis using the same stimulus set for 39 differential neurons that had no significant f1 during the delay period. Figures 8D and 8E show that the initiation of the differential population responses were significantly longer than those of the population with delay activity: 160 and 200 ms for 8 and 0 Hz differences between f1 and f2, respectively. Thus, although the response levels of the two neuronal populations were similarly affected by the task difficulty, their latencies were quite different. Neurons that carry information about f1 during the delay period interact earlier with f2.

Correct versus Incorrect Discriminations

An important question is whether the comparison responses are associated with discrimination performance. In general, this is hard to prove; however, a strategy that may be useful is to compare evoked neural responses for correct and incorrect trials (Shadlen and Newsome, 1996; Salinas and Romo, 1998b; Kim and Shadlen, 1999). This was done for the neurons that discharged differentially. Separate analyses were performed for the neurons that carried information about f1 during the delay period (Figure 8C) and for those that did not (Figure 8F). We considered all trials where the difference between f1 and f2 was 4 Hz and sorted the responses into hits and errors according to sign of f2-f1, normalizing the activity against the mean response of the last 300 ms of the comparison period from trials where f2 > f1 or f2 < f1, depending on the preference neuron's response. The dynamics of the neuronal population around the comparison period was determined using a sliding window of 100 ms duration incremented in 20 ms, beginning 1000 ms before and ending 1000 ms after the comparison period.

Figures 8C and 8F show the results. Black and gray lines indicate preferred and nonpreferred responses, respectively (for f2 > f1 or f2 < f1, depending on the preference neuron's response); continuous and broken lines indicate correct and incorrect trials, respectively. When the subject discriminates incorrectly, the preferred and nonpreferred responses shift in opposite directions (black and gray dashed lines). The differences between correct and incorrect responses with opposite preferences were not significantly different (Wilcoxon-Mann-Whitney test, $p = 0.12$). Thus, a movement to the lateral push-button, for instance, on average evoked similar activity whether it corresponded to a correct or incorrect discrimination. The differential activity could

thus be interpreted as encoding the motor response, because the same movements are associated with similar levels of evoked activity. However, as shown in Figures 4C and 4D, the differential discharges were not observed when the motor responses were guided by visual cues (all neurons for the analysis of Figures 8C and 8F lost their differential activity in this condition). Therefore, the differential activity may represent either the final decision for the trial (f2 $>$ f1 or f2 $<$ f1) or the motor plan that results from the comparison process and that is specific to the context of the somatosensory discrimination task.

Discussion

The results indicate that activity in the MPC reflects many aspects of the vibrotactile discrimination task, not just the motor component. Most notably, MPC neurons are activated during the presentation of the first stimulus, during the delay period, and during the period where the comparison between stimuli presumably takes place. Furthermore, in the early stages of a trial, the evoked activity varies systematically as a function of stimulation parameters, as would be expected from sensory responses, and only later during the presentation of the second stimulus does it become consistent with the motor component of the task. It is conjectured that this chain of neuronal operations may represent the links between sensation and motor action.

Sensory Processing

Tanji and colleagues recorded neurons in MPC that responded to auditory, visual, and somatosensory cues that triggered or instructed a voluntary movement (Kurata and Tanji, 1985; Tanji and Kurata, 1985). Though subsequent studies confirmed this finding (Romo and Schultz, 1987, 1992), none of them inquired as to whether these stimulus-related responses carried detailed information about stimulus features. Our vibrotactile discrimination task allows us to make this inquiry. The responses of S1 and S2 neurons are monotonic functions of vibrotactile stimulus frequency (Hernández et al., 2000; Salinas et al., 2000). The responses of many MPC neurons had similar dependencies on stimulus frequency, especially when compared to S2, except that they appeared later (Salinas et al., 2000). Neurons in S1 respond to base stimulus with a latency of 20.2 $\pm$ 4.5 ms, those in S2 respond with a latency of 29.9 $\pm$ 7.4 ms (R.R., A.Z., and A.H., unpublished data), and those in MPC respond with a latency of 67 $\pm$ 13 ms. Thus, information about the base stimulus frequency appears to reach the MPC after S1 and S2. This is consistent with anatomical studies demonstrating that S2 projects to MPC (Luppino et al., 1993; Geyer et al., 2000), but the large difference in latencies between S2 and MPC suggests that other inputs to MPC may be necessary or that MPC activity develops relatively slowly. In fact, S2 neurons project to the posterior part of MPC (SMA-proper) but not to the anterior part of MPC (pre-SMA) (Luppino et al., 1993), although neurons in the two regions of MPC respond to somatosensory stimuli (Matsuzaka et al., 1992) and to the vibrotactile stimuli. Thus, the vibrotactile stimulus used in this task is represented in the firing rate of MPC neurons, an S1 transformation of the vibrotactile stimulus that took place in S1 and S2 (Hernández et al., 2000; Salinas et al., 2000). This representation could be used in the subsequent operations of the vibrotactile discrimination task.

