

Exploring the cortical evidence of a sensory-discrimination process

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Humans and monkeys have similar abilities to discriminate the difference in frequency between two consecutive mechanical vibrations applied to their fingertips. This task can be conceived as a chain of neural operations: encoding the two consecutive stimuli, maintaining the first stimulus in working memory, comparing the second stimulus with the memory trace left by the first stimulus and communicating the result of the comparison to the motor apparatus. We studied this chain of neural operations by recording and manipulating neurons from different areas of the cerebral cortex while monkeys performed the task. The results indicate that neurons of the primary somatosensory cortex (S1) generate a neural representation of vibrotactile stimuli which correlates closely with psychophysical performance. Discrimination based on microstimulation patterns injected into clusters of S1 neurons is indistinguishable from that produced by natural stimuli. Neurons from the secondary somatosensory cortex (S2), prefrontal cortex and medial premotor cortex (MPC) display at different times the trace of the first stimulus during the working-memory component of the task. Neurons from S2 and MPC appear to show the comparison between the two stimuli and correlate with the behavioural decisions. These neural operations may contribute to the sensory-discrimination process studied here.

Keywords: behaving monkeys; sensory discrimination; cerebral cortex

1. INTRODUCTION

An important problem in brain physiology is the isolation of the sensory representations that guide behavioural decisions. This problem has been investigated in behavioural tasks where the sensory stimuli are under precise quantitative control and the subject's psychophysical performances are quantitatively measured (Talbot *et al.* 1968; Newsome *et al.* 1989; Mountcastle *et al.* 1990). This strategy has allowed the investigation of which attributes of the neural responses elicited by a sensory stimulus are sensorily meaningful (Romo & Salinas 1999, 2001). Indeed, it has been shown that the sensory areas of the cerebral cortex generate representations of the sensory stimuli that correlate closely with psychophysical performances (Newsome *et al.* 1989; Vogels & Orban 1990; Hernández *et al.* 2000). Alternatively, behavioural decisions are reported through motor actions, but it is not clear where and how a sensory representation is converted into a motor output. To answer this question, neurophysiologists have studied the neuronal responses of motor areas during perceptual tasks, and have found that a fraction of the neurons show a link between the sensory inputs and the behavioural decisions (Romo *et al.* 1997, 1993; Merchant *et al.* 1997; Salinas & Romo 1998; Horwitz & Newsome 1999). However, decision making is more than a simple

input–output operation (Shadlen & Newsome 2001). For example, regardless of the perceptual task, subjects reach a behavioural decision after the comparison of the current sensory input against a sensory referent, which can be stored in working memory or in long-term memory. Therefore, to understand how the brain carries a perceptual process, we need to isolate where and in what form the current sensory input interacts with a sensory referent that is stored in the memory (Hernández *et al.* 2002). This neural operation, we believe, is the key to understanding how the neuronal circuits elaborate a perceptual process.

We have addressed some of the issues mentioned here in a behavioural task where monkeys discriminate the difference in frequency between two consecutive mechanical vibrations delivered to their fingertips (figure 1; for details see Hernández *et al.* (1997) and Mountcastle *et al.* (1990)). In this task the stimulus can be finely controlled; the same primary afferents are activated by the two stimuli; there is sensory and motor lateralization; it involves a working-memory mechanism; and decision making is based on the comparison between the current sensory input and the memory trace left by the first stimulus. Thus, the task can be viewed as a chain of neuronal operations. In this paper, we review recent results obtained in this sensory-discrimination task. § 2 contains a brief description of the general organization of the somatosensory system and the experiments that paved the way to studying the neuronal processes involved. § 3 then describes the neuronal correlates that seem to be associated with the different components of the vibrotactile discrimination.

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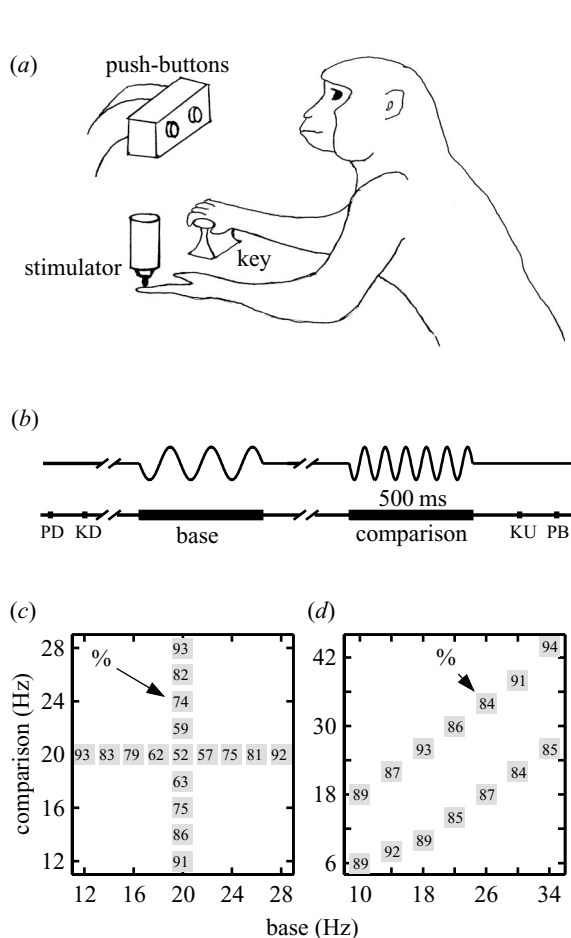


Figure 1. The discrimination task. (a) Drawing of a monkey working in the discrimination task. (b) The sequence of events during the discrimination trials. The mechanical probe is lowered, indenting the glabrous skin of one digit of the hand (PD); the monkey places his free hand on an immovable key (KD); 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 medially placed push-button (PB) to indicate whether the comparison frequency was higher or lower than the base. (c,d) Stimulus sets used during recordings. Each box indicates a base–comparison frequency stimulus pair used; the numbers inside the box indicate the overall percentage of correct trials for the base–comparison pair. The stimulus set illustrated in (c) is used to determine the discrimination thresholds; the stimulus set illustrated in (d) is used to explore the working-memory component of the task. The combinations of both sets are often used during the recording sessions.

2. THE SOMATOSENSORY SYSTEM

The somatic and visual systems are useful models for investigating stimulus information processing, and some general principles behind the functional organization of the brain. There are some elements of the organization of the somatosensory system that are relevant in investigating neural coding of sensory stimuli both at the periphery and in the brain. For the sake of simplicity, we restrict this review to the cutaneous information-processing channel.

(a) *Cutaneous primary afferents*

The human hand contains four types of cutaneous afferent fibres that transmit information of the mechanical stimulus features to the central nervous system (Talbot *et al.* 1968; Darian-Smith 1984; Vallbo & Johansson 1984; Vallbo 1995). Two of these afferent fibres are rapidly adapting: one is anatomically linked to QA and the other to PC. The other two afferent fibres are slowly adapting and are linked to SA-I and SA-II, respectively. The monkey hand possesses these afferent fibres, except SA-II. Although all these afferent fibres respond to a cutaneous stimulus, they become specialized to encoding spatiotemporal features of the stimuli (Talbot *et al.* 1968; Phillips and Johnson 1981). This has been demonstrated in well-designed experiments aimed at exploring their capacities. The degree of sensitivity of these afferent fibres is evidenced by the fact that a psychophysical observer can detect even a single spike evoked in one single primary afferent (Vallbo & Johansson 1984; Vallbo 1995).

