



Contents lists available at SciVerse ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio



Conversion of sensory signals into perceptual decisions

Ranulfo Romo ^{a,b,*}, Victor de Lafuente ^c

^a Instituto de Fisiología Celular-Neurociencias, Universidad Nacional Autónoma de México, 04510 México, D.F., Mexico

^b El Colegio Nacional, 06020 México, D.F., Mexico

^c Instituto de Neurobiología, Universidad Nacional Autónoma de México, 76230 Querétaro, Mexico

ARTICLE INFO

Article history:

Received 8 December 2011

Received in revised form 17 March 2012

Accepted 20 March 2012

Available online xxx

Keywords:

Perception

Decision-making

Sensory encoding

Working memory

Somatosensory

ABSTRACT

A fundamental problem in neurobiology is to understand how brain circuits represent sensory information and how such representations give rise to perception, memory and decision-making. We demonstrate that a sensory stimulus engages multiple areas of the cerebral cortex, including primary sensory, prefrontal, premotor and motor cortices. As information transverses the cortical circuits it shows progressively more relation to perception, memory and decision reports. In particular, we show how somatosensory areas on the parietal lobe generate a parameterized representation of a tactile stimulus. This representation is maintained in working memory by prefrontal and premotor areas of the frontal lobe. The presentation of a second stimulus, that monkeys are trained to compare with the first, generates decision-related activity reflecting which stimulus had the higher frequency. Importantly, decision-related activity is observed across several cortical circuits including prefrontal, premotor and parietal cortices. Sensory information is encoded by neuronal populations with opposite tuning, and suggests that a simple subtraction operation could be the underlying mechanism by which past and present sensory information is compared to generate perceptual decisions.

© 2012 Elsevier Ltd. All rights reserved.

Contents

1. Introduction	000
2. Sensory detection	000
2.1. Psychophysics of sensory detection	000
2.2. Neuronal S1 activity during sensory detection	000
2.3. Neuronal S1 activity and perceptual reports	000
2.4. Neural correlates of varying perceptual detection judgments occur outside S1	000
2.5. Microstimulation of MPC triggers perceptual detection reports	000
2.6. Comments on the functional role of MPC in perceptual detection reports	000
2.7. Perceptual detection reports gradually build up across cortical areas	000
2.8. Covariations between responses across cortex and perceptual judgments	000
2.9. Timing of detection decision signals across cortical areas	000
2.10. Sensory versus motor responses across cortex during perceptual detection reports	000
2.11. Perceptual reports are gradually constructed across cortex	000
3. Sensory discrimination	000
3.1. Optimal conditions for studying the neuronal correlates of sensory discrimination	000
3.2. Neural coding of vibrotactile stimuli in S1 during discrimination	000
3.3. Neuronal correlates of sensory discrimination in S1	000
3.4. Artificial induction of activity in S1 underlying sensory discrimination	000
3.5. The functional role of S1 in sensory discrimination	000
3.6. Coding sensory discrimination in cortical areas central to S1	000

Abbreviations: S1, primary somatosensory cortex; S2, second somatosensory cortex; VPC, ventral premotor cortex; DPC, dorsal premotor cortex; MPC, medial premotor cortex; PFC, prefrontal cortex; M1, primary motor cortex.

* Corresponding author at: Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, 04510 México, D.F., México. Tel.: +52 55 56225586; fax: +52 55 56225607.

E-mail address: rromo@ifc.unam.mx (R. Romo).

3.7. Coding sensory stimuli in S2	000
3.8. Coding sensory stimuli in frontal cortex	000
3.9. Coding sensory stimuli during working memory	000
3.10. Comparison and decision-making processes	000
3.11. Decision-making in the motor cortex	000
3.12. Is there any coding scheme across cortex for decision-making?	000
3.13. Decoding postponed decision reports across cortex	000
3.14. Context dependent responses across cortex	000
3.15. Further comments on the neural mechanisms of sensory discrimination	000
4. Conclusions	000
Acknowledgements	000
References	000

1. Introduction

More than two thousands years ago, based on an intellectual *tour de force*, the Greek philosopher Democritus (430–420 B.C.) suggested that objects of the external world were constituted of moving atoms that reached the brain, where they generated dynamic images that are processed for thinking (Jung, 1984). For him, this process provided the raw material for sensation, perception, learning and action. In this manner, the subject could voluntarily use these internal representations to guide thoughts and actions. Unintentionally, Democritus suggested a working hypothesis that many contemporary scientists use to investigate where and how in the brain a sensory representation transforms in perception, memory and action. But, in now days, what is known about this millenary hypothesis?

It was Adrian (1928) the first to scientifically test this ancient hypothesis. He recorded the peripheral fibers innervating skin receptors and observed how the firing rates varied as a function of the stimulus strength applied to the skin. These experiments opened a vast field of research aimed to elucidate how sensory inputs are represented in the peripheral nervous systems (Hartline et al., 1956; Johnson and Hsiao, 1992; Werner and Mountcastle, 1965; Connor et al., 1990). This experimental approach paved the way for new questions associated with the problem of neural coding. The underlying belief was that unraveling the neural representations of sensory stimuli, from periphery to early stages of cortical processing, was key to understanding brain function. Indeed, investigations across the sensory systems have shown how neural activity represents the physical or chemical parameters of sensory stimuli in both the periphery (Connor et al., 1990; Axel, 2005; Barlow, 1957; Buck, 2005; Hartline et al., 1956) and central brain areas (Creutzfeldt and Nothdurft, 1978; Hubel and Wiesel, 1998; Merzenich and Brugge, 1973; Mountcastle et al., 1969; Ruiz et al., 1995; Stettler and Axel, 2009). These results constitute the bases for new questions relating to the cognitive processing of sensory inputs. For example: where and how in the brain are the sensory representations converted into perceptual decisions? Specifically, what components of the neuronal responses evoked by a sensory stimulus are directly related with perception and decision making? Where and how in the brain the sensory information is stored in memory? How stored sensory information combines with current sensory information and how the resulting interactions are linked to perceptual reports?

Here we review the available experimental evidence that relates to the above questions using somatosensory detection and discrimination tasks in which the neuronal activity across cortex can be directly linked to the monkeys' psychophysical detection and discrimination reports. This comparative analysis allows tracking neuronal activities from distinct cortical circuits that might be associated with the diverse components of these two tasks.

2. Sensory detection

Detecting sensory stimuli is among the simplest perceptual experiences and is a prerequisite for any further sensory experience. A fundamental problem posed by sensory detection tasks is that repeated presentations of a near-threshold stimulus unpredictably fail or succeed to generate a sensory percept. Where in the brain are the neuronal correlates of these varying perceptual judgments? Pioneer studies on the neuronal correlates of sensory detection showed that, in the case of vibrotactile stimuli, the responses of primary somatosensory cortex (S1) neurons account for the measured psychophysical accuracy (Mountcastle et al., 1969). However, direct comparisons between S1 responses and detection performance could not be addressed and, therefore, it is not clear whether the activity of S1 accounts for the variability of the behavioral responses. In these earlier studies, psychophysical performance was measured in human observers and S1 recordings were made in anesthetized monkeys.

2.1. Psychophysics of sensory detection

The detection of sensory stimuli has been recently addressed by de Lafuente and Romo (2005, 2006). These authors trained monkeys to perform a vibrotactile detection task. On each trial, the animal had to report whether the tip of a mechanical stimulator vibrated or not (Fig. 1A). The 20 Hz sinusoidal stimuli were delivered to the glabrous skin of one fingertip. Crucially, they varied in amplitude across trials. Stimulus-present trials (amplitude > 0 μm) were interleaved with an equal number of stimulus-absent trials in which no mechanical vibrations were delivered (amplitude = 0 μm). Depending of the monkeys' behavioral reports, trials could be classified into four types: hits and misses in the stimulus-present condition, and correct rejections and false alarms in the stimulus-absent condition (Fig. 1B). Stimulus detection thresholds were calculated from the behavioral responses (Fig. 1C). By simultaneously recording the behavioral responses along with the neuronal activity in the brain, these studies attempted to elucidate the neuronal mechanisms underlying the detection of sensory stimuli.

2.2. Neuronal S1 activity during sensory detection

de Lafuente and Romo (2005) simultaneously characterized the activity of S1 neurons (areas 3b and 1) and the monkey's psychophysical performance. Figs. 1C and 2A show the monkey's psychometric curve and the spike trains of an S1 neuron recorded in the same trials. To test whether the responses of S1 neurons accounted for the monkey's psychophysical performance, de Lafuente and Romo (2005) calculated neurometric detection curves and compared them with the psychometric curves. The proportion of 'yes' responses for neurometric curves was defined as

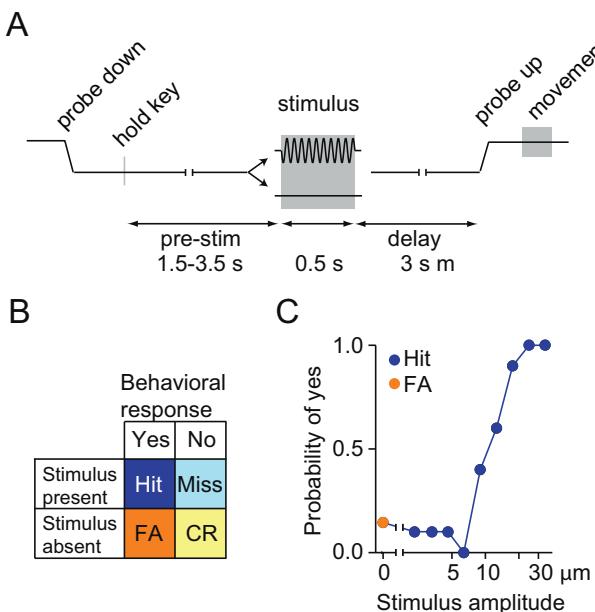


Fig. 1. Vibrotactile detection task. (A) Vertical displacement of the mechanical stimulator as a function of time. Trials started by indenting the glabrous skin of one fingertip of the right hand (probe down). The monkey then placed its left non-stimulated hand on an immoveable key at waist level (hold key). After a variable pre-stimulus delay a sinusoidal mechanical vibration was presented on randomly selected half of the trials. The stimulator moved up after a fixed delay period (probe up), cueing the monkey to communicate its decision about stimulus presence or absence by pressing one of two push-buttons (movement). (B) Depending on the behavioral response and on whether the stimulus was present or not, trials were classified as hit, miss, false alarm (FA) or correct rejection (CR). (C) Psychometric detection curves were obtained by plotting the proportion of "yes" responses as a function of stimulus amplitude.

Adapted from de Lafuente and Romo (2005).

the proportion of trials in which the neuron's firing rate reached or exceeded a criterion value (Green and Swets, 1966; de Lafuente and Romo, 2005). For each neuron, this criterion was chosen to maximize the number of correct responses (Fig. 2B). Pairwise comparisons of detection thresholds obtained from logistic fits to the simultaneously obtained neurometric and psychometric data showed that the detection thresholds of individual S1 neurons were not significantly different from the animals' psychophysical thresholds, and the two thresholds measures highly covaried. In addition, the shape of the mean neurometric curve resulting from the activity of the S1 neurons showed close correspondence with the shape of the mean psychometric curve (Fig. 2C).

2.3. Neuronal S1 activity and perceptual reports

An important question addressed in this study is whether the activity of S1 neurons covaries with the perceptual "yes" and "no" judgments that the monkeys made on a trial-by-trial basis (de Lafuente and Romo, 2005). To test this, these authors compared the activity during hit and miss trials for the near-threshold stimulus, as well as for the corresponding activity in correct reject and false alarm trials in the stimulus-absent condition (Fig. 2D). They found no significant differences in the activity of S1 neurons between hits and misses (Fig. 2D, upper left panel), nor between correct rejections and false alarms (Fig. 2D, upper right panel). This indicated that activity of individual S1 neurons did not predict the monkey's behavior. To further quantify this, de Lafuente and Romo (2005) calculated a choice probability index, which estimates the probability with which the behavioral outcome can be predicted from the neuronal responses (Britten et al., 1996; Hernández et al., 2002; Romo et al., 2002). As shown in the lower panels of Fig. 2D,

they found no significant differences between hits and misses, or between correct rejections and false alarms trials.

The low choice probability values are consistent with a detection mechanism in which the activity of S1 serves as input to an additional processing stage(s) that determines whether a stimulus has occurred or not. Under this hypothesis, correlation between S1 activity and the final decision about the stimulus presence or absence is highly dependent on the amount of correlated-noise among sensory neurons (Zohary et al., 1994). Indeed, de Lafuente and Romo (2005) found that mean noise correlation coefficient across pairs of S1 neurons was 0.16 ± 0.02 . This amount of correlated-noise is similar to those reported in previous studies (Bair et al., 2001; Romo et al., 2003), and is also consistent with the near chance choice probability values reported in the study of de Lafuente and Romo (2005). These results further support a detection model in which a central area(s) must be observing the activity of S1 neurons to judge about the stimulus presence or absence. Therefore, the functional role of S1 in this and other perceptual tasks may be mainly to generate a neural representation of the sensory stimulus for further processing in areas central to it (de Lafuente and Romo, 2005, 2006; Hernández et al., 2000, 2002, 2010; Romo et al., 1999, 2002, 2003, 2004; Salinas et al., 2000).