Working Memory Processing

Previous studies have shown delay activity in MPC (Kurata and Tanji, 1985; Tanji and Kurata, 1985; Tanji, 1996; Romo and Schultz, 1987, 1992), and other recent studies have sought evidence of working-memory processing in MPC (Petit et al., 1998; LaBar et al., 1999; Pollmann and von Cramon, 2000). The somatosensory discrimination task offers an unprecedented opportunity to probe whether the activity during the delay between the two stimuli carries information of the parameter of the base stimulus frequency. Our results show that some MPC neurons encode the vibrotactile stimuli in a smoothly graded fashion. Interestingly, this representation is not different from that found in the S2 and in the prefrontal cortex during the vibrotactile discrimination task (Romo et al; 1999; Salinas et al., 2000). The main difference between these structures is that S2 encodes the base stimulus frequency during the early component of the delay period (Salinas et al., 2000); prefrontal cortex neurons show early, persistent, and late encoding (Romo et al., 1999); and MPC neurons show late delay activity, just before the beginning of the second comparison stimulus. Could the memory-related responses in MPC be driven by the prefrontal cortex? Anatomical studies show that the prefrontal cortex is directly connected with the anterior (pre-SMA) but not the posterior part of MPC (SMA-proper) (Luppino et al., 1993). However, similar responses were found in pre-SMA and SMA-proper. One possibility is that this activity is imposed by S2. However, S2 is anatomically connected with the SMA-proper and not with the pre-SMA (Luppino et al., 1993; Geyer et al., 2000). Thus, it is not clear to what extent the delay activity in MPC depends on S2 and prefrontal inputs, or to what extent it is elaborated by the MPC circuits. It could also be argued in this case that the delay activity in MPC shows expectation for the second stimulus, or preparation for the later motor plan to report discrimination rather than memory. However, the same arguments mentioned before apply here: the activity is a monotonic function of the base stimulus frequency, and the stimulus set used hinders the prediction of the second stimulus and the early implementation of the motor plan used to report discrimination. Based on these results, we suggest that MPC forms part of large cortical network (Fuster, 1997) that combines past and current sensory information to generate motor actions.

Comparison Processing

Previous studies have revealed neural correlates of decision processes in sensory, association, and motor areas of the brain (Mountcastle et al., 1992; Romo et al., 1993, 1997; Shadlen and Newsome, 1996; Merchant et al., 1997; Zhang et al., 1997b; Kim and Shadlen, 1999; Horwitz and Newsome, 1999; Dodd et al., 2001). These studies are based on paradigms that require the interpretation of a sensory stimulus, and any such interpretation

must combine current sensory evidence with a sensory referent stored in memory (Johnson, 1980a, 1980b, 2000), whether this referent is stored in long-term memory, as a result of training, or in working-memory, as in the task used here. The responses we recorded from MPC seem to reflect a transformation from a sensory representation to a representation of the animal's decision. During the early part of the comparison period, some MPC neurons responded as if they were recalling the memorized base stimulus, whereas others displayed a signal correlated with the current comparison stimulus. This sensory-like activity lasted roughly 100 ms and was followed by what appeared to be a comparison process. The differential activity that then developed was strong, and it correlated with the animal's motor response. This decision signal indicating one of two alternatives is comparable to that observed in discrimination tasks that used a sensory referent stored in long-term memory (Romo et al., 1993, 1997; Shadlen and Newsome, 1996; Salinas and Romo, 1998a; Kim and Shadlen, 1999; Horwitz and Newsome, 1999; Dodd et al., 2001). Thus, the perceptual act does seem to employ some common mechanisms whether the current sensory evidence is compared against a short- or long-term memory referent. On the other hand, it is not clear whether the development of the final differential activity reflects the comparison process itself or the generation of the motor command used to express the output of the decision-making process. This is a crucial problem. In general, however, decision correlates are neither purely sensory nor purely motor (Shadlen and Newsome, 1996, 2001; Salinas and Romo, 1998a). This is consistent with our data as well. A recent study by Gold and Shadlen (2000) suggests that, in fact, the consolidation of the decision and preparation for movement may be indistinguishable. Our findings support this idea, which should be explored more carefully.

