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Neuronal Correlates of a Perceptual Decision in Ventral Premotor Cortex

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Summary

The ventral premotor cortex (VPC) is involved in the transformation of sensory information into action, although the exact neuronal operation is not known. We addressed this problem by recording from single neurons in VPC while trained monkeys report a decision based on the comparison of two mechanical vibrations applied sequentially to the fingertips. Here we report that the activity of VPC neurons reflects current and remembered sensory inputs, their comparison, and motor commands expressing the result; that is, the entire processing cascade linking the evaluation of sensory stimuli with a motor report. These findings provide a fairly complete panorama of the neural dynamics that underlies the transformation of sensory information into an action and emphasize the role of VPC in perceptual decisions.

Introduction

Converging lines of evidence suggest that ventral premotor cortex (VPC) is involved in the processes that link sensory information with an action. First, VPC receives projections from sensory areas of the parietal cortex (Godschalk et al., 1984; Matelli et al., 1986; Luppino et al., 1999) and association areas of the prefrontal cortex (Lu et al., 1994), and it sends projections to motor areas of the frontal lobe (Godschalk et al., 1984; Matelli et al., 1986), subcortical structures (McFarland and Haber, 2000), and spinal cord (Keizer and Kuypers, 1989; Dum and Strick, 1991; He et al., 1993). Second, VPC neurons possess both sensory (Rizzolatti et al., 1988; Graziano et al., 1997, 1999) and motor (Gentilucci et al., 1988) fields and encode complex sensorimotor actions (Gentilucci et al., 1988; Umilta et al., 2001; Kakei et al., 2001; Rizzolatti and Luppino, 2001). Third, inactivation of VPC affects performance of sensorimotor tasks (Fogassi et al., 2001). Thus, VPC seems potentially well suited to evaluate sensory events and convert them into a decision or motor report. But, whether VPC is involved in this cognitive operation is still an open question.

We addressed this question by recording from single neurons in VPC while trained monkeys report a decision based on the comparison of two mechanical vibrations applied sequentially to the fingertips (Figure 1; Mountcastle et al., 1990; Hernández et al., 1997). The task can be conceptualized as a chain of neural operations or cognitive steps: encoding the first stimulus frequency (*f1*), maintaining it in working memory, encoding the second stimulus frequency (*f2*), comparing it to the memory trace left by *f1*, and communicating the result of the comparison to the motor apparatus (Romo and Salinas, 2001). Here we report that the activity of VPC neurons reflect the entire processing path required to solving this perceptual task. Many neurons encoded *f1* during both the stimulus presentation and during the delay period between *f1* and *f2*. The responses during the comparison period were a function of both the remembered (*f1*) and current (*f2*) stimulus and were observed to change, after a few hundred milliseconds, into responses that were correlated with the animal's decision. In addition, we reanalyze and discuss the relative contributions of some other cortical areas responding during the vibrotactile discrimination task (Hernández et al., 2000, 2002; Romo et al., 2002, 2003). The result provides a complete description of the neural dynamics that transforms sensory information into action and emphasizes the role of VPC in perceptual decisions.

Results

Two monkeys (*Macaca mulatta*) were trained in the vibrotactile discrimination task (Figure 1A) until their psychophysical thresholds were stable (Mountcastle et al., 1990; Hernández et al., 1997). After training, we recorded single neurons from VPC (Figure 1E) while monkeys performed the task. We recorded 434 neurons that had task-related responses (see Experimental Procedures). All these neurons were initially recorded using a stimulus set that had large differences between *f1* and *f2* frequencies (Figure 1B). In this set, trials can be divided into two types: those in which $f2 = f1 + 8$ Hz (black in Figure 2) and those in which $f2 = f1 - 8$ Hz (gray in Figure 2). This corresponds to the monkey's two possible choices. Notice also that, in this set, three comparison frequencies (18, 22, and 26 Hz) can be preceded by base frequencies either 8 Hz higher or 8 Hz lower. In other words, each of these three *f2* frequencies can be judged higher or lower, depending on *f1*. Thus, the neuronal responses across trials can be analyzed as functions of *f1*, *f2*, $f2 - f1$, or as functions of the monkey's two possible motor choices.

When the discharges of VPC neurons were analyzed as functions of *f1*, we found 76 neurons (62% of 122 that responded during the *f1* period) that modulated their firing rate as a function of *f1*. Forty-one neurons (54%) varied their firing rate as a positive monotonic function of increasing *f1* (Figures 2A, 2B, 2J, and 2K), while 35 (45%) varied their firing rate as a negative monotonic function of increasing *f1* (Figures 2G and 2H). This type of *f1* encoding was also observed in 59 of 126 neurons (46%) that responded during the delay period between *f1* and *f2*. Of these, 31 (52%) had rates that increased monotonically with increasing *f1* (Figures 2J and 2K), and 28 (47%) had rates that decreased monotonically with increasing *f1* (Figures 2D and 2E). How-