However, a previous study of sensory detection found that fMRI signals in primary visual cortex (V1) reflected the percepts of human subjects, rather than the encoded stimulus features (Ress and Heeger, 2003). This result suggests that, in V1, top-down signals (non-sensory inputs delivered to visual cortex via feedback projections) can be combined with bottom-up (sensory) information and contribute to sensory percepts (Leopold and Logothetis, 1996; Meyer, 2011; Ress and Heeger, 2003). S1 data did not show evidence for this type of neural interaction; rather, it indicated that S1 represents the physical properties of stimuli and contributes little to the variability of near-threshold percepts (de Lafuente and Romo, 2005). The discrepancy could be due to fundamentally different organizations across sensory cortices, or to differences between species. Another possibility to consider is that the modulation revealed through fMRI may have an effect that is invisible from the point of view of single neurons. This would happen if, for instance, such modulation acted to synchronize the spikes of multiple target neurons (Fries et al., 2001a,b). If not in S1, where in the brain are the neuronal correlates of the varying perceptual judgments observed in the detection task?

2.4. Neural correlates of varying perceptual detection judgments occur outside S1

One possibility is that they are mediated by neurons of more central areas downstream in the processing hierarchy. To test whether the neuronal correlates of the perceptual decisions associated with detection might reside outside S1, de Lafuente and Romo (2005) recorded neurons from the medial premotor cortex (MPC), a frontal cortical area known to be involved in the evaluation of sensory information and in decision-making processes (Hernández et al., 2002, 2010; Lemus et al., 2007; Romo et al., 1993). They found that, in contrast to the graded dependence on stimulus amplitude observed in S1, MPC neurons responded in an all-or-none manner that was only weakly modulated by the stimulus amplitude (Fig. 3A–C), but that closely correlated with "yes" and "no" behavioral responses (Fig. 3B). The mean activity across MPC neurons was strong and sustained, and with near-threshold stimuli it was clearly different for hit and miss trials (Fig. 3D, upper left panel). Moreover, almost 70% of the false alarm trials were predicted from increases in neuronal activity in stimulus-absent trials (Fig. 3D, upper right panel). They also found that the MPC activity preceding stimulus onset was higher

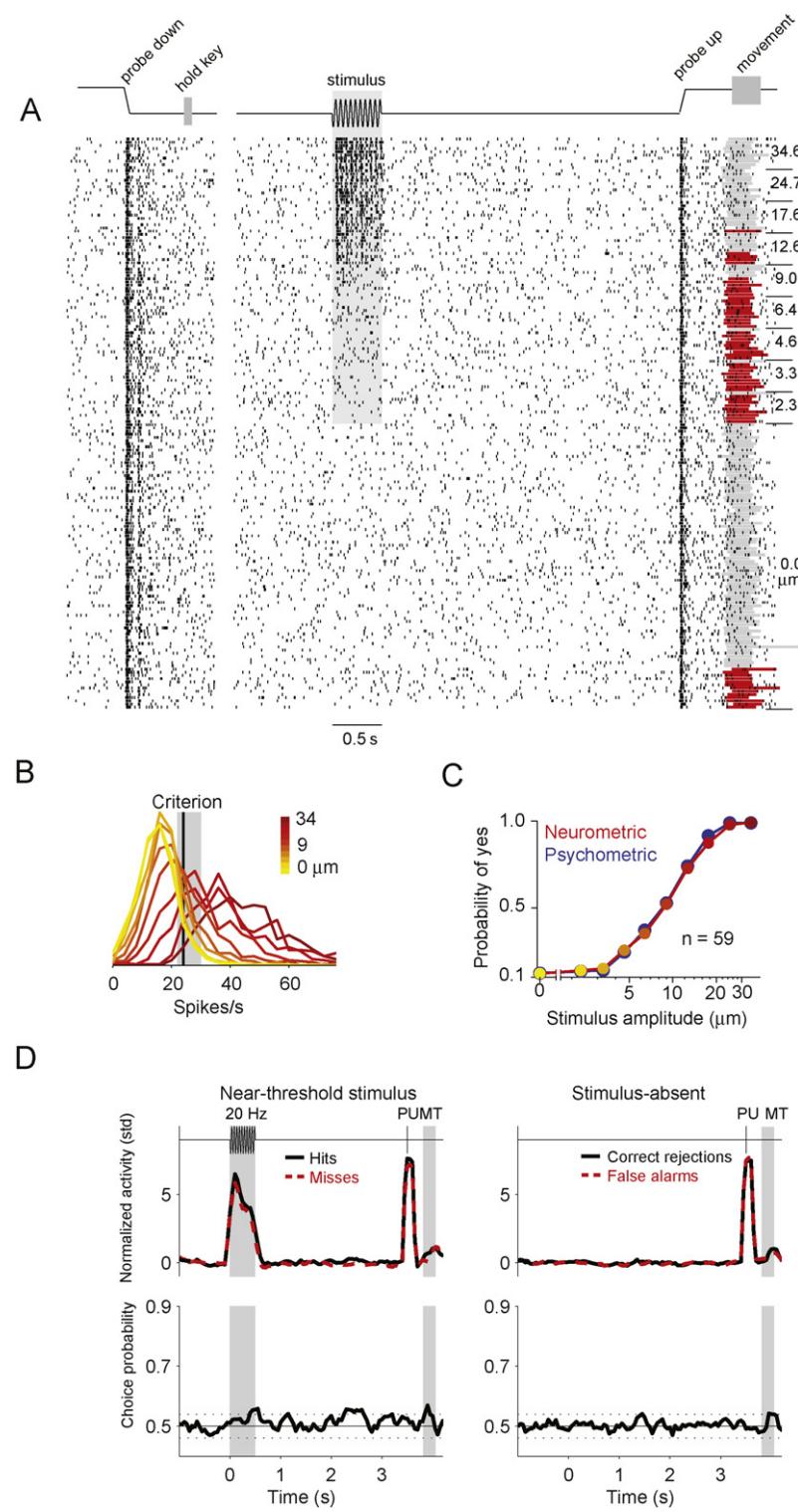


Fig. 2. Activity of S1 neurons on the detection task. (A) In the rasterplot of the example neuron, each dot marks the time of an action potential, and each row represent activity on a single trial. Trials are sorted by stimulus amplitude. Red markers on the movement period indicate misses on stimulus-present trials and false alarms on stimulus-absent trials. Gray box marks the time of stimulus presentation for stimuli with amplitudes larger than zero. (B) Distribution of the firing rates evoked by the stimulus. The black vertical line marks the median criterion value (22 spikes per s) used to generate the neurometric detection curve for each neuron. Gray box indicates inter-quartile range. (C) Mean psychometric and neurometric detection curves. (D) Comparison of mean standardized activity during hits and misses for near-threshold stimuli, and during correct rejections and false alarms in stimulus-absent trials. Lower panels show the choice probability index as a function of time. Dotted lines indicate the values where the choice probability significantly departs from 0.5.

Adapted from de Lafuente and Romo (2005).

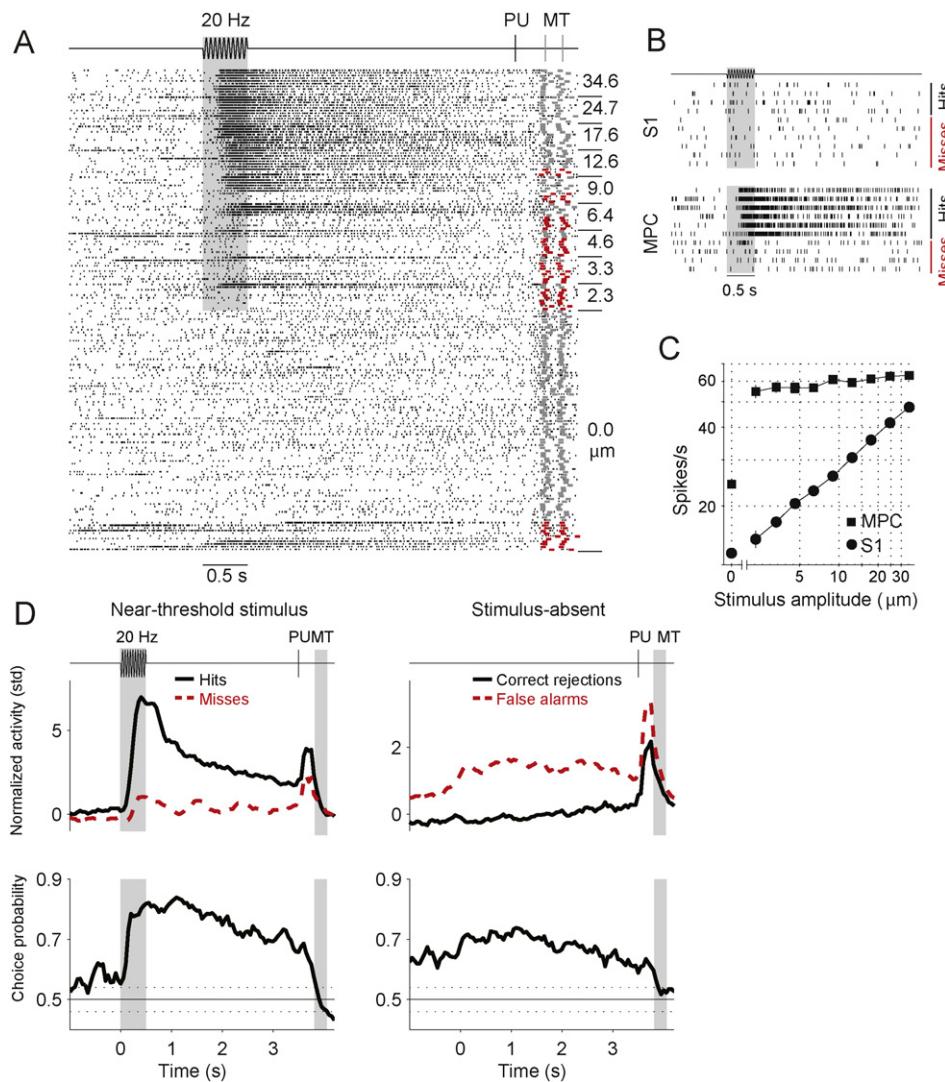


Fig. 3. Activity of MPC neurons during the detection task. (A) Rasterplot of an example MPC neuron. (B) Comparison of single trial responses of the example S1 and MPC neurons to 10 repetitions of a near threshold stimulus (9 μm). (C) Mean response to the stimulus on hit trials for S1 ($n = 59$) and MPC neurons ($n = 50$). (D) Comparison of standardized activity during hits and misses in near-threshold stimulus trials, and during correct rejections and false alarms in stimulus-absent trials. Lower panels show the average choice probability index as a function of time.

Adapted from de Lafuente and Romo (2005).

during hits than during misses (Fig. 3D, upper right panel). These early increases in activity predicted detection success significantly above chance levels, as is shown by the choice probability plots (Fig. 3D, lower left panel).