(b) *Neocortical somatosensory areas*

After a relay in the dorsal column nuclei and in the basal complex nuclei of the thalamus, somatosensory information reaches S1. Primate S1 is subdivided into four areas (area 3a, 3b, 1 and 2), each containing a somatotopic representation of the body (Kaas *et al.* 1979; Nelson *et al.* 1980). Tactile information is processed mainly by areas 3b, 1 and 2, which are interconnected (Shanks *et al.* 1985). To a certain extent, neurons in S1 replicate the functional properties of QA, SA-I and PC afferent fibres (Powell & Mountcastle 1959; Mountcastle *et al.* 1969; Sur *et al.* 1984) and are referred to as QA, SA and PC neurons. These subtypes are clustered in columns (Mountcastle 1957; Powell & Mountcastle 1959; Sur *et al.* 1984).

Information flows from S1 to the posterior parietal cortex and to the lateral somatosensory areas. As for the visual system, it appears that there is also a dorsal stream and a ventral stream in the cortical organization of the somatosensory system (Mishkin 1979; Murray & Mishkin 1984). According to this organization, the dorsal stream flows through areas 5 and 7b (Pearson & Powell 1985; Shanks *et al.* 1985; Cavada & Goldman-Rakic 1989), and the ventral stream flows through the lateral somatosensory areas (Pons *et al.* 1987, 1992; Burton *et al.* 1995; Krubitzer *et al.* 1995). The dorsal stream is more likely to be associated with processing the somatosensory information that reaches the PM cortex (Godshalk *et al.* 1984; Cavada & Goldman-Rakic 1989; Leichnetz 1989; Tokuno & Tanji 1993). The operations through this dorsal stream could be important for self-initiated or stimulus-triggered voluntary movements involving sensory processing. The ventral stream is more likely to be associated with fine discrimination and the recognition of stimulus patterns. This processing reaches also the PM cortex (Godshalk *et al.* 1984; Cavada & Goldman-Rakic 1989; Leichnetz 1989) and the PFC (Preuss & Goldman-Rakic 1989; Carmichael & Price 1995), and might be associated with the fine discrimination of stimulus objects. Interestingly, both streams reach M1 (Leichnetz 1989; Tokuno & Tanji 1993), and both should drive the motor representations during sensory tasks that require an indication of decision making. The functional meaning of these

streams, however, needs to be investigated further, especially with regard to what aspects of somatosensory perception they contribute to.

3. FORMING A SENSATION VIA A NEURAL CODE

Talbot *et al.* (1968) and Werner & Mountcastle (1965) pioneered this enterprise almost four decades ago. The key conceptual advance was to combine psychophysics and neurophysiology, two experimental disciplines that had previously been divorced in sensory research. Talbot *et al.* (1968) and Werner (1980) used mechanical stimuli, applied to the fingertips of humans, that changed in one dimension; they measured the subjective estimates quantitatively. Then they recorded in anaesthetized monkeys the responses of cutaneous afferent fibres using the same stimuli in the psychophysical experiments (Werner & Mountcastle 1965; Talbot *et al.* 1968). Their goal was to determine the relationship between the subjective sensation and the evoked peripheral activity produced by the stimuli. Indeed, they found a close relationship between the psychophysical performance and the neural activity evoked by the stimuli (Werner & Mountcastle 1965; Talbot *et al.* 1968). These pioneering experiments have been adapted since then as a tool for exploring the neural codes that underlie a sensation in the different sensory modalities.

(a) *Peripheral coding of vibrotactile stimuli*

A sensory neural code is activity produced by a natural stimulus, which correlates with the psychophysical performance. Defining the peripheral coding of a somatosensory stimulus implies that this approach might facilitate exploring the central neural mechanisms of somatosensory perception. Talbot *et al.* (1968) pioneered this research area using the sensory modality of the sense of flutter vibration. They showed that, depending on the range of frequency of the mechanical vibrations applied to the skin on the hand, two sensations can be elicited: the sensation of flutter at low frequencies (range of 5–50 Hz) and the sensation of vibration at high frequency (range of 60–300 Hz). Talbot *et al.* (1968) first quantified amplitude detection thresholds in humans, and then showed that the sensitivities of QA and PC afferents account for performance in the low- and high-frequency regimes, respectively. This correspondence between perceptual and anatomical submodalities was later confirmed and extended by recording and microstimulating afferent fibres in human subjects (Ochoa & Torebjörk 1983; Macefield *et al.* 1990; Vallbo & Johansson 1984; Vallbo 1995).

There were two major observations about the nature of the peripheral neural code underlying flutter–vibration perception (Talbot *et al.* 1968). First, the QA and PC afferents respond periodically to the periodic structure of the stimulus frequency. Second, the QA afferents hardly change in firing rate over a frequency range of 10–50 Hz, while the PC afferents increase their firing rate as a function of increasing stimulus frequency (60–250 Hz). It was thus concluded that high frequencies could be encoded by the total number of PC spikes produced—a rate code (Shadlen & Newsome 1994; Singer & Gray 1995)—but low frequencies could not, because the number of QA spikes seemed to be constant in the flutter range; they had

to be encoded in the regular, periodic spikes produced by the flutter stimuli in the QA afferents—a temporal code. However, direct microstimulation of QA afferents produced flutter sensations of frequencies that were perceived to increase with the evoked firing rate (Ochoa & Torebjörk 1983). If the frequency of the microstimulation current increases in the range of 5–100 Hz—presumably producing a proportional increase in QA firing rate—human subjects report gradual increases in the perceived flutter frequency at a constant intensity (Ochoa & Torebjörk 1983).

The experiments established the roles that the different cutaneous afferents play in coding temporal stimuli. Clearly, the QA and PC systems encode the temporal features of the stimuli. Interestingly, it has been shown that the SA-I afferent system transmits information regarding the spatial properties of the stimulus features (Johnson & Hsiao 1992). The neural coding of the physical properties of the stimuli seems to define and limit the capacity of the psychophysical observer to detect, recognize and discriminate the stimuli. These important observations paved the way for further investigation of the cortical processing of somatosensory inputs during perceptual tasks.

4. CORTICAL CODING OF VIBROTACTILE STIMULI AND THE LINK TO PERCEPTION

Compared with our knowledge of tactile coding in afferent fibres, the central mechanisms are less understood. This has been due in part to the difficulties in adapting somatosensory tasks in behaving monkeys. Tracing a neural code from the periphery to the cerebral cortex has remained the leading idea in understanding somatosensation. The key here is the use of well-designed psychophysical tasks in behaving monkeys. In §4 we review developments in this research area.