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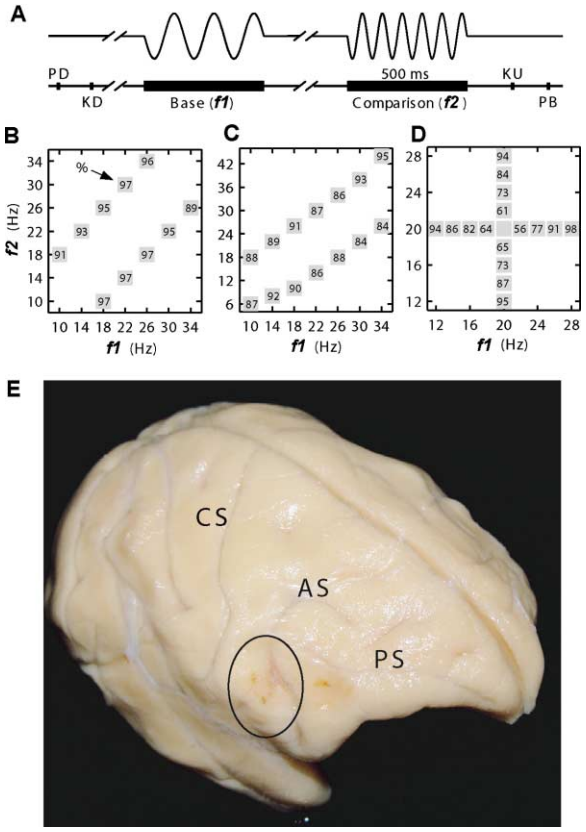

Figure 1. Discrimination Task

(A) Sequence of events during discrimination trials. The mechanical probe is lowered, indenting the glabrous skin of one digit of the hand (PD); the monkey places its 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 lateral or a medial 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/comparison frequency stimulus pair; the number inside the box indicates overall percentage of correct trials for that base/comparison pair.

(E) Picture of brain surface of one of the two monkeys used in the study. Black circle indicates the site of recordings in VPC (area F5). Abbreviations: AS, arcuate sulcus; CS, central sulcus; PS, principal sulcus.

ever, these monotonic responses recorded during the stimulus presentation and during the delay period could be encoding information about *f1* or future actions. To distinguish between these two possibilities, we studied neurons that encoded *f1* during the stimulus presentation (17 of 76) or during the delay period (8 of 59) with a stimulus set in which the *f1* did not carry information about future actions (Figure 1C). The responses of these neurons during the stimulus set were monotonic functions of *f1* in such a way that the slopes were similar with those obtained during the stimulus set illustrated in Figure 1B (permutation test, $p > 0.05$). These results suggest that VPC neurons with positive and negative slopes encoded *f1* through their firing rates both during the base stimulus and working memory periods of the task.

As the task progressed, responses reflected both *f1* and *f2*. We found 129 neurons (57% of 224 that responded during the *f2* period) that modulated their firing rates during the *f2* period, as described below. Twenty-eight neurons (22%) responded selectively to *f2*: 15 (54%) had rates that varied as positive monotonic functions of *f2* (third panel of Figure 2B), while 13 (46%) had rates that varied as negative monotonic functions of *f2*. Only 3 of the 129 neurons (2%) had firing rates that depended exclusively on *f1*. Thus, considerably fewer neurons had purely sensory responses during the *f2* period than during the *f1* period. However, the task requires that the difference $f2 - f1$ be calculated, and the large majority of neurons that responded during the *f2* period reflected this operation. Ninety-eight neurons (76%) discharged differentially during the *f2* period; that is, their responses depended on $f2 - f1$. To characterize this activity, we calculated receiver operating characteristic (ROC) curves (Green and Swets, 1966; Hernández et al., 2002; Romo et al., 2002). This analysis was done for each of the three *f2* comparison frequencies (18, 22, and 26 Hz) that could be preceded by lower or higher base frequencies in different trials. This quantified during correct trials how different the distributions of responses to high and low *f1* values were. According to this analysis, 53 neurons (54%) increased their firing rates selectively for $f2 > f1$ trials (Figures 2G and 2H) and 45 (46%) did so for $f2 < f1$ trials (Figures 2J and 2K). Some of the differential responses invaded the reaction time ([RT] 44%; 43 of 98 neurons) and movement time ([MT] 37%; 36 of 98 neurons) periods, in the latter case continuing until the monkey pressed one of the two push buttons. RTs and MTs were similar for $f2 > f1$ trials ($RT = 392.50 \pm 57.55$ ms; $MT = 301.45 \pm 63.84$ ms) and $f2 < f1$ trials ($RT = 387.0.6 \pm 53.87$ ms; $MT = 309.96 \pm 59.99$ ms). Thus, these discharges depended on both *f1* and *f2*, and we investigated this dependence further.

In principle, the response during *f2* could be an arbitrary linear function of both *f1* and *f2* (Draper and Smith, 1966; Hernández et al., 2002; Romo et al., 2002): $\text{firing rate}(t) = a1(t)\, f1 + a2(t)\, f2 + a3(t)$. In this formulation, t represents time, and the coefficients a1 and a2 serve as direct measurements of firing rate dependence on *f1* and *f2*, respectively. These measures were calculated in sliding windows of 100 ms moving in steps of 20 ms. To illustrate this analysis, the resulting coefficients a1 and a2 for the four neurons of Figure 2 were plotted in panels C, F, I, and L as a function of time. We also plotted the values of a1 and a2 against each other to compare the responses at different points during the task (Figure 3A). Three lines are of particular relevance in these plots: points that fall on the $a2 = 0$ axis represent responses that depend on *f1* only (green dots in Figure 3A); points that fall on the $a1 = 0$ axis represent responses that depend on *f2* only (red dots in Figure 3A); and points that fall near the $a2 = -a1$ line represent responses that depend on the sign of $f2 - f1$ (blue dots in Figure 3A). This last consideration is of particular importance, since the sign of the difference between *f1* and *f2* determines correct task performance. However, the result of the analysis is not only restricted to these three conditions. For example, in those hypothetical cases where the modulation imposed by *f1* and *f2* results