The close association between neuronal and behavioral responses, and the weak relationship between activity and stimulus amplitude, supported the interpretation that MPC neurons do not code the physical attributes of stimuli, but rather represent perceptual judgments about their presence or absence. As the monkeys reported their decisions by a motor act, a key question was whether the MPC activity reflected stimulus perception or just different motor actions associated with the two response buttons. To test this, de Lafuente and Romo (2005) designed a control task in which the correct response button was illuminated at the beginning of every trial. In this variant of the detection task, the monkeys simply had to wait until the end of the trial to push the illuminated button, without the need to attend to the presence or absence of the mechanical vibration. The raster plot of the neural activity for an example neuron shows that the responses to the stimulus in this control condition (Fig. 4B) were very similar to the responses in the standard detection task

(Fig. 4A). It is important to note that in this test condition all-or-none activity was still observed in response to the near-threshold stimulus, and that firing rates were similar to those observed during the normal detection task (Fig. 4D). Given that in the control test the monkeys did not have to choose a response button based on the vibratory stimulus, the results are consistent with the interpretation that the activity of these MPC neurons is related to the subjective perception of sensory stimuli, rather than to the selection of the motor plan. To further examine whether MPC activity was associated with the preparation of movements in different directions, they performed a second control experiment in which, again, the correct response button was illuminated at the beginning of every trial, as before. In this case, however, they switched response buttons so that the "yes" button was now illuminated during stimulus-absent trials and, conversely, the "no" button was illuminated during stimulus-present trials. The results showed that reversing the direction of the arm movements did not change the all-or-none character of the evoked MPC activity (see the mean response for 14 neurons in Fig. 4D and during trial repetitions in the example neuron in Fig. 4C). Had these neurons participated primarily in movement choice or movement generation, their firing

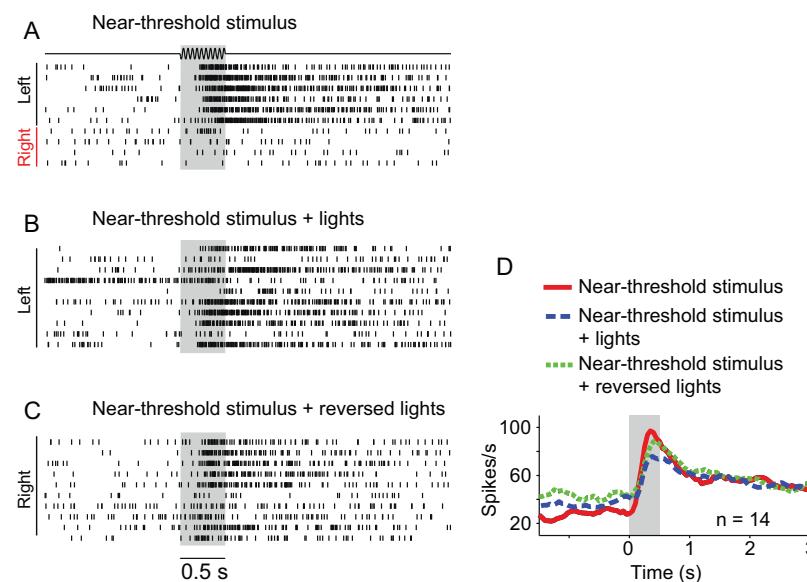


Fig. 4. Testing the sensory-related versus the motor-related hypotheses of MPC activity. (A) Spiking activity of the example neuron to 10 repetitions of the 9 μm stimulus during the normal detection condition. (B) The same neuron recorded in a control condition in which the correct response button (left button) was illuminated at the beginning of each trial. (C) Responses of the same neuron in a control condition in which the positions of the buttons were reversed. Note that the activity evoked by the stimulus is similar even when monkeys plan different motor commands. (D) Mean responses to near-threshold stimulus during the standard detection task (continuous red line) and during the two control conditions (broken red and blue lines).

Adapted from de Lafuente and Romo (2005).

rates should have been consistently higher for one movement but not to the other. The fact that all-or-none responses were still observed during these control tasks favors the hypothesis that this MPC population reflects the failure or success of the near-threshold stimulus in triggering a sensory percept.

2.5. Microstimulation of MPC triggers perceptual detection reports

Given the close association between MPC activity and the behavioral reports of stimulus detection, de Lafuente and Romo (2005) wondered whether artificial activation of MPC neurons through electrical microstimulation would increase the monkey's probability of detecting the vibratory stimuli. To test this, they injected a weak electrical current through the recording electrode in randomly selected stimulus-present and stimulus-absent trials. The resulting detection curves, separated into mechanical-plus-electrical, and mechanical-only curves (Fig. 5A), show that monkeys tended to answer "yes" more often on microstimulation trials than with mechanical stimuli only. The increased probability of "yes" responses observed during microstimulation trials agreed with the hypothesis that MPC activity is related to perceptual judgments. Finally, to further test whether artificial activation of MPC neurons could mimic neuronal activity related to sensory percepts, they carried out an experiment in which the mechanical vibrations were substituted by electrical stimuli of varying current strengths. Detection curves for purely electrical stimuli are shown in Fig. 5B, together with the detection curves for the mechanical stimuli that were randomly interleaved. Although it is difficult to compare these two stimulus quantities, the results show that psychometric performance based on microstimulation of MPC resembled that based on vibrotactile stimuli delivered to the skin.

2.6. Comments on the functional role of MPC in perceptual detection reports

Frontal lobe neurons, which are known to be involved in decision-making, working memory and motor planning, did seem to be fundamental to perceptual judgments during sensory

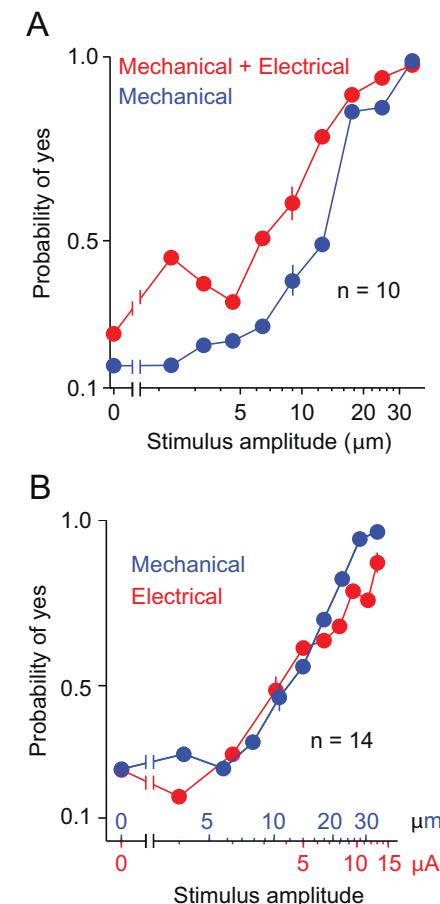


Fig. 5. Detection curves obtained during microstimulation of MPC. (A) Mean detection curves for mechanical stimuli and for mechanical-plus-electrical stimuli. Trials were randomly interleaved. (B) Mean detection curves for purely mechanical and electrical stimuli. Small vertical lines indicate SEM.

Adapted from de Lafuente and Romo (2005).

detection. This is consistent with the idea that perceptual judgments result from the interaction between internal signals (working memory, expectation, attention) and sensory inputs, because the MPC is ideally situated to integrate these different types of information. For the same reason, it is possible that other circuits of the frontal and parietal lobes also contribute to perceptual judgments in a similar way. An important clue about this interpretation is that the electrical current injected into MPC led to behavioral responses that resembled those elicited by mechanical vibrations, suggesting that, although it did not originate in S1, the artificial signal was still interpreted as sensory evidence. However, [de Lafuente and Romo \(2005\)](#) are uncertain of whether microstimulation in MPC evoked the same somatosensory sensation as that evoked by natural stimuli, despite the fact that they produced the same behavioral reactions. Another possibility is that microstimulation of MPC does not produce any somatic sensation but, instead, it activates a task rule such 'a stimulus is present'. In this manner, varying the microstimulation strength could vary the probability of engaging a population of MPC neurons associated with this rule, thus producing a psychometric detection curve similar to that produced by varying the mechanical stimulus strength.

The contribution of different cortical areas to perceptual processing has also been investigated using binocular rivalry and other paradigms in which a fixed but ambiguous visual stimulus gives rise to multiple, alternating percepts; that is, the same sensory input is consistent with multiple perceptual interpretations ([Leopold and Logothetis, 1996](#)). The results discussed above agree with these studies in that high-order cortices show much stronger correlations with behavioral (perceptual) reports than primary sensory areas.

2.7. Perceptual detection reports gradually build up across cortical areas

An important question posed by the above results is whether the neuronal correlates of the perceptual detection judgments arise abruptly in a given cortical area or whether they gradually build up as sensory information is transmitted across areas between S1 and MPC. [de Lafuente and Romo \(2006\)](#) addressed these questions by recording neurons in somatosensory cortices of the parietal lobe and premotor cortices of the frontal lobe while trained monkeys reported the presence or absence of a mechanical vibration of varying amplitude applied to the skin of one fingertip (Fig. 6A). These authors found that the activity evoked by the vibrotactile stimulus is distributed from early somatosensory cortices to a large number of areas, including association and motor areas. Fig. 6B shows that the majority of the recorded neurons across cortical areas transiently increase their firing rates in response to a suprathreshold stimulus. They also found a small number of neurons (<10%) that had transient decreases in their firing rate during the stimulus presentation. These responses were observed in the secondary somatosensory cortex (S2) and in the premotor areas only (ventral premotor cortex, VPC; dorsal premotor cortex, DPC and MPC). In addition, [de Lafuente and Romo \(2006\)](#) also recorded neurons in the frontal lobe that had sustained increased or decreased activity beginning during the stimulus onset and ending during the probe up, which triggered the initiation of decision motor report.

The responses in different cortical areas might play distinct roles in the processing of sensory stimuli. To test this possibility, [de Lafuente and Romo \(2006\)](#) measured to what extent the neuronal firing rate was modulated by the stimulus strength. They carried linear-regression analysis on the normalized firing rates as a function of stimulus amplitude across the recorded areas. Results show that the slopes of the fitted lines progressively approached

zero in neurons downstream to the primary somatosensory areas (Fig. 6C; linear fits were performed on the logarithm of stimulus amplitude and thus appear curved on a linear axis). The decreasing slope values imply that neuronal responses of higher-order areas do not encode stimulus amplitude with the same fidelity as those in early somatosensory cortex. Thus, the representation of the stimulus gradually transforms from a parametric one to a more abstract representation, all-or-none response that does not depend on the amplitude but only on whether the subject felt or missed the stimulus.

2.8. Covariations between responses across cortex and perceptual judgments

The mere fact that neurons respond during the detection task does not imply that they participate in the construction of a sensory percept. One way to estimate the relationship between the neuronal activities and the sensory reports is by means of the choice probability index ([Britten et al., 1996](#); [Green and Swets, 1966](#); [Hernández et al., 2002](#)). This quantifies the proportion of behavioral responses that can be predicted from single neuronal responses. By analyzing the neuronal responses to repeated presentations of the same near-threshold stimuli, [de Lafuente and Romo, 2006](#)) estimated the proportion of behavioral responses that could be predicted as a function of time and across cortical areas (Fig. 7). As reported before, S1 showed little predictive capacity regarding the behavioral outcomes in response to near-threshold stimulus presentations ([de Lafuente and Romo, 2005](#)). They also found that this was also the case for somatosensory areas 2 and 5, which showed choice probability indices close to 0.5. However, variations in the activity of S2 neurons onwards were correlated with the behavioral outcomes significantly above chance (Fig. 7). It must be noted that the predictive activity of S2 neurons was restricted to the stimulus period whereas neurons from VPC, DPC and MPC showed predictive activity also during the delay period between stimulus offset and the initiation of the decision motor report. Note also that primary motor cortex (M1) neurons showed no significant predictive activity. This result suggests that the activity in premotor cortices does not constitute a motor signal alone.

In addition to predicting whether subjects would fail (miss) or succeed (hit) to perceive the vibration in stimulus-present trials, premotor activity also predicted the behavioral outcome on stimulus-absent trials (this was made by calculating the choice probability index between correct reject and false alarm responses). In the majority of stimulus-absent trials the monkeys correctly answered "no" (correct reject), but on ~10% of trials monkeys erroneously answered "yes", producing a false alarm response. Remarkably, the neuronal activity from premotor areas predicted a significant fraction of these false alarm responses (Fig. 7, right column).