(a) *Psychophysics*

Mountcastle *et al.* (1972) adapted the vibrotactile task used initially in human subjects to behaving monkeys. They trained monkeys to detect amplitudes and discriminate stimuli frequencies in the flutter range (Mountcastle *et al.* 1972; LaMotte & Mountcastle 1975). With intense training, monkeys developed stimulus-frequency amplitude-detection thresholds that were almost indistinguishable from those quantified in human subjects in identical conditions (Mountcastle *et al.* 1972). In addition, the discrimination of two consecutive stimulus frequencies delivered to the hands (figure 1) was similar to those measured in humans in identical conditions (LaMotte & Mountcastle 1975; Mountcastle *et al.* 1990). These results indicate that monkeys could be an appropriate model for exploring the central neural mechanisms associated with the flutter task. The discrimination flutter task is particularly rich in that comparison of f_2 is made against the memory trace left by f_1 . To solve this task the psychophysical observer requires a number of cognitive processes such as detection, working memory, comparison and decision making (Mountcastle *et al.* 1990; Hernández *et al.* 1997; Romo *et al.* 1998). Some other tasks require that monkeys categorize moving tactile stimuli (Romo *et al.* 1993, 1996), detect roughness in surfaces (Sinclair & Burton 1993; Jiang *et al.* 1997) or discriminate tactual

stimulus orientation and form (Hsiao *et al.* 1993; Burton *et al.* 1997). All these tasks require attention to be focused on the stimulus with indication of performance given through voluntary movements; that is, from sensation to action. Investigators using these somatosensory tasks want to unravel the central mechanisms associated with the different components of these psychophysical tasks.

(b) *Coding of vibrotactile stimuli in S1*

If QA afferents reliably encode the periodic structure of the flutter stimulus frequency, the question then is whether QA neurons of S1 do this in a similar fashion, or whether there is another way of encoding the stimuli. Shortly after their work on cutaneous afferent fibres, Mountcastle *et al.* (1969) studied the responses of S1 neurons. Two decades later, S1 neurons were re-recorded, this time in behaving monkeys trained to detect and discriminate flutter-stimuli frequencies (Mountcastle *et al.* 1990). The results support the previous findings. First, it was found that QA neurons of S1, like their afferent fibres, fire periodically in phase with mechanical oscillations. Second, their firing rates seem to change little in the flutter range (this conclusion was based, however, on data from 17 neurons). Third, the psychophysical performance matched the inferred performance based on the discriminability of the periodic inter-spike intervals (Mountcastle *et al.* 1990). It followed that, as proposed before, the stimulus frequency could not be encoded by S1 firing rates; the stimulus frequency had to be encoded temporally, in the serial order of evoked spikes (Talbot *et al.* 1968; Mountcastle *et al.* 1969, 1990).

In support of this proposal, using flutter stimuli, Recanzone *et al.* (1992) compared psychophysical data from monkeys to S1 recordings in separate experiments from the same animals. The comparison was consistent with a temporal coding mechanism, and firing rates were not seen to vary with the stimulus frequency (however, the range of frequencies tested was quite narrow and the animals were anaesthetized). Recanzone *et al.* (1992) made another important observation: that spike timing associated with the sine wave was much more precise in trained animals compared with untrained monkeys. Thus, on the basis of these results, a psychophysical observer should exploit the periodic spike timing evoked in the QA neurons of S1 for sensory discrimination.

Arguments in favour of this proposal could be strengthened if a large number of neurons were studied, and if neurons were studied in awake animals during the flutter-discrimination task (figure 1). Hernández *et al.* (2000) and Salinas *et al.* (2000) trained monkeys to discriminate between flutter stimulus frequencies and recorded many neurons with QA properties in areas 3b and 1 of S1. Each recorded neuron with QA properties was studied during the discrimination task. There were three major results. First, the majority of neurons from S1 were phase-locked to the input stimulus frequency; however, almost one-third of the QA neurons modulated their firing rates as a function of the stimulus frequency (Salinas *et al.* 2000). The second important finding was that QA neurons that modulate their firing rates were affected by the task condition; that is, they increased their transmitted information about the stimulus frequency during task performance (Salinas *et al.* 2000). Third, only those neu-

rons that varied their firing rates as a function of the stimulus frequency were affected in the error trials (Salinas *et al.* 2000).

These findings question the unique role of periodic spike timing in discrimination of flutter stimuli, and indicate that a firing rate code cannot be discarded (Salinas *et al.* 2000). But, apart from this, what do these findings indicate? They indicate the presence of two subpopulations of QA neurons in S1 that behave differently in response to a periodic mechanical stimulus (Hernández *et al.* 2000; Salinas *et al.* 2000). These two subpopulations might be arranged in an hierarchical fashion: QA neurons that respond periodically might be closer to the input stimulus, and those that modulate their firing might integrate the responses of the periodic neurons and transform them into a rate code (Hernández *et al.* 2000). Such last-order neurons of the QA circuit could distribute the neural representation to those structures anatomically linked to S1, in order to solve the sensory-discrimination task. However, further studies are needed to see whether this is so.

(c) *Neuronal correlates of vibrotactile discrimination in S1*

A more direct test of the role of periodicity in flutter discrimination is measuring the discrimination capabilities of these subtypes of QA neurons associated with psychophysical performance (figure 1). Another test is to prove whether the evoked neural activity during discrimination in S1 is sufficient for sensory performance. Finally, it is necessary to test whether the temporal order of the spikes is important for sensory discrimination. These are incisive tests to validate the meaning of the neural encoding of the flutter stimuli in S1. We now review recent findings on these points.

The vibrotactile-discrimination task requires the comparison of f_2 against f_1 (Hernández *et al.* 1997). As indicated in § 4c Hernández *et al.* (2000) and Salinas *et al.* (2000) found two types of responses in QA neurons of S1: one that is periodically entrained by the stimulus frequency, and another that, although not periodically entrained, has average firing rates during the stimulus period that are modulated as a function of the stimulus frequency. To investigate which one of these two representations is associated with psychophysical performance, Hernández *et al.* (2000) determined the probability that an observer (a cortical region central to S1) could distinguish the difference between the two stimuli. This could be based on a comparison of the neuronal response distributions of f_2 made against the neuronal response distributions of f_1 . According to this, the observer could use a simple rule: if the number of spikes during the second stimulus is higher than during the first stimulus, then f_2 is higher than f_1 . The same rule can be used when considering the periodicity values: if the periodicity (estimated as the frequency with greatest power in a Fourier transform of the spiking responses) during the second stimulus period (f_2) is higher than during the first stimulus (f_1), then f_2 is higher than f_1 . The effect of this type of rule is equivalent to determining the area under the curve ROC (Green & Swets 1966) generated by the neuronal response distributions for each pair of stimulus frequencies, using both periodicity and firing rate values (Hernández *et al.*

2000). The area under each of these two ROC curves is an estimate of the proportion of correct trials that an optimal observer would obtain by comparing the numbers of spikes or periodicity. In pairs of stimulus frequencies where the neuronal response distributions of f_2 are much higher than the neuronal distributions of f_1 , the ROC values are close to 1; if the neuronal response distributions of f_2 are much lower than the neuronal response distributions of f_1 , then the ROC values are close to zero; and for overlapping distributions, intermediate ROC values are found. The ROC values were then used to compute the neurometric functions. Psychophysical and neuronal discrimination thresholds are calculated as half the difference between the stimulus frequency identified as higher than the standard in 75% of trials and that frequency identified as higher in 25% of the trials. These are read directly from the logistic functions expressed in hertz. Using this analysis, we are now in the position to address the question of which of the two representations is meaningful for frequency discrimination.