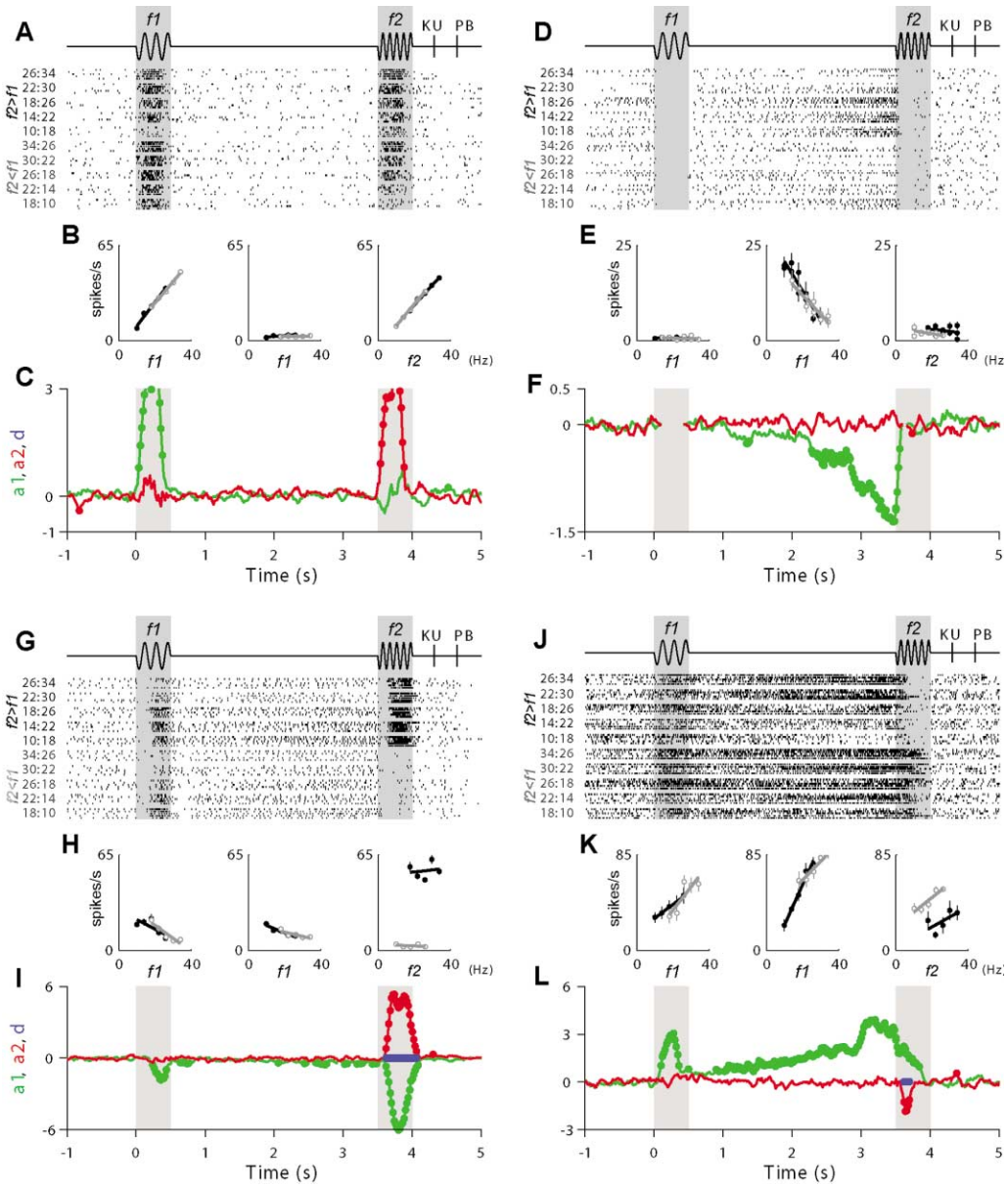

Figure 2. Responses of Four VPC Neurons during the Vibrotactile Discrimination Task

(A) Raster plot of a neuron that responded during *f1* and *f2* stimulation. Each row of ticks is a trial, and each tick is an action potential. Trials were delivered in random order (only 5 trials per stimulus pair are shown; all neurons were tested with 10 trials per stimulus pair). Labels at left indicate *f1, f2* stimulus pairs. The stimulus set illustrated in Figure 1B was used.

(B) Average firing rate as a function of *f1* or *f2*. Black indicates $f2 > f1$ ($f2 = f1 + 8$ Hz for this stimulus set); gray indicates $f2 < f1$ ($f2 = f1 - 8$ Hz). Data for left and middle panels are displayed as a function of *f1*; data for right panel are displayed as a function of *f2*.

(C) Coefficients a1 (green line) and a2 (red line) as functions of time. Filled circles indicate significant values.

(D–F) Same as in (A)–(C), but for a neuron that encoded information about *f1* during the delay period only.

(G–I) This neuron responds to *f1* during stimulation and during the delay period. However, the strongest response is for condition $f2 > f1$ during the *f2* period. Blue circles indicate points at which a1 and a2 were significant and of similar magnitude, but had opposite signs.