2.9. Timing of detection decision signals across cortical areas

The time it takes for a given area to start responding to the stimulus presentation can be related to the location of this area within the sensory processing hierarchy. To quantitatively address the relationship between the predictive capacity of neurons and the hierarchy of the recorded areas, [de Lafuente and Romo \(2006\)](#) plotted the choice probability indices as a function of the response latency (Fig. 8A). As evidenced by the 1-sigma contours of two-dimensional Gaussian fits ([Romo et al., 2002](#)), neurons located in areas with longer mean latencies (i.e., downstream in the processing stages) covaried with the subjects' perceptual reports. This increase in the predictive capacity of neurons can be also appreciated by plotting the mean choice probability index as a

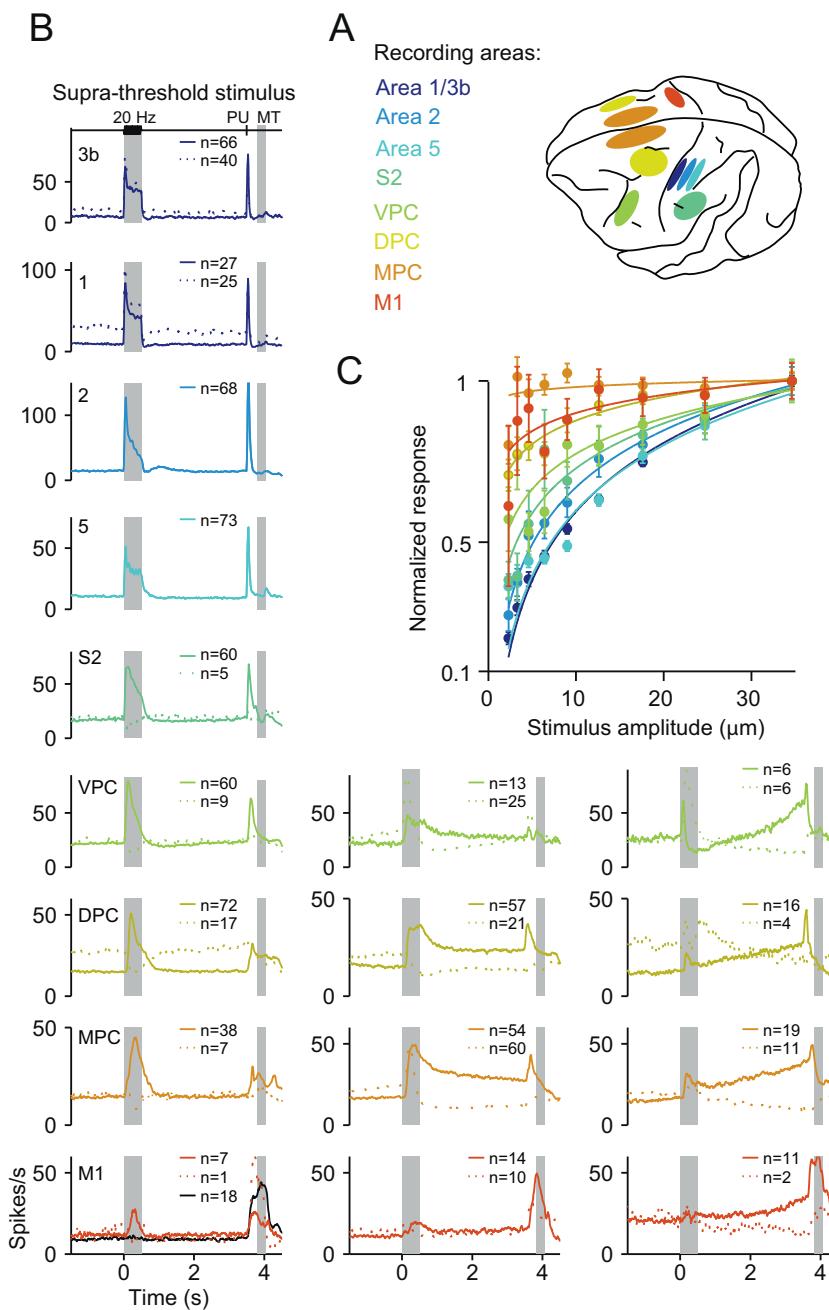


Fig. 6. Neuronal activity across cortical areas recorded during the vibrotactile detection task. (A) Recorded areas include 1/3b, 2, 5, second somatosensory cortex (S2), and ventral premotor cortex (VPC) on the left hemisphere; dorsal premotor cortex (DPC) and MPC bilaterally; and primary motor cortex (M1) on the right hemisphere. (B) Each row plots mean firing rates in a given cortical area, and each column groups the neuronal responses with similar dynamics. Neurons from each cortical area were sorted in three categories (ordered into three columns). Left column: neurons with transient responses to the stimulus. The continuous line indicates rapidly adapting responses and dashed lines indicate slowly adapting responses in areas 3b and 1. Solid red lines in the remaining panels show neurons that transiently decreased their firing rate in response to the stimulus. Red dashed line in M1 shows mean activity of neurons that activated only during the movement period. Center column: activity of neurons that responded during the stimulus period and remained active during the delay period. Right column: mean activity of neurons with ramping changes in firing rate during the delay period. (C) Mean normalized firing rates as a function of stimulus amplitude. Colored curves are linear fits to the firing rates as a function of the logarithm of stimulus amplitude. Adapted from de Lafuente and Romo (2006).

function of the mean response latency for each cortical area (Fig. 8B). M1 was excluded from the regression analysis because the majority of neurons showed responses during the movement period and only a small fraction of them weakly responded to the stimulus (Fig. 6B).

de Lafuente and Romo (2006) also tested whether the choice probability values were correlated with the response latency in neurons within each cortical area. As evidenced by the positive slope of the major axis of the ellipses, the choice probability indices for neurons within areas VPC, DPC and MPC were positively

correlated with the response latencies. This means that even neurons within the same processing stage tended to be more correlated with the subjects' perceptual reports if their responses to the stimulus appeared later.

To further analyze the information flow between the recorded cortical areas, de Lafuente and Romo (2006) performed an analysis of variance on the response latencies, followed by a Tukey's multiple comparison test (Daniel, 2009). This analysis showed that the cortical areas could be arranged according to the response latency into 5 possible processing stages (Fig. 8C). Neuronal

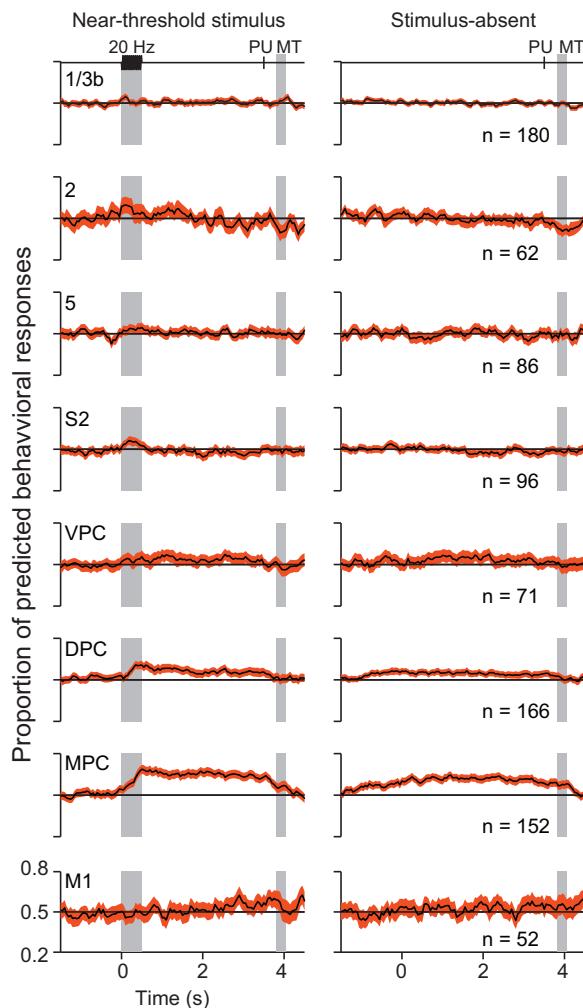


Fig. 7. Proportion of behavioral responses that can be predicted from the neuronal activity. Mean choice probability indices are plotted as a function of time for each cortical area. Left column: stimulus-present trials. Right column: stimulus-absent trials. Note how choice probability values increase from the primary sensory areas to the premotor areas (black lines indicate mean values and red areas SEM). Adapted from de Lafuente and Romo (2006).

responses appear first in areas 1/3b, then in area 2. After this, responses to the stimulus appear simultaneously in S2 and area 5 (response latencies of these two areas are statistically indistinguishable). The fact that the responses appear simultaneously in these two areas is consistent with the idea of parallel ventral and dorsal streams of somatosensory information processing (Mishkin, 1979). However, the fact that S2 neurons showed larger choice probability indices suggests that this area is more related to the detection task than area 5.

Responses to the vibratory stimulus appear then in the DPC and the VPC, which correspondingly show more predictive capacity about the subjects' perceptual reports than early sensory areas (Fig. 8B). Finally, the statistical tests showed that the last responses to the stimulus appear in neurons from M1 and MPC. It is important also to note that the choice probability index reaches its maximum value in area MPC, and drops to chance levels in the neurons from M1.

2.10. Sensory versus motor responses across cortex during perceptual detection reports

The results reviewed above show that neurons from the frontal lobe relate to the subjects' perceptual reports. However, an

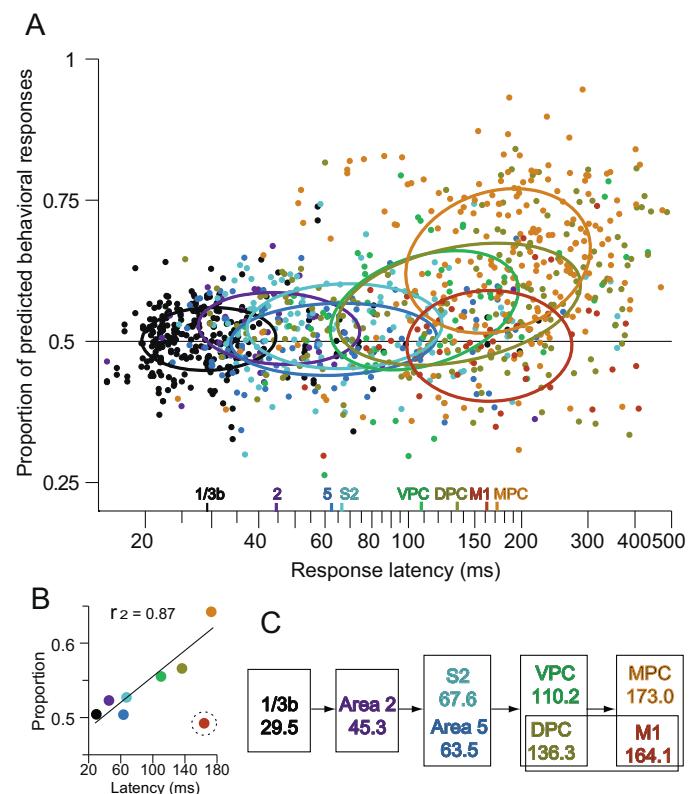


Fig. 8. The ability to predict the behavioral responses increases with time as information is transmitted across cortical areas. (A) Choice probability indices of individual neurons plotted as a function of response latency for each cortical area. Neurons from each area were fitted with two-dimensional Gaussians. Color markings at the abscissa indicate mean response latency for each cortical area. (B) Mean choice probability index for each cortical area plotted as a function of mean response latency. A linear fit illustrates the increase in choice probability indices as a function of latency (M1 neurons were excluded from the fit (red dot and dotted circle)). (C) Recorded areas grouped into five processing stages by an analysis of variance on response latencies. Each rectangle groups the areas with latencies that were statistically indistinguishable from each other.
Adapted from de Lafuente and Romo (2006).

alternative interpretation of these results is that, instead of relating to a sensory percept, responses of frontal lobe neurons are more likely associated with the motor plan implemented during the detection task. To evaluate the influence of movement direction on the neuronal responses, de Lafuente and Romo (2006) carried control experiments in which the correct response button was illuminated at trial beginning. In this condition the monkeys were not required to attend the vibratory stimuli but just to press the illuminated button at the end of each trial to get a reward. Importantly, in the control task the response buttons were reversed so that monkeys had to push the "no" button in stimulus-present trials and the "yes" button in stimulus-absent trials. The control task provided a condition in which both the decision to make a movement and the movement direction were given at trial beginning. If the predictive activity we observed in the frontal lobe were due to the decision process or to the onset of a motor plan we would expect this activity to be modified by the onset of the light cue and the reversed movements.

Comparison of activity in detection and control trials revealed that, although some areas showed significant changes in basal firing rates, responses to the stimulus were neither abolished nor changed in sign. In other words, increases or decreases in the firing rates observed during the normal detection task were also observed during control trials. These results do not support the view that the predictive activity recorded in the frontal lobe is due to motor planning only.

2.11. Perceptual reports are gradually constructed across cortex

Analysis of the relationship between the neuronal responses and stimulus amplitude revealed that the activity of early somatosensory areas encode the stimulus strength. This sensory representation gradually transforms, starting in the somatosensory areas S2 and area 5, into an all-or-none response in the premotor areas of the frontal lobe that highly covaries with the monkeys' reports about the presence or absence of the vibratory stimulus.

Choice probability analysis revealed that neuronal activity in response to the stimulus spreads from the somatosensory cortex to the premotor areas within a 180 ms period, and it progressively correlates more with the subjects' perceptual reports. This gradual increase in the choice probability across the cortical hierarchy is consistent with the hypothesis that sensory perception develops through time and across cortical areas. This might also suggest that no particular area plays a preponderant role in the sensory-to-motor transformation leading from a stimulus representation to a perceptual report.

The hierarchy suggested by the statistical analysis of neuronal response latencies across cortical areas seems to favor a serial processing. However, it must be noted that there is high variability in response latencies and a high amount of overlap across the recorded areas (Fig. 8A). This overlap reveals that there are some neurons from higher cortical areas that show shorter latencies than some neurons from lower cortical areas. This leaves room for feedback inputs from higher to lower areas, a process that has recently been acknowledged to play important roles in sensory processing (Pascual-Leone and Walsh, 2001).