Neurometric functions based on the periodicity or firing rate of single S1 neurons were directly compared with the psychometric thresholds (Hernández *et al.* 2000). The results of this analysis show that neurometric threshold values based on periodicity are far lower than the psychometric thresholds (figure 2*a,b*). This is not the case when neurometric thresholds based on the firing rate are compared with the psychometric thresholds (figure 2*c,d*). They are very close to the psychometric thresholds. The goal of computing neurometric functions was not only to reveal the relationship between the neuronal responses of S1 to the mechanical stimulus, but also to discern whether these neural signals account for the psychometric behaviour. However, this leads to the question: what is the functional meaning of the periodic neural signal in S1? One possible role is that they simply represent the temporal structure of the stimulus and that monkeys do not use this exquisite representation for frequency discrimination. This would be the case if, for example, discrimination was based on the mean number of spikes (or bursts) fired by the population of QA neurons as a function of the stimulus frequency. Consistent with this idea, Hernández *et al.* (2000) found QA neurons in S1 whose firing rates are modulated by the stimulus frequencies, and their neurometric thresholds based on firing rates are similar to the monkey's psychophysical thresholds (figure 2*c,d*). However, these measurements do not prove they are sufficient for discrimination (Romo *et al.* 1998, 2000).

One experiment that could give an insight about the functional meaning of the periodic spike structure of the evoked activity in S1 would be to test whether monkeys could discriminate between the two stimuli when the periodicity is broken. If monkeys failed to discern the difference in the mean frequency between the two stimuli, this would support the proposal that the flutter-stimuli discrimination depends on the periodic structure of the spike trains evoked in S1. However, Romo *et al.* (1998) noted that monkeys were able to extract the mean frequency from the non-periodic signals and that the psychophysical measures were almost identical with the periodic stimuli.

Hernández *et al.* (2000) then studied QA neurons in one of two conditions: as monkeys discriminated periodic

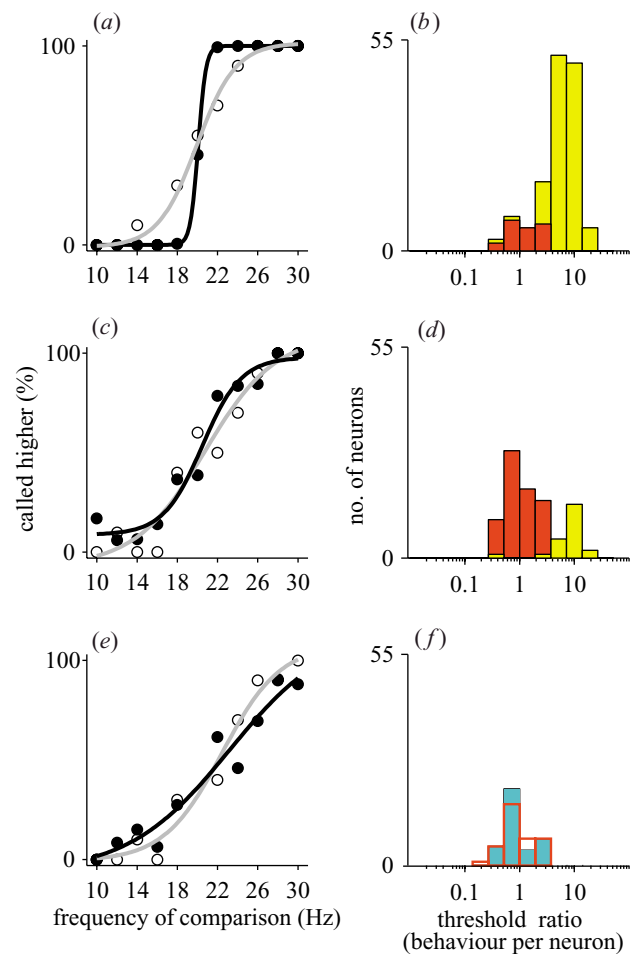


Figure 2. Comparison between S1 neurons and the psychophysical responses during vibrotactile discrimination (illustrated in figure 1*c*). (*a,c,e*) Percentage of trials in which the comparison was higher or lower than the base. The solid lines are sigmoidal fits to the data; for each curve, the threshold is proportional to its maximum steepness. White circles and grey lines indicate the monkey's performance during one discrimination run. The black circles and black curves indicate the performance of an ideal observer that based his decision on the periodicity (*a*) or mean firing rate (*c*) of evoked spike trains of single neurons recorded while the monkey discriminated. (*b*) Numbers of S1 neurons with the indicated threshold ratios. The yellow bars correspond to neurometric thresholds based on the periodicity of evoked spike trains; the red bars correspond to neurometric thresholds based on the evoked firing rate. The data are from all neurons with significant periodic spike entrainment. (*d*) As in (*b*), but data are from all neurons with significant rate modulation. (*e*) As in (*a*) but aperiodic stimuli were applied. (*f*) Threshold ratios from all neurons tested with both periodic and aperiodic stimuli. Neurometric thresholds were computed from firing rates in periodic (red thick lines) and aperiodic (cyan bars) conditions. (Modified from Hernández *et al.* 2000.)

stimuli; and as monkeys discriminated aperiodic stimuli. Due to the aperiodic stimulus design, even highly stimulus-entrained neurons do not carry information about stimulus frequency in their periodicity. Clearly, neurometric thresholds based on the firing rate were again closely associated with the psychometric thresholds (figure 2*e,f*). As in the periodic condition, a psychophysical observer could exploit the firing rate for the frequency

discrimination of aperiodic stimuli. These results indicate that an observer could solve this task with a precision similar to that of a monkey, based only on the firing rate produced during the stimulus periods.

(d) *Probing the flutter coding by microstimulation of S1*

Unequivocal proof that the activity of a localized cortical neuronal population provides sufficient basis for a specific cognitive function has not been obtained. Neurophysiological studies often reveal close associations between neuronal activity and sensory events, but then does such activity have an impact on perception and subsequent behaviour? We typically assume this to be so, but this is hard to verify. Intracortical microstimulation has provided the most compelling evidence to date of a causal link between the activity of localized populations of neurons and specific cognitive functions (Britten & Wezel 1998; Salzman *et al.* 1990; Romo *et al.* 1998, 2000). Electrical microstimulation directly activates small cluster of neurons, and has been shown to bias a monkey's choice during the decision stage of an ongoing perceptual task (Seidemann *et al.* 1998; Gold & Shadlen 2000). A convenient model that can be used to answer this question is the flutter sensation, for which humans and monkeys have similar discrimination thresholds (Hernández *et al.* 1997; Mountcastle *et al.* 1990). During the vibrotactile-discrimination task, subjects pay attention to the frequency of the first (base) stimulus, store a trace of it during the delay period between the two stimuli and compare the stored trace with the frequency of the second (comparison) stimulus. This task, therefore, contains a number of cognitive processes, such as stimulus detection, working memory, discrimination between the two stimuli and decision making. These cognitive processes should be initiated by the evoked neuronal activity in S1 (Romo & Salinas 1999, 2001). As reviewed in § 2b, the QA circuit of S1 distributes the representation of the flutter stimuli to more central structures anatomically linked to it to solve this task. Romo *et al.* (1998) used intracortical microstimulation in S1 to manipulate the neural code for flutter discrimination.

An initial approach was to manipulate the comparison stimulus frequency during the discrimination task (Romo *et al.* 1998). In each trial of the task, the monkeys discriminated between the frequency of two successively presented sinusoidal vibrations, termed the base stimulus and the comparison stimulus, that were delivered to the fingertips. After the animals mastered the discrimination of the mechanical stimuli, microstimulation of S1 was substituted for the comparison stimulus in half of the trials (figure 3a). The artificial stimuli consisted of periodic current bursts delivered at the same comparison frequencies as the mechanical comparison stimulus. The microstimulation sites in S1 were selected to have QA neurons with receptive fields on the fingertips at the location of the mechanical stimulating probe. Remarkably, the monkeys could discriminate between the mechanical (base) and electrical (comparison) signals with performance profiles indistinguishable from those obtained with natural stimuli only (figure 3a). The artificially induced sensation probably closely resembled natural flutter (Romo *et al.* 1998).