(J–L) This neuron shows a strong *f1*-dependent response during stimulation and during the delay periods. During *f2* the response is selective for the condition $f2 < f1$.

in $f1 + f2$, the point would fall close to a1 = a2 line. In this case, the memory of *f1* is added to the *f2* representation, but this result was rarely observed (see Figure 5f of Romo et al., 2002). Remarkably, the larger area of the plane represents those conditions where the strengths of a1 and a2 are significantly different from zero and significantly different in the strengths between them. This last consideration indicates that the effect imposed by the strength of one of the two stimulus frequencies is more important ($|a1| \neq |a2|$; $a1 \neq 0$; $a2 \neq 0$; black dots in the comparison panel of Figure 3A and black traces of Figures 3B, 4, and 6).

Figure 3B shows the numbers of cells with significant a1 or a2 coefficients, as functions of time. The graph

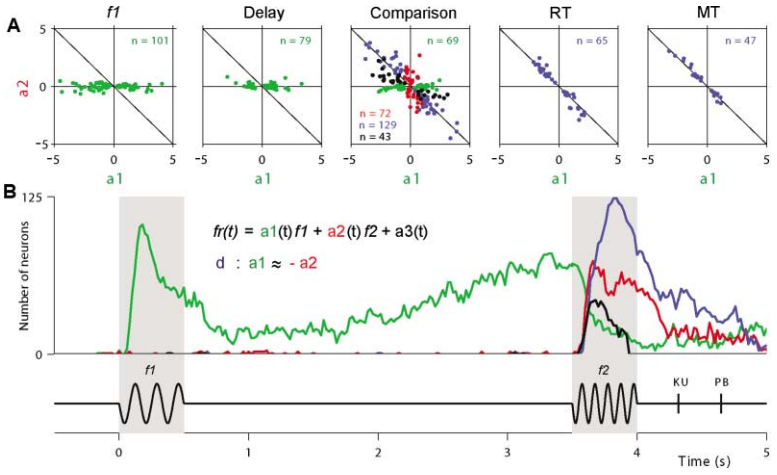

Figure 3. Dynamics of VPC Population Response during the Vibrotactile Discrimination Task

(A) Values of a1 and a2 coefficients for all neurons. For each point, at least one coefficient is significantly different from zero. Different plots are for various times of highest peak activity in (B); n = number of neurons.

(B) Number of neurons with significant coefficients as a function of time. Green and red traces correspond to a1 and a2, respectively. Blue trace indicates number of neurons with coefficients a1 and a2 of opposite sign but similar magnitude; these produce a differential signal. Black trace indicates number of neurons whose coefficient a1 during the comparison period combines with a2, then switch to a differential response. The number of differential responses increases during *f2* and decreases during the actual motor report. RT, reaction time; MT, movement time.

indicates that some VPC neurons encode *f1*, both during the base stimulus period (the beginning of the population response was 61 ± 10 ms [mean ± standard error (S.E.)] after *f1* onset) and during the working memory period between *f1* and *f2* (green trace). Later, during the comparison, some VPC neurons carry information about *f1* (green trace) while others respond as a function of the current stimulus, *f2* (red trace; the beginning of the response was 101 ± 09 ms after *f2* onset). But, in addition, the information about *f1* and *f2* is combined to generate a differential response (blue trace). An interesting finding is the fact that the dynamic of some neurons during the comparison period switched from an *f1* encoding to a combination with *f2* (black trace), then evolved to a differential response (blue trace). The comparison signal of this group (black trace) began 190 ± 16 ms after *f2* onset, whereas for that group of neurons with purely differential responses (blue trace) it began slightly later (238 ± 18 ms; t test, $p < 0.01$).

Although the graph of Figure 3B shows the dynamics of the entire population as function of time, however, it does not tell us the combinatorial responses of VPC neurons. Figure 4 shows the different subgroups of VPC neurons that contributed to the graph of Figure 3B. Figure 4A shows that there is a group of neurons whose responses were confined exclusively to the stimulation periods (see also Figure 2A). These neurons modulated their firing rates as a function of *f1* (green trace), then later as a function of *f2* (red trace). Some VPC neurons encoded *f1* during the delay period only (Figure 4B; see also Figure 2D), then during the comparison period encoded *f2* and the difference of *f2* − *f1*. Figure 4C shows the group of neurons that were modulated as a function of *f1* both during the base stimulation period and during the delay period between *f1* and *f2* (green trace). During the *f2* period, some of the neurons of this group responded as a function of *f2* − *f1* (blue trace). Notice also that during the *f2* period some of the neurons of this group switched from a *f1* encoding to a combination with *f2* (black trace), then evolved to a differential response (blue trace). Figure 4D shows the neurons whose responses during the *f2* period were functions of *f2* − *f1* (blue trace in Figure 4D; see also Figures 2G and 2J). Few of these neurons also coded *f1* both during the stimulus presentation and during the delay period between *f1* and *f2* (green trace). As for the group of Figure 4C, some of these neurons during the comparison period switched from an *f1* encoding to a combination with *f2* (black trace), then evolved to a differential response (blue trace). Figures 4E and 4F show the groups of neurons with similar activity to Figure 4D, but the *f2* − *f1* responses were confined to the RT and MT periods, respectively. Thus, VPC neurons show a rich combinatorial capacity along the temporal evolution of the task. But which neurons predict in their activity the motor choice?