Because the neuronal activity with the highest correlation with perceptual reports was recorded in the premotor areas, a trivial explanation of the results would be that this activity is related to the motor component of the detection task. We don't think this explanation is satisfactory because the control task of reversed movements guided by visual cues shows that basal neuronal activity was only weakly modulated by the direction of movement. In addition, given that the light cues indicated the correct response button at trial beginning, we consider unlikely the possibility that the responses to the stimulus could be due to motor processes. The fact that neurons from M1 do not show large predictive capacities renders the motor explanation unlikely.

The picture of somatosensory processing that has emerged from the experiments is far from complete. For instance, there are many areas that were not record from, that nonetheless are known to show somatosensory responses (Robinson and Burton, 1980). However, we think the results are complete enough to show that the activity arising from somatosensory cortex gradually relates more to the subjects' perceptual reports as it reaches the premotor areas. These results are consistent with observations in the frontal eye field of monkeys performing a masking task (Thompson and Schall, 1999, 2000). In this task, the monkeys reported the location of a briefly flashed visual cue that was rapidly substituted by a masking stimulus. Responses of frontal eye field neurons were highly correlated with the subjects' behavioral reports, whereas neurons in areas closer to the periphery did not.

To conclude, the gradual transformation of a sensory representation might be a fundamental process by which the cortex builds up a sensory percept. This is evidenced by the fact that covariations between the neuronal responses and perceptual reports grow across cortical areas, from lower covariations detected in early sensory cortices to higher covariations detected in frontal lobe neurons. Thus the subjective sensory experience might be consolidated in the frontal lobe (de Lafuente and Romo, 2005, 2006), after a gradual transformation of the sensory representation. This interpretation is also supported by the fact that in the absent-stimulus trials, the activity of frontal lobe neurons

predicted the false alarms, whereas the somatosensory areas of the parietal lobe did not. One limitation of the present data set, however, is that neurons in different areas were recorded separately, so it is very likely that de Lafuente and Romo (2006) have missed important functional relations between neurons within and across the processing stages. In the future, more information about the neuronal correlates of sensory and perceptual transformations and about the dynamics of real-time neuronal interactions should be obtained by using multiple-site simultaneous recordings and more demanding perceptual tasks.

3. Sensory discrimination

The results reviewed above show the neural operations across diverse cortical areas that are engaged by a sensory detection task. However, a detection report results from the combination of an internal representation of the "task rule" with the current sensory input. The mnemonic processes associated with this internal representation can not be studied with a detection task. To further address this problem we require a cognitive task, where the subject is forced to combine present and past sensory information and that the result of this operation can be decoded from the neuronal responses. An interesting cognitive task – sensory discrimination – was introduced by Mountcastle and colleagues several years ago (LaMotte and Mountcastle, 1975; Mountcastle et al., 1972, 1990), and served to Romo and colleagues (Barak et al., 2010; Brody et al., 2003; Chow et al., 2009; Deco et al., 2010; Hernández et al., 1997, 2000, 2002, 2010; Kun et al., 2010; Lemus et al., 2007, 2010; Luna et al., 2005; Machens et al., 2005, 2010; Martínez-García et al., 2011; Romo et al., 1998, 1999, 2000, 2003, 2004; Salinas et al., 2000) to further explore the role of sensory cortices in working memory and perceptual decision making. In the discrimination task they designed (LaMotte and Mountcastle, 1975; Mountcastle et al., 1990), animals had to indicate whether the frequency of a comparison stimulus (f_2) was lower or higher than the frequency of a base stimulus (f_1) presented earlier (Fig. 9A). In principle, this task can be conceptualized as a chain of neural operations or cognitive steps: encoding f_1 , maintaining it in working memory, encoding f_2 and comparing it to the memory trace left by f_1 , and communicating the result of the comparison to the motor apparatus. Thus the vibrotactile discrimination task offers a number of advantages as a model for sensory processing in the brain (Romo and Salinas, 2001, 2003): not only do humans and monkeys perform similarly, but the items to be compared are spread out across time and always activate the same, well-defined population of primary receptors (Macefield et al., 1990; Mountcastle et al., 1967; Ochoa and Torebjörk, 1983; Talbot et al., 1968; Vallbo, 1995; Vallbo and Johansson, 1984). So spatial variations are basically taken out of the picture (Connor et al., 1990). However, for the vibrotactile discrimination task to be a useful model it is essential that it generates a reliable sequence of cognitive events like the ones just mentioned. How do we know that this is so?

3.1. Optimal conditions for studying the neuronal correlates of sensory discrimination

A crucial step is to scrutinize the psychophysics. Importantly, in the original paradigm the base frequency (f_1) did not vary from trial to trial during a run (LaMotte and Mountcastle, 1975; Mountcastle et al., 1990). When Romo and colleagues (Hernández et al., 1997) re-examined the flutter discrimination task, they found the paradigm to be ambiguous: when f_1 is kept constant, the task can be solved either by comparing the two stimuli or by categorizing f_2 as "high" or "low", ignoring f_1 . What were the monkeys actually doing? When f_1 was held constant during long blocks of trials, as done originally, the discrimination thresholds

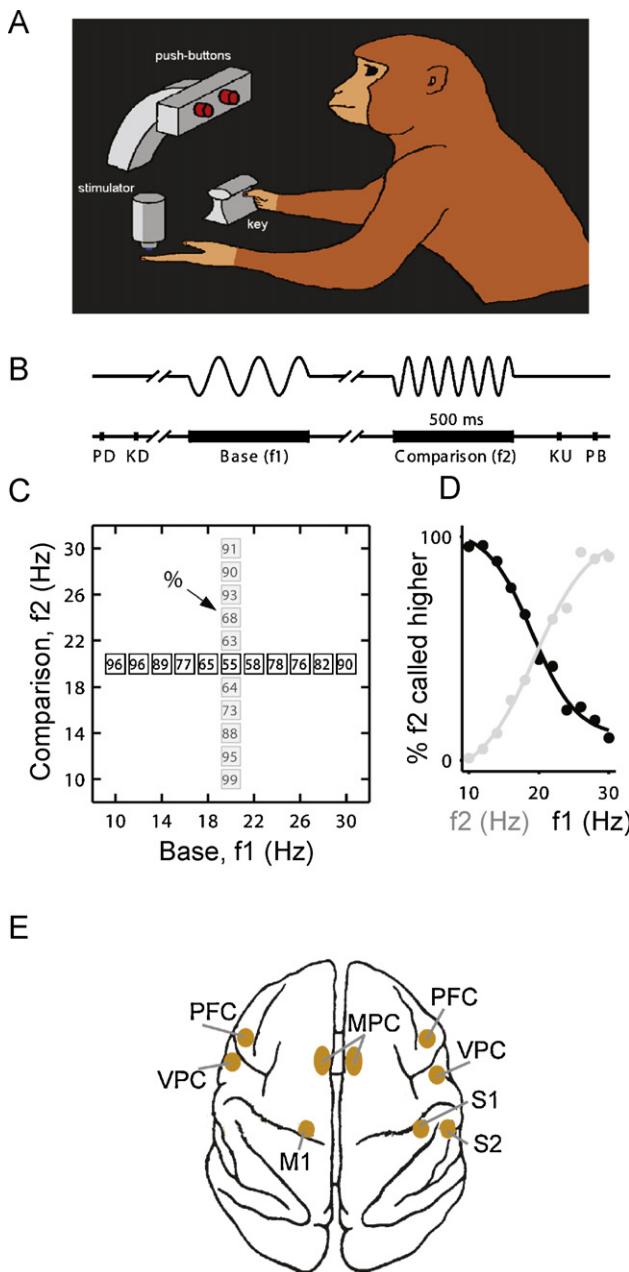


Fig. 9. Discrimination task. (A) Drawing of a monkey working in the discrimination task. (B) Sequence of events during the discrimination trials. Trials began when the stimulation probe indented the skin of one fingertip of the left, restrained hand (probe down, PD). The monkey then placed its right, free hand on an immovable key (key down, KD). The probe oscillates at the base frequency (f_1), after a delay (3 s), a second mechanical vibration is delivered at the comparison frequency (f_2). The monkey then releases the key (KU) and presses either the medial or lateral push-button to indicate whether the comparison frequency was lower or higher than the base frequency. (C) Stimulus pairs used during recordings. The number inside the boxes indicate mean percentage of correct trials for each base/comparison pair (for the 20/20 Hz pair, it is the percentage of responses in which the animal pressed the lateral push button). (D) Psychophysical performance when f_1 was maintained fixed at 20 Hz and f_2 was variable (gray curve), and when f_2 was fixed at 20 Hz and f_1 was variable (black curve). (E) Top view of the monkey brain and the cortical areas recorded during perceptual discrimination (orange spots). Recordings were made in primary somatosensory cortex (S1) and secondary somatosensory cortex (S2) contralateral to the stimulated hand (right hemisphere) and in primary motor cortex (M1) contralateral to the responding hand/arm (left hemisphere). Recordings were made contralateral and ipsilateral to the stimulated fingertip prefrontal cortex (PFC), ventral premotor cortex (VPC), and medial premotor cortex (MPC).

Adapted from Hernández et al. (1997).

and Weber fractions were similar to those reported before. If the monkeys had been discriminating the differences in frequency between the two stimuli, they would also have been able to do so when the frequency of f_1 changed from trial to trial. However, this was not the case: their performance dropped to chance levels. It seemed that the monkeys were paying attention only to f_2 , categorizing it as low or high with respect to an internal reference, perhaps the frequency of f_1 used during training. To test this possibility, in separate runs f_1 was removed and single stimuli were delivered in each trial. In this new condition the monkeys were rewarded for correctly categorizing stimulus frequency as lower or higher than an arbitrary reference (20, 30, or 40 Hz) kept constant during a block of trials; monkeys had to determine this reference by trial and error. The monkeys learned this task very quickly, and the psychometric curves (Hernández et al., 1997) measured in this condition were practically identical to those measured during the classical discrimination task (Mountcastle et al., 1990).

For true discrimination, monkeys were retrained using multiple pairs of base and comparison frequencies (Fig. 9B and C). The key was to vary f_1 in each trial but such that each frequency could be followed either by a higher or a lower comparison; this forced the subjects to compare (Hernández et al., 1997). After retraining, which took a few months, performance in this situation was similar to that in the classical discrimination task (Fig. 9D). From these results it seems almost certain that the animals truly learned to discriminate between frequencies on a trial-by-trial basis.

The lesson is that, although monkeys may indeed learn to discriminate, they can also develop alternate strategies to solve the task, as suggested earlier based on theoretical arguments (Johnson, 1980). In particular, in the classical vibrotactile discrimination paradigm monkeys tend not compare the two stimuli at every trial; instead they classify f_2 , possibly setting the limits of each category during the first few trials in a run. Whenever animals are assumed to discriminate, this problem should not be underestimated, regardless of the sensory modality (Johnson, 1980; Vogel and Orban, 1990; Vázquez et al., 2000).

This appears as a simple observation, but it may reflect fundamentally different mechanisms at work. Consider a task that involves variations in a single feature across trials. To identify or classify a current sensory stimulus, it must be compared to a reference stored in long-term memory, but it is not clear how the comparison process can be studied in this situation. How is information stored in long-term memory read out and made comparable to current sensory events? Where is this information stored and how does it differ from the original sensory-evoked activity? In contrast, in discrimination tasks in which two stimuli are presented sequentially in each trial, the comparison is made against the short-term memory trace left by the first stimulus. This means that if we can identify the neural correlate of the working-memory component, it might be possible to study the comparison or decision-making mechanisms that underlie task performance. Indeed, such neural correlate has been recently reported (Barak et al., 2010; Brody et al., 2003; Chow et al., 2009; Kun et al., 2010; Hernández et al., 2002, 2010; Lemus et al., 2007; Machens et al., 2005; Romo et al., 1999, 2002, 2004). Below we describe the neuronal correlates associated with the different task components of the vibrotactile discrimination task.

3.2. Neural coding of vibrotactile stimuli in S1 during discrimination

Mountcastle et al. (1990) recorded S1 (Fig. 9E) responses in behaving monkeys trained to discriminate the frequencies of vibrotactile stimuli. The results support previous findings (Mountcastle et al., 1969). First, it was found that quickly adapting (QA) neurons of S1 (areas 3b and 1), like their afferent fibers, 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, 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, stimulus frequency could not be encoded by S1 firing rates; stimulus frequency had to be encoded temporally, in the serial order of evoked spikes (Mountcastle et al., 1969, 1990; Talbot et al., 1968).

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 stimulus frequency (however, the range of frequencies tested was quite narrow, and 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 to untrained monkeys. Thus, based on these results, a psychophysical observer should exploit the periodic spike timing evoked in the QA neurons of S1 cortex for sensory discrimination.