To investigate the role of spike periodicity in flutter dis-

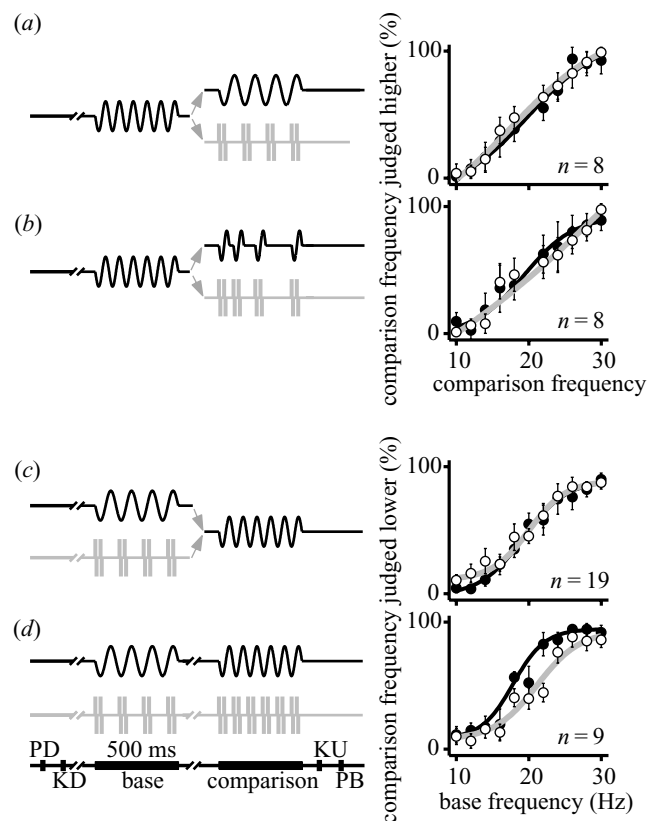


Figure 3. Psychophysical performance in frequency discrimination with natural mechanical stimuli delivered to the fingertips and with artificial electrical stimuli delivered to clusters of neurons of area 3b. Monkeys were trained to compare two vibratory stimuli presented sequentially to the fingertips (illustrated in figure 1). To receive a reward, they had to indicate correctly whether the frequency of the comparison stimulus was higher or lower than the first. Both frequencies changed from trial to trial. The diagrams on the left show two types of trials that were interleaved during the experiments. In half of the trials, the monkeys compared two mechanical vibrations delivered on the skin. In the other half, one or both stimuli could be replaced by electrical frequencies microinjected into clusters of QA neurons of area 3b. The curves on the right-hand side show the animals' performance in the different situations, illustrated on the left-hand side. Black and white circles indicate the mechanical and electrical stimuli, respectively. (a) Psychophysical performance using periodic stimuli; the comparison stimulus could be either mechanical or electrical frequencies. (b) Psychophysical performance when the comparison stimulus was aperiodic and could be either mechanical or artificial stimulus frequencies. (c) Psychophysical performance when the base stimulus was periodic and could be either mechanical or artificial stimulus frequencies. (d) Psychophysical performance when both periodic mechanical stimuli could be replaced by periodic artificial stimulus frequencies. In (a) vibrotactile stimuli were trains of short mechanical sinusoids. In (b) vibrotactile stimuli were trains of short mechanical pulses; each of these pulses consisted of a single-cycle sinusoid lasting 20 ms. In (a) and (b), the y-axis corresponds to the percentage of times the monkeys called f_2 (x-axis) higher than f_1 (20 Hz). In (c) and (d), the y-axis corresponds to the percentage of times the monkeys called the comparison stimulus (20 Hz) lower than base stimuli at the frequency specified in the x-axis. (Modified from Romo *et al.* 1998, 2000.) PD, probe down; KD, key down; KU, key up; PB, push-button.

crimination, aperiodic microstimulation patterns were also applied in the QA neurons of S1 (Romo *et al.* 1998). The same mean frequencies were also used in this condition—20 Hz still corresponded to 10 current bursts delivered in 500 ms—but the current bursts were separated by random time intervals. The monkeys had to compare the base and comparison frequencies just as before, and microstimulation and mechanical stimulation trials were again interleaved. From the very beginning, the animals were able to discriminate between the aperiodic signals with practically the same performance level as that reached with natural, periodic vibrations (figure 3*b*). Periodic and aperiodic stimuli are, of course, different in the time course of the stimulating pulses, but the neural codes for flutter frequency underlying the discriminations performed by the monkeys might be the same for both. If so, the result might imply that spike periodicity does not play a functional role in our monkey's performance of the frequency discrimination task.

Due to the design of this task, comparison of f_2 is made against the memory trace of the first stimulus. Romo *et al.* (2000) wondered whether, in addition to using artificial stimuli during the decision-making stage of the task, monkeys could store and use a quantitative trace of an electrical stimulus delivered to the QA neurons in S1 in place of the first mechanical stimulus. They also wondered whether monkeys could perform the entire task on the basis of purely artificial stimuli. This would demonstrate that the activation of QA neurons was sufficient to initiate the entire cognitive process involved in the task.

Again, the mixed mechanical–microstimulation protocol was used, in which microstimulation trials were randomly intermixed with standard, purely mechanical, trials (Romo *et al.* 2000). The frequency pairs and event sequence were the same in both the mechanical and microstimulation trials, except that in the microstimulation trials the first or both mechanical stimuli were replaced by trains of current pulses injected in the S1 and delivered at the frequency of the mechanical stimulus they were replacing. The design of the stimulus set allowed the exploration of the working-memory component of the task and the determination of the discrimination thresholds.

Psychophysical performance with the electrical microstimulation patterns in S1, at the mechanical base stimulus frequencies they were replacing, was similar to those measured with the mechanical stimulus (figure 3*c*). These results show that monkeys were able to memorize the base artificial stimulus frequency and make quantitative comparisons of f_2 against the trace left by the artificial stimulus. As for replacing the comparison stimulus with electrical patterns, monkeys could not reach the usual level of performance when clusters of SA neurons were microstimulated; nor could they discriminate when microstimulation patterns were made at the border between the QA and SA clusters (Romo *et al.* 2000). These control experiments tell us about the specificity of the QA circuit of S1 in flutter discrimination. Finally, in most sessions in which the two mechanical stimuli were replaced by microstimulated patterns, monkeys were able to reach discrimination levels close to those measured when mechanical stimuli were delivered to their fingertips (figure 3*d*). This indicates that microstimulation elicits quantitative memorizable and discriminable percepts, and

shows that activation of the QA circuit of S1 is sufficient to initiate the entire subsequent neural process associated with flutter discrimination (Romo *et al.* 2000).

In flutter discrimination, the first stimulus has to be detected and memorized. Comparison of the second stimulus is made against the trace left by the first stimulus, and a decision is then projected to the motor apparatus to indicate discrimination. Accurate performance of the task can be consistent only with induction of a sensory percept during both stimulus periods. The reviewed results indicate that the whole sequence of events that leads to discrimination could be initiated by artificial stimulus patterns injected into the QA circuit of S1. Thus, the neural activity produced by either the natural or the artificial stimulus can be used as the basis for sensory discrimination by a psychophysical observer. The results tell us also that periodicity does not play a functional role in our monkey's performance of the frequency discrimination. Psychophysical performance with periodic or aperiodic electrical patterns injected in S1 can be discriminated similarly to when they are delivered to the fingertips.