To answer this question, for each neuron we sorted the responses into hits and errors and calculated a choice probability index (Green and Swets, 1966; Britten et al., 1996; Hernández et al., 2002; Romo et al., 2002). This quantified for each (*f1*, *f2*) pair whether responses during error trials were different from responses during correct trials. If the responses were exclusively stimulus dependent, they should show little or no difference between error and correct trials. In contrast, if the responses were linked to the monkey's choice, then the responses should vary according to which button the monkey chose to press. We computed a choice probability index separately for (1) neurons that responded as a function of *f2* only (Figure 5A, red trace); (2) neurons that carried information about *f1* and later depended on *f2* − *f1* (Figure 5A, black trace); and (3) neurons that depended on *f2* − *f1* only (Figure 5A, blue trace). Figure 5A shows that the motor choice was predicted by neurons that had differential responses (groups 2 and 3), but not by those that responded as a function of *f2* only. The result of this analysis shows that there are significant differences between hits and errors during the same stimulus pair of frequencies (*f1, f2*). These differences were mainly confined to the comparison period, in such a way that they predicted the animal's error. These signals were maintained during the execution of the motor act. Notice that the neuronal population that carried *f1* information during the delay period shows large choice probability values (above 0.5), just before the comparison period (Figure 5A, black trace). We suggest that this activity is related to the working memory

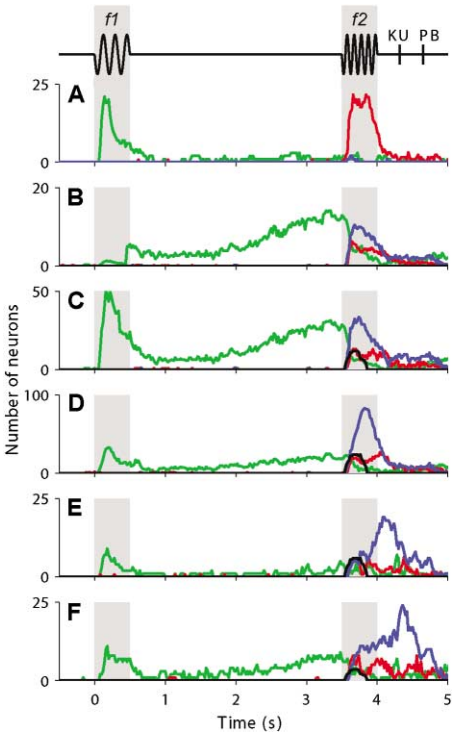

Figure 4. Dynamics of Response Groups of VPC Neurons during the Vibrotactile Discrimination Task

These are groups of neurons of the total number (n = 434) that had task-related responses. The same labels as for Figure 3B.

(A) Number of neurons that had a1 (*f1*; green trace) or a2 (*f2*; red trace) significant coefficients during the stimulus presentation.

(B) Number of neurons that had a1 significant coefficient during the delay period between *f1* and *f2*. During the f2 period, some of these neurons had a1, a2, or a1 = −a2 (*f2* − *f1*, blue trace) significant coefficients.

(C) Number of neurons that had a1 significant coefficients both during the *f1* stimulation period and during the delay period between *f1* and *f2*. As for group (B), this group of neurons also showed during the *f2* period, a1, a2, or a1 = −a2 significant coefficients. Some neurons of this group showed the interaction between the memory trace of *f1* and *f2* ($|a1| \neq |a2|$; $a1 \neq 0$; $a2 \neq 0$; black trace).

(D) Number of neurons that had preferentially $|a1| \approx |-a2|$; $a1 \neq 0$; $a2 \neq 0$ significant coefficients during the *f2* period. Few neurons of this group had a1 significant coefficients both during the *f1* stimulation period and during the delay period between *f1* and *f2*.

(E) and (F) are similar to (D), but the peaks of a1 = −a2 significant coefficients are preferentially during the RT and MT periods, respectively.

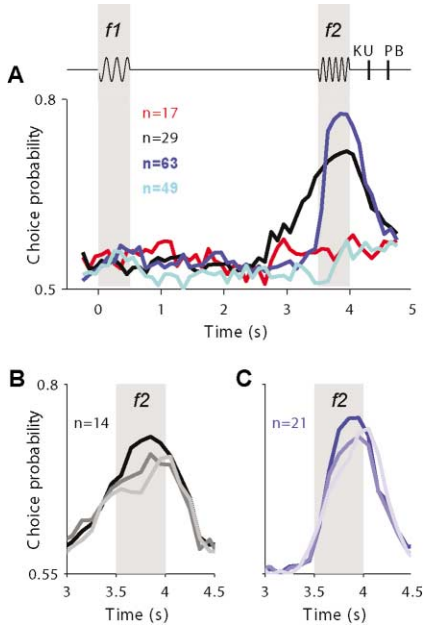

Figure 5. Correlation between Neuronal and Behavioral Responses

(A) Choice probability indices as functions of time for three different groups of neurons. Results are averaged over (*f1*, *f2*) pairs. Red trace, responses that depended only on *f2* during the comparison period. Black trace, neuronal responses that depended on *f1* during the delay period and on *f2* − *f1* during the comparison period. Blue trace, neuronal responses that depended on *f2* − *f1* during the comparison period but were not significant during the delay period between *f1* and *f2*. Cyan trace, neuronal responses that had large choice probability indices (black and blue traces) but tested in a control task in which animals had to follow a visual cue to produce the motor response.