Arguments in favor of the proposal reviewed above could be strengthened if a large number of neurons were studied, and if neurons were studied in behaving animals during the vibrotactile discrimination task. To this end, Romo and colleagues trained monkeys to discriminate between vibrotactile stimulus frequencies and recorded many neurons with QA properties in areas 3b and 1 of S1 (Hernández et al., 2000, 2010; Lemus et al., 2010; Luna et al., 2005; Salinas et al., 2000). 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 (Fig. 10A); however, almost a third of QA neurons modulated their firing rates as a function of the stimulus frequency (Fig. 10D; Hernández et al., 2000, 2010; Lemus et al., 2010; Luna et al., 2005; 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 neurons that varied their firing rates as a function of the stimulus frequency were affected in error trials (Salinas et al., 2000).

These findings question a unique role of periodic, spike timing in discrimination of vibrotactile stimuli, and suggest that a firing rate code cannot be discarded (Salinas et al., 2000). But, apart of this, what do these findings suggest? They suggest the presence of two sub-populations of QA neurons in S1 which behave differently in response to a periodic mechanical stimulus (Hernández et al., 2000, 2010; Lemus et al., 2010; Luna et al., 2005; Salinas et al., 2000). These two sub-populations might be arranged in hierarchical fashion: QA neurons that respond periodically might be closer to the input stimulus, and those that modulate their firing rates 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.

3.3. Neuronal correlates of sensory discrimination in S1

A more direct test for the role of periodicity in sensory discrimination is measuring the discrimination capabilities of these subtypes of QA neurons associated with the psychophysical performance (Fig. 10B and C). A second test is to prove whether the

evoked neural activity during discrimination in S1 cortex is sufficient for sensory performance (see Section 3.4). Finally, whether the temporal order of the spikes elicited by the periodic stimuli is important for sensory discrimination. These are incisive tests to validate the meaning of the neural encoding of the vibrotactile stimuli in S1 cortex.

The vibrotactile discrimination task requires the comparison of f_2 against f_1 (Hernández et al., 1997). As indicated above, Romo and colleagues found two types of responses in QA neurons of S1 cortex: one that is periodically entrained by the stimulus frequency (Fig. 10A), and a second that, although not periodically entrained, has average firing rates during the stimulus period that are modulated as a function of the stimulus frequency (Fig. 10D; Hernández et al., 2000, 2010; Lemus et al., 2010; Luna et al., 2005; Salinas et al., 2000). To investigate which of these two representations is associated with the psychophysical performance, these authors determined the probability that an observer (a cortical region central to S1 cortex) could distinguish the difference between the two stimuli (Hernández et al., 2000; Salinas et al., 2000; Luna et al., 2005). This could be based on a comparison of the neuronal response distributions elicited by f_2 made against the neuronal response distributions elicited by f_1 . According to this, the observer could use a simple rule: if the number of spikes during f_2 is higher than during f_1 , then f_2 is higher than that of 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 f_2 period is higher than during the f_1 period, 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 (receiver operating characteristic; Green and 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; Luna et al., 2005). The areas under each of these two ROC curves are an estimate of the proportion of correct trials that an optimal observer would obtain by comparing numbers of spikes or periodicity. In pairs of stimulus frequencies where the neuronal response distributions during f_2 are much higher than the neuronal response distributions during f_1 , ROC values are close to 1; if the neuronal response distributions during f_2 are much lower than the neuronal response distributions during f_1 , ROC values are close to 0; for overlapping distributions, intermediate ROC values of 0.5 are found. The ROC values were then used to compute 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 terms of Hz. Using this analysis, Romo and colleagues (Hernández et al., 2000; Luna et al., 2005) were in the position to address the question of which of the two representations is meaningful for frequency discrimination.

Neurometric functions based on periodicity (Fig. 10B) or firing rate (Fig. 10E) of single S1 neurons were directly compared to the psychometric thresholds (Hernández et al., 2000; Luna et al., 2005). The results of this analysis show that neurometric threshold values based on periodicity are far lower than psychometric thresholds (Fig. 10C). This is not the case when neurometric thresholds based on firing rate are compared to the psychometric thresholds (Fig. 10F). 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 behavior. However, what is then 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

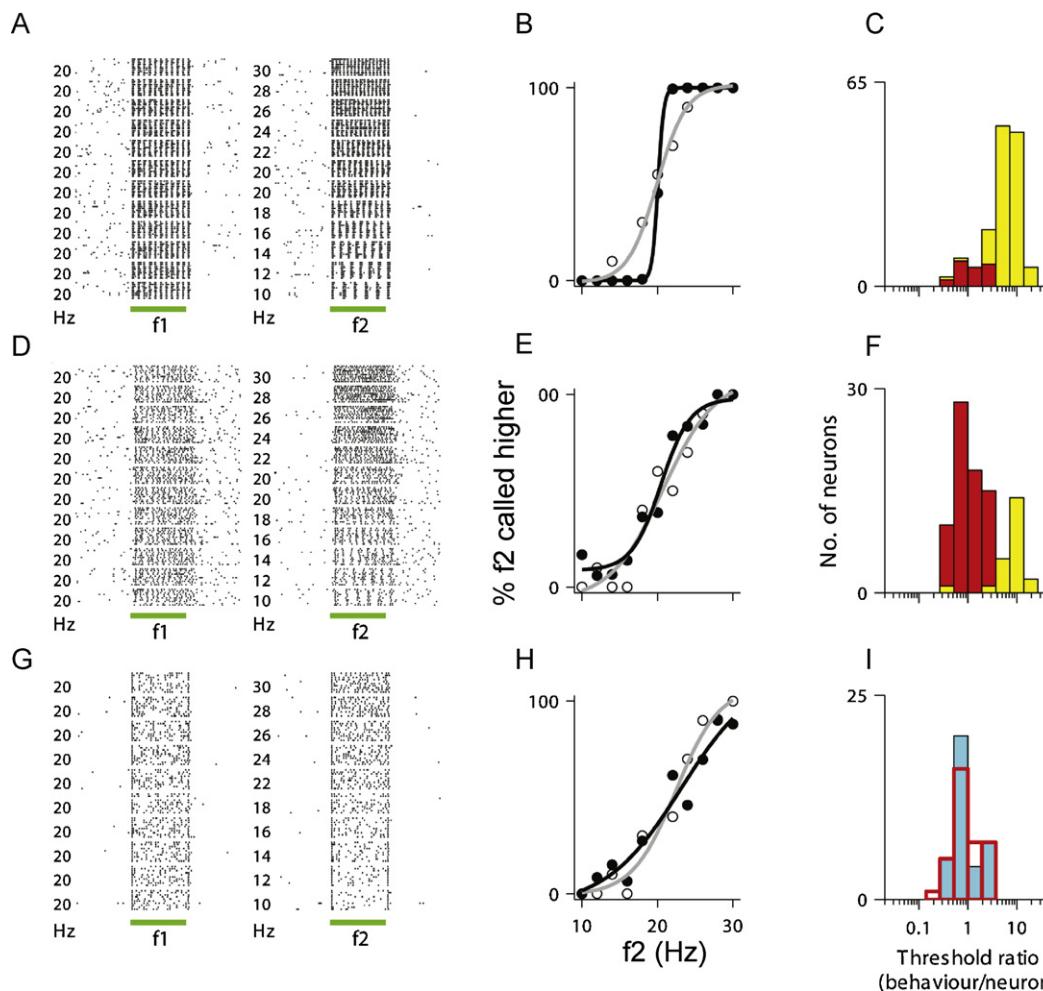


Fig. 10. Comparison between S1 activity and psychophysical performance. (A, D, G) Responses of three area 1 neurons recorded during discrimination. Each line represents a trial and each dot an action potential. Trials were delivered randomly. Green lines mark stimulation periods; first (f_1) and second (f_2) stimulus frequencies are indicated. (A) Responses showing little rate modulation but faithfully reflecting the periodicity of the stimuli. (D) Responses showing strong rate modulation but little regularity in spike timing relative to the periodic stimuli. (G) Responses to aperiodic stimuli. (B, E, H) Psychometric and neurometric curves. Y-axis is percentage of trials in which f_2 was called higher than f_1 , where f_1 was 20 Hz. Open circles and gray curves correspond to monkey's performance. Filled circles and black curves indicate performance of an ideal observer that based his decisions on the responses of a single neuron. Continuous lines are sigmoidal fits to the data; the discrimination threshold is inversely proportional to steepness. (B) Performance of the ideal observer was based on the periodicity of the neuron in (A). (E, H) Performance of the ideal observer was based on the firing rates of the neurons in (D) and (G), respectively. (C, F, G) Numbers of S1 neurons with the indicated threshold ratios. In (C) and (F), neurometric thresholds based on spike-train periodicity (yellow bars) were much smaller than those based on mean firing rate modulation (red bars), which matched the behavioral thresholds. (I), Threshold ratios based on mean firing rates evoked by aperiodic stimuli (cyan bars) were similar to those obtained with periodic stimuli (open bars).

Adapted from Hernández et al. (2000).

exquisite representation for frequency discrimination. This would be the case if, for example, discrimination were 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, Romo and colleagues (Hernández et al., 2000; Luna et al., 2005) found that QA neurons in S1 whose firing rates are modulated by the stimulus frequencies and their neurometric thresholds based on firing rates are closely to the monkey's psychophysical thresholds (Fig. 10F). However, these correlations do not prove they are sufficient for discrimination (Romo et al., 1998, 2000).

One experiment, which could give an insight about the functional meaning of the periodic spike structure of the evoked activity in S1, is testing whether monkeys could discriminate the difference between the two stimuli when periodicity is broken. If monkeys fail to discriminate the difference in mean frequency between the two stimuli, this would strengthen the proposal that discrimination of vibrotactile stimuli depends on the periodic structure of the spike trains evoked in S1 (Fig. 10A–C). However, monkeys were able to extract the mean frequency from the

non-periodic signals and the psychophysical measures were almost identical with the periodic stimuli (Fig. 10G–I; Romo et al., 1998).

Romo and colleagues then studied QA neurons in each of two conditions: while monkeys discriminated between periodic stimuli, and while monkeys discriminated aperiodic stimuli (Hernández et al., 2000; Luna et al., 2005; Salinas et al., 2000). Due to the aperiodic stimulus design, even highly stimulus-trained neurons do not carry information about stimulus frequency in their periodicity (Fig. 10G). Clearly, neurometric thresholds based on the firing rate were again closely associated with the psychometric thresholds (Fig. 10H and I). As in the periodic condition, a psychophysical observer could exploit firing rate for frequency discrimination of aperiodic stimuli. These results suggest that an observer could solve this task with a precision similar to that of the monkey, based only on the firing rate produced during the stimulus periods.

There are, however, some further unexplored possibilities. For example, QA neurons of S1 typically respond to each stimulus

pulse with a discrete burst of spikes. Encoding of vibrotactile stimuli could therefore be based on the number or rate of events, where each event is defined as a burst instead of being defined as a single spike. An observer counting bursts would obtain a good estimate of the count of stimulus pulses, and this estimate would be independent of variability in the number of spikes fired in response to each pulse. Indeed, there is experimental evidence suggesting that bursting activity could efficiently encode the stimulus features (Reinagel et al., 1999; Martínez-Conde et al., 2000; Kepcs et al., 2002; Krahe and Gabbiani, 2004). But whether bursting actually contributes directly to the psychophysical behavior is not known (Luna et al., 2005). Finally, the temporal window on which vibrotactile discrimination is based has not been determined. In Romo and colleagues previous experiments, stimulus periods were always 500 ms long. Under those conditions, the use of a code based on counting events and the use of a code based on the rate of events could not be distinguished.

To distinguish between all these alternatives, Romo and colleagues conducted new combined psychophysical and neurophysiological experiments in the vibrotactile discrimination task (Luna et al., 2005). They reasoned that if an observer uses firing rate, bursting rate, or a measure of periodicity, then increases or decreases in the duration of either of the two stimuli used in each trial of the task should not lead to a systematic bias in

discrimination, in either of the two possible directions. (On the other hand, under this hypothesis stimulus duration could affect the sensory signal-to-noise ratio and therefore affect the psychometric threshold.) Alternatively, if the observer uses a strategy based on the total number of spikes or bursts fired in response to each stimulus, then manipulation of the stimulus duration should systematically bias performance, with longer stimuli being perceived as having been of higher frequencies than they actually were. Romo and colleagues found that when the duration of one of the two stimuli was changed by 50% relative to the other stimulus, monkeys indeed biased their discrimination performance (Luna et al., 2005). Monkeys treated shortened stimuli as if the applied stimulus frequency had been slightly but significantly lower than it actually was; conversely, monkeys treated lengthened stimuli as if the applied frequency had been slightly but significantly higher than it actually was. These effects were observed with both periodic and aperiodic stimuli (Fig. 11A and B). These investigators then sought an explanation for these psychophysical biases by recording QA neurons of S1 while the monkeys performed in variable-stimulus-length conditions (Luna et al., 2005). They found that the effects can be qualitatively explained if one assumes that the neural signal used by the observer to solve the task is an integral of either spikes or bursts over a time window that concentrates most of its mass within the first 250 milliseconds of the stimulus, but also has a small tail into later parts of the stimulus (Fig. 12). Finally, examining trial-by-trial covariations of weighted counts of spikes and weighted counts of bursts, they found that only the weighted count of spikes covaried with performance on a trial-by-trial basis (Luna et al., 2005).