It may be argued that the neuronal responses during the task's periods simply reflect the monkey's moment-to-moment estimation of which of the two motor outputs is the more likely on the basis of the sensory inputs received up to that moment, and not to the evolution of the decision-making process. This would be true if, for example, monkeys predicted their behavioral decisions from the beginning of the task's sequence. The stimulus sets rule out this possibility, and the base stimulus responses—as shown in Results—did not predict the behavioral decision, which required the comparison between base and comparison stimuli. In their activities, some of the neurons reflected the difficulties of the discrimination process—which is determined by the difference between the two stimulus frequencies—and many reflected the temporal evolution of the decision-making process. This may be consistent with the interpretation that MPC forms part of a cortical network that compares past and current sensory information at the service of motor decisions.

Concluding Remarks

The present discrimination task involves perceiving a stimulus, storing it in working-memory, combining the stored trace with current sensory input, and producing a decision, which is communicated to the motor apparatus. All of these processes are important ingredients of a perceptual act (Leon and Shadlen, 1998; Schall, 2001; Shadlen and Newsome, 2001). Our results indicate that the MPC does not simply wait for a signal-encoding decision, but instead, participates in every step of its generation by integrating working-memory and sensory inputs. This neural operation may represent the actual decision-making process leading to the selection of a motor action. Whether this is a unique property of MPC remains to be investigated, in this and similar perceptual tasks.

Experimental Procedures

Discrimination Task

The sensory discrimination task used here has already been described (LaMotte and Mountcastle, 1975; Mountcastle et al., 1990; Hernández et al., 1997). Briefly, stimuli were delivered to the skin of the distal segment of one digit of the left, restrained hand via a computer-controlled stimulator (2 mm round tip, BME Systems, MD). The initial indentation was 500 μm. Vibrotactile stimuli were mechanical sinusoids. Stimulation amplitudes were adjusted to produce equal subjective intensities (LaMotte and Mountcastle, 1975; Mountcastle et al., 1990; Hernández et al., 1997). During trials, two vibrotactile stimuli (f1 and f2) were delivered consecutively to the glabrous (hairless) skin, separated by a fixed interstimulus delay period, often 3 s, and the animal was rewarded for correct discriminations with a drop of liquid. Discrimination was indicated by pressing one of two push-buttons with the right hand. The two push-buttons were located in front of the animal, 25 cm away from the shoulder, and at eye level. The centers of the switches were located 7 and 10 cm to the right of the midsagittal plane; the medial push-button was used to indicate that f2 was lower than f1, while the lateral one was used to indicate that f2 was higher than f1. Performance was measured using psychophysical techniques (Mountcastle et al., 1990; Hernández et al., 1997). Monkeys were handled according to the institutional standards of the National Institutes of Health and Society for Neuroscience.

Visual Instruction Task

A simpler task, in which the same vibrotactile stimuli were delivered to the skin but the hand/arm movements were triggered by visual cues, was used as a control. Trials in this test began exactly as described above and in Figure 1A, with the probe touching the skin and one of the target switches being illuminated; after which the monkey had to hold the immovable key. Then, after a variable delay period during which the light was kept on and the two consecutive stimuli were delivered exactly as in the vibrotactile discrimination task, the light was turned off, and the probe was simultaneously lifted from the skin. The monkey was rewarded for pressing the previously illuminated push-button. Arm movements in this situation were identical to those in the discrimination task but were cued by visual stimuli.

Recordings

Neuronal recordings were obtained with an array of seven independent microelectrodes (2–3 MΩ) inserted into the MPC, contralateral and ipsilateral to the stimulated hand (Mountcastle et al., 1990, 1991; Romo et al., 1998). We used well-established criteria to distinguish between the two subdivisions of the MPC (Matsuzaka et al., 1992). The locations of the penetrations were confirmed through standard histological techniques. Recording sites changed from session to session.

Data Analysis

We considered a neuron with task-related responses if during one of the periods of the task (f1, delay between f1 and f2; f2, reaction [Rt] and movement [Mt] times) its mean firing rate was significantly different from a control period (Wilcoxon test, $p < 0.01$). The control period was the same duration as that of the relevant period, and it was recorded in each trial during the immediate period preceding

the probe tip that indented the skin. The delay period was divided in intervals of 500 ms beginning from the end of f1 to the beginning of f2. By the definition, f2 corresponds to the comparison period. For the Rt, we used that period from the end of f2 to the beginning of the KU (Figure 1A). For the Mt, we used that period from KU to PB (Figure1A).

Responses tuned to f1 were defined as neurons that had a good linear fit (χ^2 goodness-of-fit probability, $Q > 0.05$) (Press et al., 1992) of the mean firing rate values (calculated over the entire f1 period, 500 ms) as a function of the stimulus frequency and had a slope of this linear fit that was significantly different from zero (permutation test, n = 1000 shuffles for each neuron, $p < 0.01$) (Siegel and Castellan, 1988). Response latency to f1 was estimated using a method based on the cumulative sum of the poststimulus histogram (bin width of 10 ms, n = 5) (Falzett et al., 1985).