(B and C) Choice probability index calculated separately according to the magnitude of the difference $|f2 - f1|$. Color intensity indicates differences of $|f2 - f1| = 8, 4, 2$ Hz, going from darkest to lightest. Plots are for neurons that responded to *f2* − *f1* during the comparison period and had (B) or did not have (C) *f1*-dependency.

component as opposed to the decision component of the task. If trial-by-trial variations of *f1* encoding during the working memory period correlate with trial-by-trial variations in performance, this will be reflected in the choice probability index values (Brody et al., 2003).

As the monkeys reported their decisions by a motor act, we asked to what extent responses in VPC were reflecting a purely motor signal. In addition to the standard test, some of the neurons of groups 2 and 3 (Figure 5A) were tested in a variant of the task in which the same vibrotactile stimuli were applied and the monkeys made the same push button press motions, but they could choose which push button to press based on visual, not somatosensory, information (see Experimental Procedures). Under this condition, the choice probability indices of VPC neurons dropped to near chance levels (Figure 5A, cyan trace). We also asked whether during the comparison period the activity of these neurons reflected the difference between *f1* and *f2*. When these neurons were tested at psychophysical threshold using the stimulus set illustrated in Figure 1D, they reflected the difference between *f2* and *f1* in a graded fashion (Figures 5B and 5C). These tests show that VPC responses reflect both the active comparisons between *f1* and *f2* and the motor choice that is specific to the context of the vibrotactile discrimination task.

Discussion

The data obtained in this combined neurophysiological/psychophysical experiment indicate that the neural dynamics in VPC reflect the entire sequence of processing steps that link sensation and action during a perceptual discrimination task. During this sequence, past and present sensory information are combined dynamically, such that a comparison of the two evolves into a behavioral decision.

One could argue that the neuronal events recorded during this task reflect other processes, such as preparation for a future action. This seems unlikely, however, because (1) delay responses depended on *f1* regardless of subsequent movements, (2) differential responses developed gradually, often depending exclusively on *f2* or *f1* early in the comparison, (3) choice probability indices depended on $|f2 - f1|$, and (4) when the same movements were guided by visual cues, the differential activity disappeared. Previous observations suggest that VPC neurons transform the perception of complex visual objects or actions into body movements (Rizzolatti and Luppino, 2001). But precisely what components of this cognitive operation are reflected in the activity of VPC neurons? Actions may depend on the interaction between internal and external factors; in particular, in the vibrotactile discrimination task, a voluntary motor response is triggered by the interaction between current and recalled sensory information. All of these variables—memory of a sensory stimulus, value of a current stimulus, and a comparison between the two—are directly correlated with the activity and dynamics of VPC neurons. Furthermore, the VPC units encoded *f1* both during the stimulus presentation and working memory periods of the task. Thus, the key issue is how the physical variables that are encoded in the VPC activity are transformed into an action. A mechanistic explanation is still lacking, but some observations can be made.

Our data are consistent with the finding that sensory, memory, and motor-related areas of the brain are anatomically connected with VPC (Rizzolatti and Luppino, 2001). This further supports the idea that premotor cortex is well situated for linking sensory (Hernández et al., 2002) and memory (Miller and Cohen, 2001; Ohbayashi et al., 2003; Hernández et al., 2002) events with motor actions (Wise et al., 1992; Rizzolatti, and Luppino, 2001; Schall, 2001; Hernández et al., 2002; Romo and Salinas, 2003). One crucial question emerges from these results: is the activity of neuronal populations in VPC sufficient to generate the entire perceptual decision process studied here? Considering the activity observed in other cortical areas during the same task, it would seem that this process involves the conjoined responses of many areas (Romo et al., 1999, 2002; Hernández et al., 2000, 2002; Salinas et al., 2000). Thus, a comparison with other responsive cortical areas is instructive.

We reanalyzed data from other areas recorded during the vibrotactile discrimination task (from Hernández et al., 2000, 2002; Romo et al., 2002, 2003), exactly as we did for VPC (present results). Figure 6 compares their neural dynamics and Table 1 indicates the onset of activity for each of the components of the vibrotactile task. The results suggest that the comparison between stored and ongoing sensory information takes place in a distributed fashion. It also suggests that there is a continuum between sensory- and motor-related activity. For example, *f1* is encoded in multiple cortical areas (green traces of Figure 6). Such encoding seems to proceed in a serial fashion from primary somatosensory cortex (S1) to secondary somatosensory cortex (S2) and VPC, and then to medial premotor cortex (MPC). Although the strength of this signal varies across areas, all them except for S1 store the value of *f1* at different times during the working memory component of the task (green traces of Figure 6). This is consistent with the proposal that there is a large cortical network that dynamically stores sensory information during working memory (Fuster, 1997). During the comparison period, *f2* is processed similarly by the same cortical areas (red traces in Figure 6 and Table 1). The comparison between stored and ongoing sensory information is observed in S2, VPC, and MPC (black traces in Figure 6 and Table 1), again with various strengths across cortical areas (Figure 6 and Table 1). This comparison signal evolves into a signal that is consistent with the motor choice (blue traces in Figure 6); this is again stronger in some areas than in others, but is widespread nonetheless (Figure 6 and