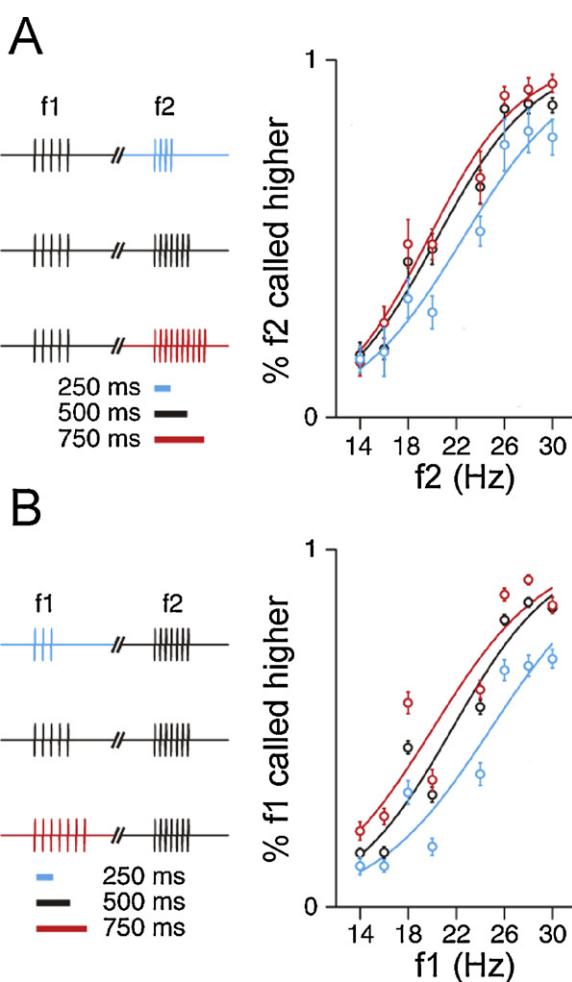


Fig. 11. Psychophysical performance during manipulation of one of the two stimuli. (A) Psychophysical performance when the duration of the second (f_2) periodic stimulus increased (red) or decreased (cyan) with respect to the first (f_1) periodic stimulus. (B) Psychophysical performance when the duration of the periodic f_1 stimulus increased (red) or decreased (cyan) with respect to f_2 .

Adapted from Luna et al. (2005).

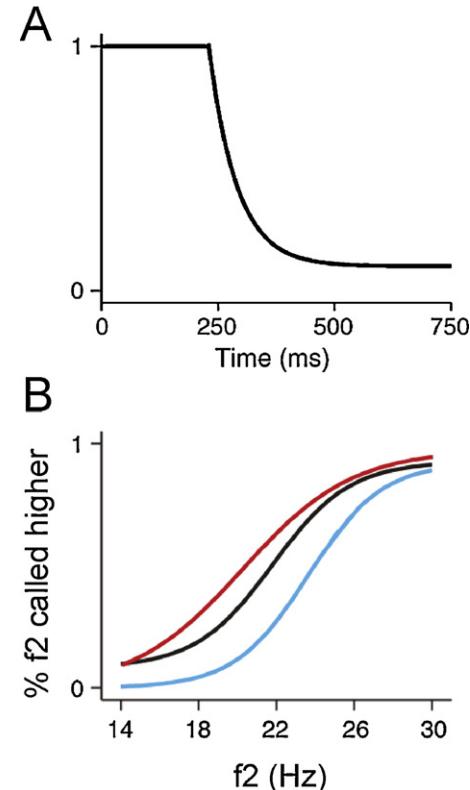


Fig. 12. The weight of sensory evidence might vary as a function of time. (A) A weighting filter that is consistent with the biases observed in psychometric and neurometric curves assigns more weight to the sensory responses evoked during the first 250 ms of the stimulus. The window measures spike events and produced neurometric curves shown in (B). Red curve when f_2 was increased as in (A) of Fig. 11. Cyan curve when f_2 was decreased as in Fig. 11 (A). Adapted from Luna et al. (2005).

In brief, firing rates that vary as functions of stimulus frequency are seen in multiple areas activated during the task, and there is evidence that these rate variations have a significant impact on behavior. Clearly, the brain must be able to extract at least some information from the precise timing of S1 spikes evoked during the task; for instance, humans can easily distinguish periodic stimuli from aperiodic. However, Romo and colleagues (Hernández et al., 2000, 2010; Luna et al., 2005; Salinas et al., 2000) found no indication that the high periodicity found in S1 contributes to frequency discrimination, although this possibility is hard to rule out entirely. There is evidence from human psychophysical experiments indicating that areas beyond primary somatosensory cortices do not encode the stimulus temporal characteristics, but only the mean vibration frequency (Harris et al., 2006). In agreement with this view, it has been demonstrated that a firing rate code is sufficient to support discrimination of rough and smooth textures by the rat barrel cortex (von Heimendahl et al., 2007).

3.4. Artificial induction of activity in S1 underlying sensory discrimination

How can we be sure that the activity recorded in S1 is actually related to perception and behavior? There are two experimental approaches to test this. First, we could remove S1 and test the subject's discrimination performance. Although this has not done in the vibrotactile discrimination task, Romo and colleagues (Zainos et al., 1997) lesioned S1 and then tested the capabilities of monkeys to categorize the speed of a mechanical probe that was displaced over the skin. Animals were never able to recuperate the categorization capabilities shown before the S1 lesion. Therefore, it is very likely that vibrotactile discrimination performance would disappear after a S1 lesion. The second approach is intracortical microstimulation (Fig. 13A), which is a powerful technique capable of establishing a causal link – not just a correlation – between the activity of localized neuronal populations and specific cognitive functions (Britten and van Wezel, 1998; de Lafuente and Romo, 2005; Romo et al., 1998, 2000; Salzman et al., 1990). For vibrotactile discrimination, this approach has provided the most compelling evidence that all the cognitive processes of the task may be triggered directly by the QA circuit in S1, and has also allowed Romo et al. (1998, 2000) to test questions about the neural code for vibrotactile stimuli. Importantly, S1 is organized in modules of neurons sharing the same receptive field and mechanoreceptor submodality (Mountcastle, 1957; Powell and Mountcastle, 1959; Sur et al., 1984). The experiments described below, were aimed to drive a column(s) of S1 – mostly of the QA type – in a way that matched the dynamic responses recorded when mechanical stimuli were applied to a patch of skin of the fingertips.

The original idea of these experiments was to manipulate the comparison stimulus only (Romo et al., 1998). The monkeys first learned to discriminate the frequencies of two sinusoidal vibrations delivered successively to the fingertips. Once they mastered the discrimination task, neurophysiological recordings were made in area 3b of S1, which allowed the identification of clusters of QA neurons. An applied microstimulation current spreads around a certain cortical area, activating many neighbouring units. Thus, a key for the success of microstimulation experiments is that the microelectrode must be located in the midst of a functionally homogeneous cluster of neurons. Fortunately, area 3b is indeed organized into modules of units with similar properties, or columns (Sur et al., 1984). So, having identified a set of QA neurons, the comparison stimulus was substituted with microstimulation in half of the trials. Artificial stimuli consisted of periodic current bursts delivered at the same comparison frequencies as mechanical stimuli. Microstimulation sites in S1

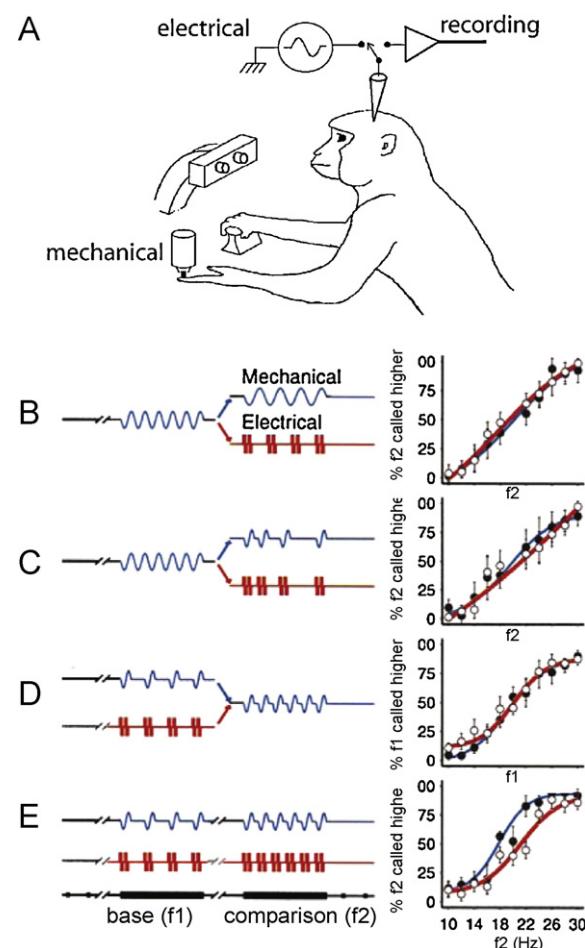


Fig. 13. The mechanical stimulation of the skin can be substituted by direct electrical microstimulation of S1 neurons. (A) Monkeys were first trained to compare two mechanical stimuli presented sequentially on the fingertips (Fig. 9). Then some of the mechanical stimuli were replaced by trains of electric current bursts microinjected into clusters of quickly adapting neurons in area 3b. Each burst consisted of two bi-phasic current pulses. Current bursts were delivered at the same comparison frequencies as natural stimuli. In half of the trials the monkeys compared two mechanical vibrations delivered on the skin; in the other half one or both stimuli were replaced by microstimulation. The two trial types were interleaved, and frequencies always changed from trial to trial. The diagrams on the left show four protocols used. The curves on the right show the animals' performance in the situations illustrated on the left. Filled and open circles indicate mechanical and electrical stimuli, respectively; continuous lines are fits to the data points. (B) All stimuli were periodic; the comparison stimulus could be either mechanical or electrical. (C) The base stimulus was periodic and the comparison aperiodic; the comparison could be mechanical or electrical. (D) All stimuli were periodic; the base stimulus could be mechanical or electrical. (E) All stimuli were periodic; in microstimulation trials both base and comparison stimuli were artificial. Vibrotactile stimuli were either sinusoids or trains of short mechanical pulses, each consisting of a single-cycle sinusoid lasting 20 ms. Monkeys' performance was practically the same with natural and artificial stimuli. Adapted from Romo et al. (1998, 2000).

were selected to have QA neurons with receptive fields on the fingertip at the location of the mechanical stimulating probe. Remarkably, the monkeys discriminated the mechanical (f_1) and electrical (f_2) signals with performance profiles indistinguishable from those obtained with mechanical stimuli only (Fig. 13B), so the artificially-induced sensations probably resembled natural vibration quite closely (Romo et al., 1998).

Going back to the question of whether periodicity is crucial for frequency discrimination, Romo et al. (1998) applied aperiodic microstimulation patterns that mimicked the random trains of mechanical pulses discussed earlier (Fig. 13C). The same mean frequencies were used in this condition – 20 Hz still corresponded

to 10 current bursts delivered in 500 ms — but the bursts were separated by random time intervals. Everything else proceeded as before, with mechanical and stimulation trials interleaved, as indicated in Fig. 13B. From the very first trials, the animals were able to discriminate both mechanical and electrical aperiodic signals (Fig. 13B), with practically the same performance level reached with mechanical, periodic vibrations (Romo et al., 1998).

An interesting effect was observed as the intensity of the microstimulation current was varied. At very low intensities, artificial stimuli were not detected; the monkeys simply kept waiting. At intermediate intensities the monkeys detected the stimuli — they reacted and pushed a button — but their psychophysical behavior was at chance levels, as if they could determine the presence but not the frequency of the artificial stimuli. At higher intensities they discriminated normally (Romo et al., 1998). These transitions parallel those observed when the amplitude of mechanical vibrations is gradually increased; in particular, there is an ‘atonal interval’, in which stimuli can be detected but their frequencies cannot be ascertained (LaMotte and Mountcastle, 1975; Mountcastle et al., 1990). In an extra control experiment these authors investigated the effect of stimulus amplitude, which could potentially act as an additional source of sensory information (Romo et al., 1998). Four frequency pairs and all stimuli were mechanical, and the other half of the comparison stimulus was electrical. In both cases, the amplitude of the comparison could take one of three values, a standard amplitude A, 0.6 A, or 1.4 A. The changes in amplitude were, in terms of percentage, of the same magnitude (40%) as the differences between base and comparison frequencies. The results showed that that performance was not affected by the large variations in amplitude; had the monkeys been guided by the amplitudes changes, one of the three combinations for each frequency pair would have fallen to <25% correct, because performance was normally >75% correct. Amplitude corrections, like those mechanical stimuli, were also applied to electrical currents in ~60% of all runs; they had no marked impact on performance (Romo et al., 1998).