To compute the delay activity between f1 and f2, a continuous-time data analysis was used. Single-neuron spike trains were convolved with gaussian kernel ($\sigma = 100$ ms) to obtain time-dependent spike density functions for each trial. A time-dependent spike rate mean and time-dependent spike rate standard error of the mean (SEM) were computed from the set of density functions for each f1 condition. At each point in time, we computed the best linear fit as a function of f1; using the standard errors, we computed whether the slope of the linear fit was significantly different from zero (Ross, 1987; Press et al., 1992). We also computed the χ^2 goodness-of-fit probability Q of a linear (2 degrees of freedom) and a sigmoidal (4 degrees of freedom) fit to the data (Press et al., 1992). Response time was calculated using the point in time at which the linear regression slope became "significantly" different from zero ($p < 0.01$), while the linear fit was considered as "significantly monotonic"; this required $Q > 0.05$ (dark horizontal lines in Figures 3A–3C). These times were further marked as "linear" or "sigmoidal" according to which fit had the higher Q. Neurons with significantly monotonic responses during a continuous period of at least 300 ms duration in the delay period were marked as delay period signal-carrying neurons (Figure 3D).

Differential responses during the f2 period were evaluated by ROC analysis. Each point of a ROC curve represents the proportion of trials of the condition f2 > f1, where the response (firing rate) was higher than a criterion value k, against the proportion of trials of the condition f2 < f1 that exceeded the same criterion; the criterion varied from 0 to 200 in increments of 1. This ROC value was estimated using equation:

$$ROCindex = \int_{-\infty}^{\infty} \Pr(r_1 = k)\, \Pr(r_2 < k) dk. \quad (2)$$

In this formulation, r1 and r2 are the response distributions for trials where f2 > f1 and trials where f2 < f1, respectively. Each neuron was tested in this condition where at least three different f2 frequencies (18, 22, and 26 Hz) were preceded by an f1 that was 8 Hz lower or higher than f2. Keeping f2 fixed guarantees that the responses marked as differential during the comparison period are the result of the interaction between f1 and f2 correct discriminations (Kim and Shadlen, 1999). For each neuron, we took the average of the ROC curve area for each of the relevant f2 frequencies and designated as the neuron's ROC index (Britten et al., 1992; Shadlen and Newsome, 1996; Kim and Shadlen, 1999). The permutation test (n = 1000 shuffles for each neuron, $p < 0.01$) (Siegel and Castellan, 1988) was used to identify significant ROC index values that were significantly different from 0.5, the value expected when the two response distributions were similar (Zhang et al., 1997a; Kim and Shadlen, 1999; Hernández et al., 2000; Dodd et al., 2001). To study its dynamics, we computed the ROC indices using a sliding window of 100 ms duration incremented steps of 20 ms, from a period beginning 1000 ms before and ending 1000 ms after the comparison period. In Figures 8A, 8B, 8D, and 8E, each curve represents the mean average of the ROC index for differences between f1 and f2 of 0, 2, 4, and 8 Hz. For example, for a 4 Hz difference, we compared the response distribution for 24 versus 20 Hz against the response distribution for 16 versus 20 Hz. For trials with identical f1 and f2 (0 Hz difference), we grouped trials according to the push-button presses.

The dependences between f2 and f1 were obtained through multivariate regression analysis. Errors in fit coefficients a1 and a2 were derived from the variance in responses to the individual (f1, f2) stimulus pairs (Draper and Smith, 1981; Press et al., 1992) and resulted in the full 2-D covariance matrix of errors (a1, a2). Coefficients were considered significantly different from (0, 0) if they were more than 2 SD away. Neuronal responses were defined unambiguously as dependent of f1, f2 if the coefficients of the planar fit were within 2 SD of one of the two lines a2 = 0 or a1 = 0; responses were considered dependent of the difference between f2 and f1 (labeled as "d" in Figures 5F, 6E, and 7E) if the coefficients were more than 2 SD away from these two lines and within 2 SD of the line a2 = −a1. Responses not satisfying this criterion were classified as "mixed" type responses. The dynamics of these coefficients were analyzed using a sliding window of 100 ms duration incremented in steps of 25 ms, from a period beginning 1000 ms before and ending 1000 ms after the comparison period. The beginning of the differential response (latency) was estimated for each neuron by identifying the first bin (25 ms) of three consecutive bins (75 ms) in this period where the coefficients a1 and a2 were significantly different from 0, and the difference between their magnitudes was not significant (labeled as "d" in Figures 5F, 6E and 7E; these values fall close to the diagonal as shown in Figures 5E, 6D, and 7D).

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