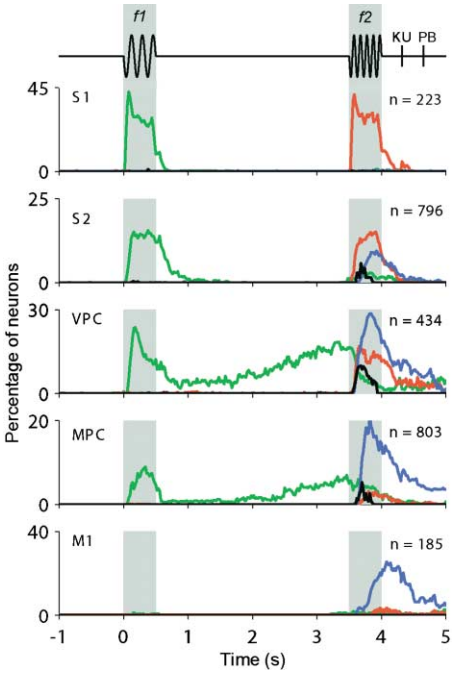

Figure 6. Dynamics of Population Responses of Five Cortical Areas during the Vibrotactile Discrimination Task

Labels as Figure 3B. The responses are expressed as percentage of the total number of neurons (n) that had task-related responses. S1, primary somatosensory cortex; S2, secondary somatosensory cortex; VPC, ventral premotor cortex (present paper); MPC, medial premotor cortex; M1, primary motor cortex. Original data from S1, S2, MPC, and M1 were previously published (Hernández et al., 2000, 2002; Romo et al., 2002) and were analyzed exactly as we did for VPC (present paper).

Table 1. Population Response Latencies

	f1	*f2*	Comparison	Differential
S1	41 ± 08	43 ± 10		
S2	58 ± 06	81 ± 05	181 ± 23	235 ± 17
VPC	61 ± 10	101 ± 09	190 ± 16	238 ± 18
MPC	135 ± 22	141 ± 19	194 ± 27	227 ± 24
M1				302 ± 25

f1, first stimulus; *f2*, second stimulus; Comparison (interaction between the memory of *f1* with the current input, *f2*; Differential (*f2-f1*); S1, primary somatosensory cortex; S2, secondary somatosensory cortex; VPC, ventral premotor cortex; MPC, medial premotor cortex; M1, primary motor cortex. Values expressed as mean ± standard error in ms.

Table 1). The resulting motor signal is also observed in primary motor cortex (M1), but M1 does not seem to participate in the sensory, memory, and comparison components of the task. Also, the signal in M1 is considerably delayed in comparison to S2, VPC, and MPC (Figure 6 and Table 1).

This comparative analysis shows that, in this task, S1 is predominantly sensory and M1 is predominantly motor, but otherwise there is broad overlap in response characteristics across all other cortical areas studied. These similarities probably reflect dynamic cross-talk between areas. The differences between S2, VPC, and MPC might best be characterized as shifts in the distributions of response types. For instance, compare VPC and MPC: their response latencies were significantly different, with the *f1* and *f2* signals beginning slightly earlier in VPC than MPC (Table 1); the percentages of neurons that encoded each component of the discrimination task were also different (Figure 6). These findings suggest that the premotor areas coordinate the sensory, memory, and decision components of the task but that these processes are first coordinated in VPC. This result, however, should be interpreted cautiously, since recordings were made in different animals and the sample population from each cortical area may vary from animal to animal.

To conclude, the dynamics of VPC neurons during the vibrotactile discrimination task reflect processing that links sensory information with action. Given the task, this processing proceeds in a hierarchical or serial fashion: (1) encoding *f1* both during the stimulus presentation and working memory periods, (2) encoding the interaction between the current sensory input (*f2*) and the memory trace of *f1*, and (3) encoding the animal's decision report. We suggest that these steps are not unique to the evaluation of somatosensory information; VPC also processes auditory (Graziano et al., 1999) and visual (Rizzolatti et al., 1988; Graziano et al., 1997) information, so it may participate in transforming sensation into action in these modalities as well. It appears that VPC is only one of several cortical areas engaged in this cognitive operation. Indeed, other premotor areas show neuronal responses quite close to those found in VPC during the task used here (Hernández et al., 2002). Thus, further studies are needed to tease apart the unique contributions of the various elements of the cortical network underlying the transformation from sensation into action. This is fundamental for understanding the cortical network mechanisms that underlie perceptual processes such as the one studied here.

Experimental Procedures

Discrimination Task

Stimuli were delivered to the skin of the distal segment of one digit of the restrained hand, via a computer-controlled stimulator (BME Systems, Inc.; 2 mm round tip). Initial probe indentation was 500 μm. Vibrotactile stimuli were trains of mechanical sinusoids. Stimulus amplitudes were adjusted to equal subjective intensities; for example, 71 μm at 12 Hz and 51 μm at 34 Hz (a decrease of $\sim$1.4% per Hz). In each trial, two vibrotactile stimuli were delivered consecutively, separated by an interstimulus delay of 3 s, and the animal was rewarded for correct discrimination with a drop of liquid. Discrimination results were indicated by pressing with the free hand/arm one of two push buttons (for details, see legend of Figure 1). Performance was quantified through psychometric techniques (Mountcastle et al., 1990; Hernández et al., 1997). Animals were handled according to institutional standards of the NIH and Society for Neuroscience.