5. CODING OF VIBROTACTILE STIMULI IN CORTICAL AREAS CENTRAL TO S1

The results reviewed here are the basis for exploring the somatosensory network central to S1. This is an important enterprise, considering that S1 is only one of many brain structures that participate in somatosensory perception. But, in the flutter task, what is the neuronal representation of flutter stimuli in structures that are central to S1? Assuming that it is periodicity, do S2 neurons represent flutter stimuli in the same format? What is the neural correlate for flutter discrimination in structures central to S1? An obvious candidate to explore these questions is S2. S1 is strongly connected with S2 (Burton *et al.* 1995; Krubitzer *et al.* 1995). This central somatosensory region belongs to the ventral stream (Mishkin 1979; Murray & Mishkin 1984).

(a) Coding of flutter stimuli in S2

Unlike the majority of S1 neurons, very few S2 neurons are periodically entrained by the flutter stimuli (Salinas *et al.* 2000). There are basically three groups of neuronal responses during the stimulus periods: the first group increases the firing rate as a function of the stimulus frequency; the second group decreases the firing rate as a function of increasing stimulus frequency; and the third group responds but is not modulated as a function of the stimulus frequency. According to this, there is a dramatic change in the flutter representation from S1 to S2. Clearly, the most interesting responses in S2 are those which modulate their firing rate as a function of the stimulus frequency. These responses are affected by the animal's state (Salinas *et al.* 2000). These responses are more prominent during the discrimination task than when the same stimuli are delivered in non-working conditions. These distinct populations operate simultaneously in S2 and should produce a computation that is useful for frequency discrimination in an analogous manner to that reported in central visual areas such as the middle temporal cortex (Britten *et al.* 1992). Finally, an important result obtained in S2 neurons is that many of them retain

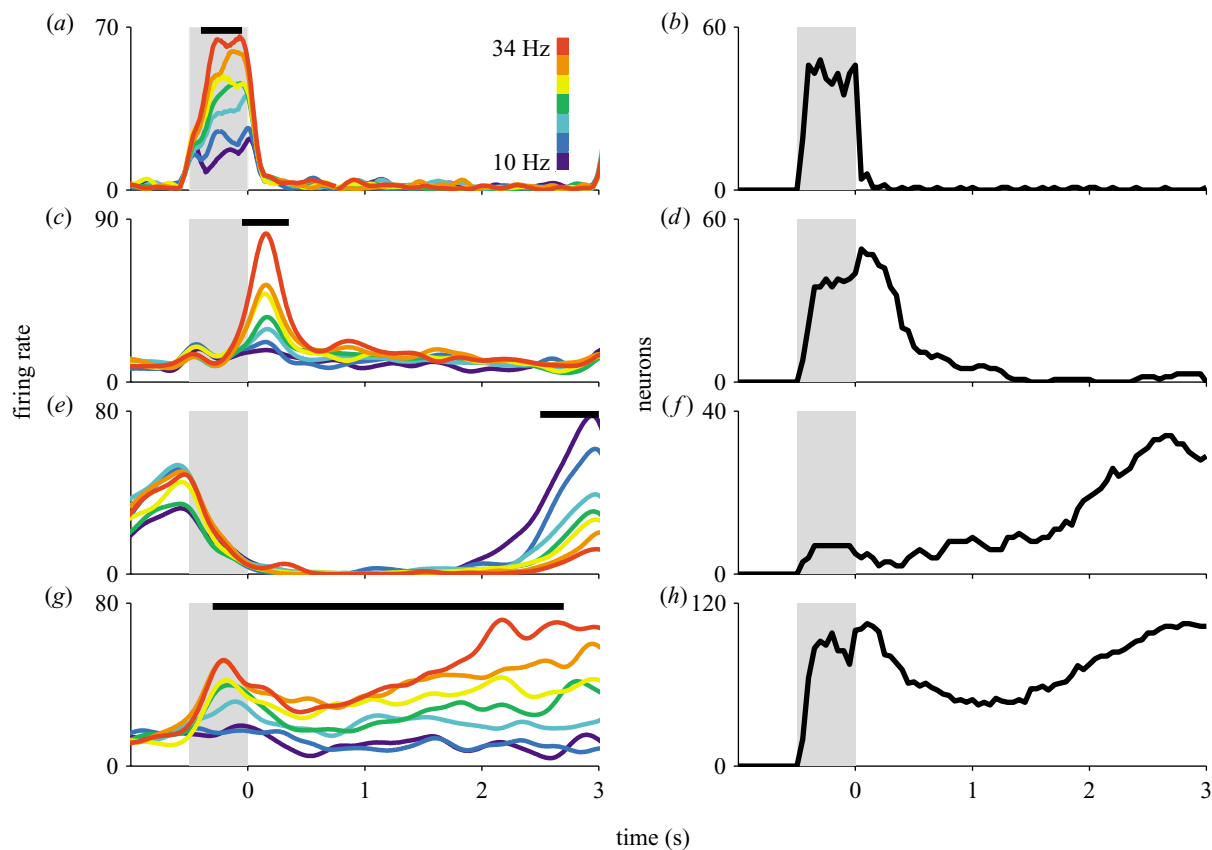


Figure 4. Neuronal response types during the delay period. (a,c,e,g) Single-neuron spike-density function from four different neurons. The dark bars above each plot indicate the times during which the neuron's firing rate carried a significant ($p < 0.01$) monotonic signal about the base stimulus (Romo *et al.* 1999). (c,g) Positive monotonic encoding neurons about the base stimulus. (e) Negative monotonic encoding neuron about the base stimulus. (b,d,f,h) Total number of recorded neurons (during fixed 3 s delay period runs) carrying a significant signal about the base stimulus, as a function of time relative to the beginning of the delay period. The base stimulus period is shaded grey; colour gradient from 10 to 34 Hz. (a,b) S1, (c,d) S2, (e,f) MPC and (g,h) PFC (Modified from Salinas *et al.* 2000; Romo *et al.* 1999; Hernández *et al.* 2002.)

information about the base stimulus during the initial part of the delay period between the two stimulus frequencies (figure 4c). This is also the case for the stimulation periods: that is, if the neuron increases its firing rate as a function of the base stimulus frequency, the same representation is maintained during the initial part of the delay. We consider this to be a neural correlate of the working-memory component of the task (Salinas *et al.* 2000). This information must be translated to structures central to S2 that contain a network for working memory in this task. An important observation is that S1 neurons do not show any trace of the base stimulus during the delay period (figure 4a).

(b) Parametric encoding of flutter stimuli during working memory

As reviewed in § 5a, some neurons of S2 retain the base stimulus frequency during the early component of the delay period (Salinas *et al.* 2000). They do so by retaining the base stimulus frequency monotonically during the early memorization component of the task (Salinas *et al.* 2000). Where, then, is this early representation projected and held during the whole delay period between the two flutter stimuli? Is this associated with the stimulus parameters? Romo *et al.* (1999) recorded in the PFC and sought to determine the neuronal correlate for the working-memory component of this task. Although there

is no clear direct input from S2 or S1 to the PFC, in a pilot experiment Romo *et al.* (1999) recorded above and below the principal sulcus in the PFC while a monkey performed the flutter-discrimination task. Recordings in the first monkey indicated that the inferior convexity of the PFC contained neurons whose activity varied, during the delay period between the two stimuli, as a monotonic function of the stimulus frequency. This finding was then further investigated in three more animals performing the flutter-discrimination task. Some of the delay responses responded most weakly after stimulation with the lowest base frequency, and increased their firing rates steadily as the frequencies increased (positive monotonic encoding; figure 4g). Others had discharge rates that varied inversely (negative encoding; not shown here). Interestingly, this representation is not different from that found in S2 (Salinas *et al.* 2000) and in the MPC (figure 4e) during the vibrotactile-discrimination task (Hernández *et al.* 2002). The main difference between these structures is that S2 encoded the base stimulus frequency during the early component of the delay period (figure 4d; Salinas *et al.* 2000), PFC neurons show early, persistent and late encoding (figure 4h; Romo *et al.* 1999), and MPC neurons show late delay activity (figure 4f), just before the beginning of the second, comparison stimulus. Thus, the base stimulus frequency, a scalar analogue value, appeared to be encoded directly in the neuron's firing rate (also a sca-

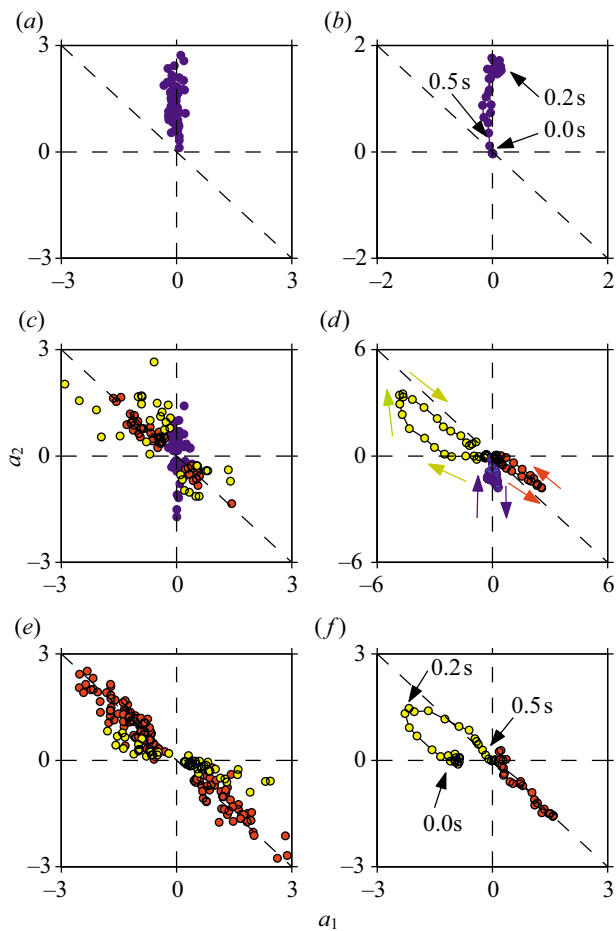


Figure 5. Responses during the second stimulus. (a,c,e) Coefficients resulting from fitting firing rates from S1, S2 and MPC neurons, during the second stimulus, as linear functions of both f_2 (a_2) and f_1 (a_1). Each dot represents coefficients for one neuron; only neurons with fits significantly different from (0,0) are shown. (b,d,f) Dynamics of individual responses for S1, S2 and MPC neurons. Each row shows data from one neuron. In all panels, time = 0 corresponds to the start of the second stimulus. Each symbol in (b), (d) and (f) corresponds to fits of 100 ms, separated from its neighbours in steps of 25 ms. Blue dots represent neurons that responded as a function of f_2 (sensory response); yellow dots represent neurons that carried the first information of f_1 (the memory trace) then f_1 interacted with f_2 (differential response); red dots represent neurons that indicated the difference between f_1 and f_2 . (a,b) S1, (c,d) S2 and (e,f) MPC (Hernández *et al.* 2002; R. Romo, A. Hernández, C. Brody, A. Zainos and L. Lemus, unpublished data).

lar analogue value), most often in a smoothly graded fashion. The smooth monotonic encoding found in S2, the PFC and the MPC is consistent with the existence of a parametric, rather than categorical, representation of the memorized stimulus during the working-memory component of this task. In the same vein, these results could indicate that monotonic encoding might be the basic representation of sensory magnitude continua during working memory, in tasks that require ordinal comparisons between scalar analogue stimuli.

Monotonic encoding of the stimulus frequency in the PFC and MPC may be derived from inputs from S2, and not from S1 (figure 4a,b). However, it is not clear to what

extent the delay activity in the PFC and MPC depends on S2, or to what extent this delay activity is elaborated in the local circuits of each of these structures. For example, S2 is anatomically connected with the MPC but it is not clear that S2 is connected with the PFC (reviewed in § 5a). At this moment, we can only say that these structures display, at different times, the encoding of the sensory stimulus during the working-memory period of this task. Further experiments are required to show the connectivity between these cortical areas and whether these structures are part of a large cortical network (Fuster 1997) that combines past and current sensory information to generate motor actions. These results constitute a neurophysiological demonstration that neurons of the PFC and MPC can retain sensory information induced by non-visual modalities.

6. NEURONAL CORRELATES OF THE COMPARISON PROCESS

Reaching a decision in the vibrotactile-discrimination task requires comparison between the memory trace of the first stimulus and the current sensory input (Hernández *et al.* 1997). We sought evidence of this process in S1, but as indicated already, the activity of these neurons do not combine past and current sensory information to generate behavioural decisions; they encode the current sensory input. This is not the case in S2 and in the MPC, where we found neuronal activity that seemed to reflect the comparison process that preceded the behavioural decision (Hernández *et al.* 2002; R. Romo, A. Hernández, C. Brody, A. Zainos and L. Lemus, unpublished data). We review in § 6 recent results that seem to indicate the dynamics of the comparison process.

(a) Neuronal correlates of the comparison process in S2

As we expected for a somatosensory cortex, S2 neurons encoded the two stimulus frequencies in their firing rate (Salinas *et al.* 2000). But, surprisingly, many S2 neurons first encoded the base (f_1) stimulus, then responded differentially during the comparison (f_2) stimulus (R. Romo, A. Hernández, C. Brody, A. Zainos and L. Lemus, unpublished data). By ‘differential’ we mean that the activity is selective for the comparison $f_2 > f_1$ or $f_2 < f_1$ trials during correct discriminations. We wondered whether the responses quantified during f_2 depended on f_1 , even though f_1 had been applied 3 s earlier, or whether they simply reflected their association with the motor responses. We studied the nature of this differential response. To quantify this, we determined the probability that an observer, measuring only the neuronal response during the f_2 period, could discriminate correctly between $f_2 > f_1$ trials and $f_2 < f_1$ trials for the same f_2 (discrimination indices have been adapted after Green & Swets (1966) by Britten *et al.* (1992), Dodd *et al.* (2001) and Kim & Shadlen (1999)). Indeed, a large number of these neurons reflected this fact. That is, they had discrimination indices that deviated from 0.5. However, a crucial question, as indicated above, is whether these differential responses indicate the comparison between f_1 and f_2 , or the differential response that is implemented to indicate discrimination. We ruled out the presence of a simple

differential motor activity associated with the push-button presses (figure 1*a*) by testing these S2 neurons in a control task where the same vibrotactile stimuli were used, but animals had to follow a visual cue to produce the motor response. In this condition, all neurons reduced the deviation from 0.5, indicating that the differential activity observed during the comparison period depends on the actual computation between f_1 and f_2 and does not reflect a purely motor response aimed to press one of the two push-buttons.