Recordings

Neuronal recordings were obtained with an array of seven independent, moveable microelectrodes (Mountcastle et al., 1990) (2–3 MΩ) inserted in VPC (area F5; see Figure 1E) contralateral to the responding hand/arm. Standard histological procedures were used to construct surface maps of all penetrations.

Data Analysis

We considered a neuron's response as task-related if during any of the relevant periods (*f1*, delay between *f1* and *f2*, *f2*, reaction time [RT], or movement time [MT]) its mean firing rate was significantly different from a control period preceding the initial probe indentation at the beginning of each trial (Wilcoxon test, $p < 0.01$) (Siegel and Castellan, 1988). By definition, *f1* and *f2* correspond to the base and comparison periods, respectively. The delay was divided in intervals of 500 ms beginning at the end of *f1* up to the beginning of *f2*. For the RT, we used that period from the end of *f2* to the beginning of the key up (KU) (Figure 1A). For the MT, we used that period from the end of KU to the beginning of the push button press (PB) (Figure 1A).

The *f1*-dependent responses during the stimulus period (500 ms) and during the delay between *f1* and *f2* (at least 500 of the 3000 ms) were defined as those that had an acceptable linear fit (χ^2 goodness-of-fit probability, $Q > 0.05$) (Press et al., 1992) for the mean firing rate as a function of stimulus frequency, where the slope was significantly different from zero (permutation test, $n = 1000$, $p < 0.01$) (Siegel and Castellan, 1988).

The dependence on *f1* and *f2* was obtained through multivariate regression analysis (Draper and Smith, 1966; Hernández et al., 2002; Romo et al., 2002). Errors in fit coefficients a1 and a2 were derived from the variance in responses to the individual (*f1*, *f2*) stimulus pairs and resulted in a full 2D covariance matrix of errors. Coefficients were considered significantly different from (0, 0) if they were more than 2 standard deviations away. Neuronal responses were defined unambiguously as dependent on either *f1* or *f2* if the coefficients of the planar fit were within 2 standard deviations away of one of the two $a2 = 0$ or $a1 = 0$ lines; responses were considered dependent on *f2* − *f1* (Figures 2–4 and 6) if the coefficients were more than 2 standard deviations away from these two lines and within 2 standard deviations of the $a2 = -a1$ line. Responses not satisfying this criterion were classified as "mixed." The dynamics of these coefficients were analyzed using a sliding window of 100 ms duration moving in steps of 20 ms.

The beginning of the *f1* tuned response (latency) was estimated for each neuron by identifying the first of three consecutive 20 ms bins after *f1* onset, in which a1 was significantly different from zero and a2 was not significantly different from zero (Table 1). The beginning of the *f2* tuned response was similarly estimated for each neuron as for the *f1* response, but a2 was significantly different from zero and a1 was not significantly different from zero (Table 1). The beginning of the comparison response was estimated for each neuron by identifying the first of three consecutive 20 ms bins after *f2* onset, in which a1 and a2 were significantly different from zero. We also required that a1 or a2 was two standard deviations away from $a2 = -a1$ line; that the signs of a1 and a2 were opposite and that only a1 was significantly different from zero between 500 ms before and 100 ms after *f2* onset; and that the response became differential (*f2* − *f1*) during the last 300 ms of *f2* (these responses fall between the $a2 = 0$ and $a1 = -a2$ lines in Figure 3A; see Table 1 for the values). The beginning of the differential response was estimated for each neuron by identifying the first of three consecutive 20 ms bins, in which the coefficients a1 and a2 were significantly different from zero and both coefficients were within two standard deviations of the $a2 = -a1$ line (these values fall close to the diagonal as shown in Figure 3A).

The choice probability index was calculated using methods from signal detection theory (Green and Swets, 1966; Hernández et al., 2002; Romo et al., 2002; Britten et al., 1996). This quantity measures the overlap between two response distributions, in this case be-

tween hits and errors for each (*f1*, *f2*) pair. We restricted the analysis for each (*f1, f2*) pair, where animals had a minimum of 30% up to a maximum of 70% errors. Notice that a value of 0.5 indicates full overlap and 1 indicates completely separate distributions. Thus, the choice probability index quantifies selectivity for one or the other outcome of the discrimination process. To compute it at different times, we used a sliding window of 500 ms duration moving in 100 ms steps, beginning 1000 ms before *f1* and ending 1000 ms after the *f2* comparison period. To establish when the choice probability index value significantly deviates from 0.5, the responses of each neuron from a control period (500 ms) immediately before *f1* were shuffled 1000 times. We then calculated the choice probability index value from two response distributions in each of the 1000 repetitions (permutation test). The values calculated in each repetition served to calculate a mean average choice probability index for each neuron and in the neuronal population. The resulting average was of 0.55 $\pm$ 0.05 (mean $\pm$ standard deviation [SD]).

Trials in the control task proceeded exactly as described in Figure 1A, but at the probe down (PD) the correct target push button was illuminated. Vibrotactile stimuli were delivered while the light was kept on and, at the end of *f2*, the probe was lifted from the skin and the light was turned off; the monkey was rewarded for pressing the previously illuminated push button. Hand/arm movements in this situation were identical to those in the somatosensory discrimination task but were cued by visual stimuli. Under this condition, the choice probability indices were calculated by comparing the response distributions for lateral versus medial push button presses (Figure 5A).

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