If the discharges during the comparison period are the product of the interaction between f_1 and f_2 , then the trace of f_1 and the current f_2 could be observed during the comparison period before the discharges indicated the motor responses. To further quantify the interaction between f_1 and f_2 during the comparison period and beyond it, we used a multivariate regression analysis (Draper & 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 f_1 and f_2 . The responses, which in principle could be an arbitrary function of both f_1 and f_2 , were reasonably well approximated by a general linear fit to both f_1 and f_2 as follows:

$$\text{firing rate} = a_1 \times f_1 + a_2 \times f_2 + \text{constant.}$$

In this formula, the coefficients a_1 and a_2 serve as direct measurements of firing rate dependence on f_1 and f_2 , respectively. Three lines are of particular importance in these fits. Points that fall on the $a_1 = 0$ axis represent responses that are a function of f_2 (the sensory evidence of f_2 ; blue dots in figure 5). Points that fall on the $a_2 = 0$ axis represent responses that are a function of f_1 (the memory trace of f_1 ; yellow dots in figure 5). And points that fall on the $a_1 = -a_2$ line represent responses that are functions of the difference between f_1 and f_2 (red dots in figure 5). This last consideration is of particular importance because, in this task, correct behaviour depends on the sign of the difference between f_1 and f_2 .

The analysis revealed the contributions of f_1 and f_2 during the comparison period for S2 neurons (figure 5*c,d*; for a comparison see in figure 5*a,b* the responses of S1 neurons during the f_2 period). Interestingly, when they are plotted as a function of the evolution of the comparison process, it is clearly observed that some neurons evolve from coding the sensory stimuli (which could be f_1 or f_2 ; see three examples in figure 5*d*: blue dots indicate a sensory response; yellow dots indicate that the neurons carry information of f_1 then show the difference between f_1 and f_2 ; red dots indicate a purely differential response) to a differential response that is consistent with the motor output. Indeed, the analysis of the error trials indicated that the differential response correlated with the behavioural choice; that is, the selection of the push-button.

These results are important because they show that an early sensory area shows not only the representation of the current sensory input (f_2 ; blue dots in figure 5*c,d*), but also the representation of the sensory referent (f_1 ; yellow dots in figure 5*c,d*) which is stored in the working memory. These two processes are important ingredients for the resulting differential responses between f_1 and f_2 (red dots in figure 5*c,d*) that correlate with the behavioural decisions. As S2 neurons do not store information about the f_1 stimulus during the later part of the delay period,

the comparison process in S2 could be made between the input from S1 that provides information on the current stimulus and an input from the frontal cortical areas that carries information on the base stimulus during the later part of the delay period. However, more experiments are needed to show whether this is so. The comparison process is reported by a voluntary motor action, and anatomical studies have shown that S2 projects to the motor areas of the frontal lobe (reviewed in § 6*a*). We explored the possibility that the motor areas reflect the behavioural decision during the vibrotactile-discrimination task.

(b) *Neuronal correlates of the comparison process in the MPC*

As indicated in § 6*a*, anatomical studies in monkeys have shown that S1 and S2 are serially connected (Pons *et al.* 1987, 1992; Burton & 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 & Powell 1969; Pandya & Kuypers 1969; Jones *et al.* 1978; Jürgens 1984; Luppino *et al.* 1993). If we consider a serial processing model, in principle S2 could process the S1 representation of the vibrotactile stimuli and transmit its output to the motor cortices. As indicated in § 6*a*, S2 neurons show a transformation of the S1 vibrotactile representation (Salinas *et al.* 2000) and appear to reflect activity associated with the comparison of the two stimuli (R. Romo, A. Hernández, C. Brody, A. Zainos and L. Lemus, unpublished data). The question that arises is whether there is a truly clear distinction between those areas presumably dedicated to sensory processing and those traditionally viewed as motor areas. 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 the 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 formation of a behavioural decision, in which case they should reflect details about the sensory inputs regardless of the motor outcome. We tested these two possibilities by recording single neurons in the MPC while monkeys performed the vibrotactile-discrimination task (Hernández *et al.* 2002).

The responses of single neurons in the MPC were extremely informative of the sequence of the discrimination process. For example, during the base stimulus, some of the neurons had graded responses as a function of f_1 and displayed a trace of it at the end of the delay period between the two stimuli. Interestingly, during the comparison period these neurons showed information about f_1 or f_2 and then reflected in their activities the difference between the two stimuli (figure 5*e,f*). This differential activity was correlated with the motor response only during the discrimination task; these neurons lost their differential responses when tested in the light-instruction task mentioned above.

As for the S2 neurons, we studied the dynamics of the comparison process, and sought evidence of whether this process is due to an interaction between the past (f_1) information and the current sensory stimulus (f_2). A subpopulation of the differential neurons displayed information about f_1 (the memory trace; yellow dots in figure

5e,f; in figure 5e the dots represent individual neurons; figure 5f details the response profiles of a neuron) during the comparison period and their responses evolved to a differential activity that corresponded to an interaction between the f_1 and f_2 stimuli (red dots in figure 5e,f; in figure 5e the dots represent individual neurons; in figure 5f the response profile of a neuron is given). These responses could be confined to the comparison period or be prolonged to the reaction and movement time periods of the behavioural motor responses. Thus, what is typically observed in the MPC during the comparison period is that initially some neurons encode f_1 or f_2 , and later these and other units encode the difference between f_1 and f_2 .

The results indicate that activity in the MPC reflects many aspects of the vibrotactile-discrimination task, not just the motor component. Distinct subpopulations of MPC neurons are activated during the period where the comparison between stimuli presumably takes place, and their activities during the end of the comparison process are consistent with the behavioural decision. This process appears to precede activity in M1 during the behavioural response associated with this sensory-discrimination task (Mountcastle *et al.* 1992; R. Romo, A. Hernández, C. Brody, A. Zainos and L. Lemus, unpublished data).

7. CONCLUDING REMARKS

The vibrotactile-discrimination task requires perceiving a stimulus, storing it in working memory, combining the stored trace with current sensory input and producing a decision that is communicated to the motor apparatus. This temporal sequence is reflected in the activity of some neuronal populations of different cortical areas of the parietal and frontal lobes. Our results indicate that neurons central to S1 do not simply wait for a signal-encoding decision, but instead participate in almost every step of its generation by integrating working-memory and sensory inputs. Similar processes may occur in other discrimination tasks that require comparison between sensory stimuli. Finally, an important question which needs to be addressed in this and in similar tasks is how the cortical neuronal circuits interact to produce a comparison between the current sensory input and those sensory representations stored in working or in long-term memory. Revealing this neural process must be key to understanding this finest brain operation that leads to behavioural decisions.

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GLOSSARY

- M1: primary motor cortex
MPC: medial premotor cortex
PC: Pacinian receptor organ
PFC: prefrontal cortex
PM: premotor
QA: Meissner receptor organ
ROC: receiver operating characteristic
S1: primary somatosensory cortex
S2: secondary somatosensory cortex
SA-I: Merkel organ
SA-II: Ruffini organs