Because of the task design, comparison of f2 is made against a memory trace of the f1 (Hernández et al., 1997). Having shown that the monkeys could use an artificial stimulus during the comparison, f2, Romo et al. (2000) wondered whether they would be able to memorize and use an electrical stimulus delivered during the f1 period. In this case, in half of the base stimulus consisted of electrical microstimulation at a frequency equal to f1 (Fig. 13D), with the electric current again being injected into QA neurons. The frequency pairs and event sequence during the task were the same as in previous experiments with natural stimuli; we stress this because careful design of the stimulus sets was particularly crucial here, in order to ensure that the monkeys paid attention to the base stimulus and stored it in working memory (Romo et al., 1999). The monkeys’ psychophysical behavior was again indistinguishable from that observed with natural stimuli only (Fig. 13D), showing that the signals evoked by mechanical and artificial stimuli could be stored and recalled with approximately the same fidelity (Romo et al., 2000). Finally, they also investigated whether monkeys could perform the entire task on the basis of purely artificial stimuli. In most sessions in which the two mechanical stimuli were replaced by microstimulation patterns, monkeys were able to reach discrimination levels close to those measured with mechanical stimuli delivered to the fingertips (Fig. 13E). This demonstrates that activation of QA neurons is sufficient to drive all the cognitive processes involved in the task with little degradation in performance (Romo et al., 2000).

A couple of additional observations derived from these experiments are also noteworthy. First, early experiments with primary afferents had demonstrated that the flutter sensation is specifically mediated by QA fibers (Ochoa and Torebjörk, 1983;

Vallbo, 1995), but this was more difficult to test at the level of S1 (Romo et al., 1998). When microstimulation was applied to clusters of neurons identified as having slowly adapting (SA) properties (top panel of Fig. 14A and labeled as a), the monkeys could barely discriminate, if at all (top panel showing the psychophysical performance in Fig. 14A; Romo et al., 2000). As the electrode was advanced to the border between SA and QA clusters (top panel of Fig. 14A labeled as b), performance became somewhat better (middle panel showing the psychophysical performance in Fig. 14), and it reached its usual degree of accuracy when QA properties became most evident in the recordings (top panel of Fig. 14A labeled as c and lower panel showing the psychophysical performance in Fig. 14A; Romo et al., 2000). Hence, QA and SA units are still functionally segregated in S1, consistent with previous observations (Powell and Mountcastle, 1959; Sur et al., 1984).

In some sessions, Romo et al. (2000) were able to introduce three microelectrodes into a cluster of QA neurons of area 3b that shared the same receptive field (top panel of Fig. 14B). They knew that the most anterior microelectrode was placed in the superficial layers (labeled as a in Fig. 4B), because another microelectrode was placed in front of it and recorded units in primary motor cortex that were driven by spontaneous or passive movements of the fingers and lacked cutaneous receptive fields. The most posterior microelectrode was placed (labeled as c in Fig. 14B), they believe, in the lower layers, and the microelectrode between these two in the middle layers (labeled as b in Fig. 14B). In separate runs, the frequency pairs and event sequence were the same in both mechanical and microestimulation trials, except that that in the microstimulation trials the first mechanical stimuli were substituted with train of current pulses delivered at the frequency of the mechanical stimulus they were substituting. Figure 14B shows that discrimination is triggered by microstimulating each of the three different clusters. Thus, activation of any part of the cluster of neurons (probably a QA column) with similar functional properties is sufficient to initiate discrimination in this task (Romo et al., 2000).

3.5. The functional role of S1 in sensory discrimination

The results obtained in these sets of experiments suggest that QA neurons from S1 represent the stimulus frequencies both in the periodic spike intervals and in the firing rate (Hernández et al., 2000; Lemus et al., 2010; Luna et al., 2005; Salinas et al., 2000), and that activation of the QA circuit is sufficient to activate the entire chain of discrimination processes of this task (Romo et al., 1998, 2000).

The conclusion previously found in the literature, that frequency discrimination is based on periodicity, came from the observation that a small number of studied QA neurons from S1 reproduced in their activity the periodicity of the mechanical stimulus frequency, and also from the fact that these neurons did not have average firing rates that were modulated by the stimulus frequency (Mountcastle et al., 1990). However, the study that reached this conclusion only determined the relationship between the neuronal responses to the mechanical stimulus frequencies; no attempt was made to quantify the neurometric thresholds based on periodicity and to compare these to the psychophysical thresholds. Romo and colleagues observed that neurometric thresholds using the periodicity values are far lower than the psychometric thresholds (Hernández et al., 2000). What is then the functional meaning of this neural signal? As discussed above, one possible role is that this simply represents the temporal structure of the stimulus and that monkeys do not use this exquisite representation for frequency discrimination. Consistent with this interpretation, these authors found QA neurons in S1 whose firing

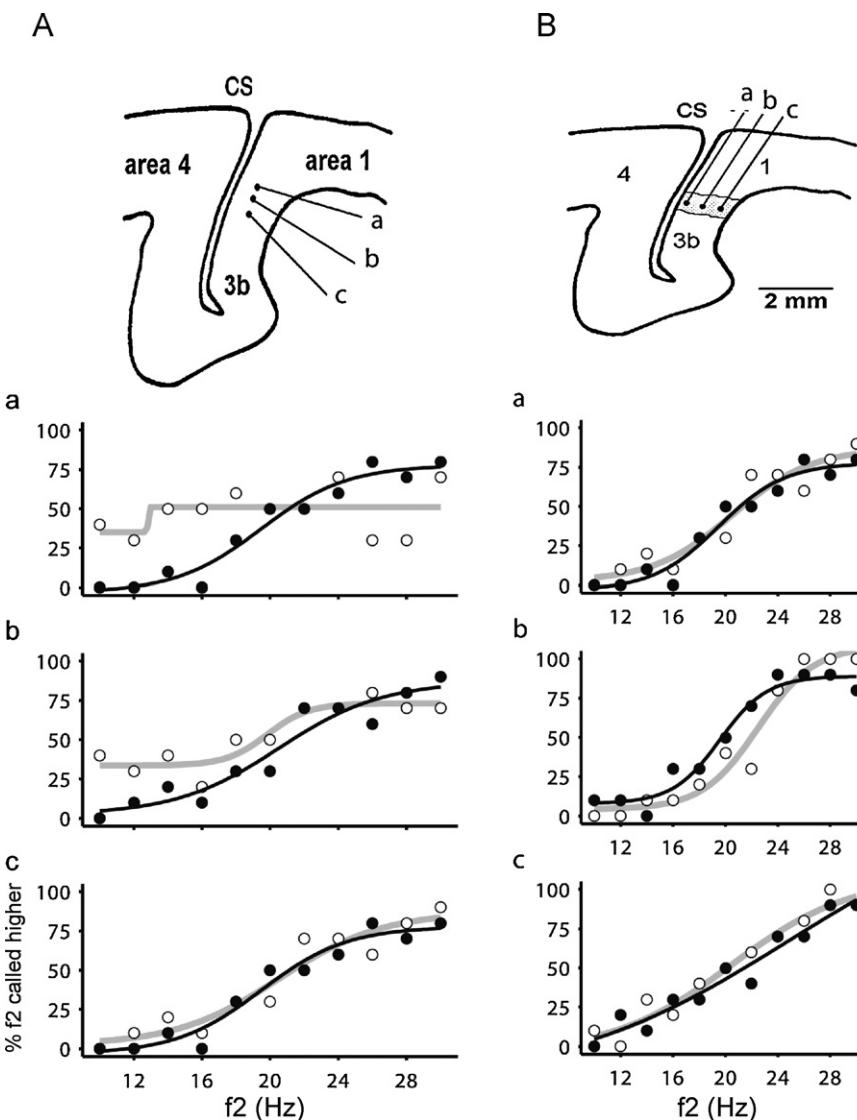


Fig. 14. Psychophysical performance elicited by microstimulating at the base frequency (f_1) in three different sites of area 3b of S1. (A) Electrode penetration in which microstimulation was made in clusters of slowly adapting (SA; panel a) or quickly adapting (QA; panel c) neurons, and in the border between clusters of SA and QA neurons (panel b). (B) Psychophysical performance elicited by microstimulation at the base stimulus frequency (f_1) with three independent microelectrodes in three different sites of a cluster of QA neurons of area 3b. Panels a–c indicate psychometric performance at the three sites for (A and B). Black circles indicate psychophysical performance with mechanical. Open circles indicate psychophysical performance when the base stimulus frequency (f_1) was substituted with artificial stimulus frequencies. Abbreviations: CS, central sulcus; 4, area 4 of primary motor cortex; 1 and 3b, somatosensory areas of S1.

Adapted from Romo et al. (2000).

rates are modulated by the stimulus frequencies (Salinas et al., 2000), and their neurometric thresholds based on this measure are similar to the monkey's psychophysical thresholds (Hernández et al., 2000; Luna et al., 2005).

These results also suggest that QA neurons of S1, which are classified according to their capacity to react to a slight mechanical indentation applied to the center of their receptive fields, may in fact be composed of two subpopulations, each of which behaves differently in response to a periodic mechanical stimulus. These two subpopulations might be organized in hierarchical fashion: QA neurons that respond periodically might be closer to the input stimulus, and those that modulate their firing rate might integrate the responses of the periodic neurons and transform them into a rate code. Such last order neurons of the QA circuit could distribute the neural representation of the stimulus to those structures anatomically linked to S1 (Burton et al., 1995; Burton and Fabri, 1995), to solve the sensory discrimination task. Relevant to this interpretation is the fact that neurons in S2 respond by encoding

the stimulus frequencies in their firing rates and this encoding correlates closely with the subject's discrimination performance (Romo et al., 2002, 2003; Salinas et al., 2000). Ascending the cortical hierarchy, neurons in S2 (Romo et al., 2002, 2003; Chow et al., 2009), prefrontal cortex (Barak et al., 2010; Brody et al., 2003; Kun et al., 2010; Machens et al., 2005, 2010; Nácher et al., 2006) and in the premotor cortices (Deco et al., 2010; Hernández et al., 2002, 2010; Lemus et al., 2007; Martínez-García et al., 2011; Romo et al., 2004) respond by encoding the entire sequence of the discrimination task and correlate closely with the decision motor report.

The results obtained in the S1 microstimulation experiments show that the relationship between the neuronal responses and the animal's behavior in the flutter discrimination task are not simple coincidences (Romo et al., 1998, 2000). Monkeys were able to discriminate the stimulus frequencies either delivered to the fingertips or artificially injected into a cluster of QA neurons. The specificity of QA stimulation for frequency discrimination is

suggested by the fact SA stimulation cannot produce discrimination (Romo et al., 2000). Interestingly, it has been shown that activity in a single cutaneous afferent fiber could produce localized somatic sensations (Macefield et al., 1990; Ochoa and Torebjörk, 1983; Vallbo, 1995), and frequency microstimulation of QA afferents linked to Meissner's corpuscles produced the sensation of flutter (Vallbo, 1995). These observations strongly support the notion that the activity initiated in specific mechanoreceptors is read out by S1; this reading is then widely distributed to those anatomical structures that are linked to S1 (Romo and Salinas, 2001, 2003). The whole sequence of events associated with this sensory discrimination task must depend on this distributed neural signal (Brody et al., 2003; Chow et al., 2009; Hernández et al., 2002, 2010; Romo et al., 1999, 2002, 2004). As discussed in the following section, a transformation of the coding scheme is observed as information flows from S1 to S2 and from S2 to frontal lobe areas.

It is important to mention that studies in humans have demonstrated that short-term memory of a vibrotactile stimulus can be affected by transcranial magnetic stimulation of S1 if delivered within the first second of the retention interval (Harris et al., 2002). This observation suggests that human S1 might be capable of storing a short-term memory of vibrotactile stimuli.

3.6. Coding sensory discrimination in cortical areas central to S1

As discussed above, one group of S1 neurons encodes the temporal structure of the periodic stimulus frequency, whereas a second group of neurons encodes the stimulus frequency in its firing rate. The S1 firing rate code seems more likely associated with the animal's discrimination performance (Salinas et al., 2000). However, S1 neurons do not store information about the stimulus during the working memory component and therefore they do not have the capacity to compare the two stimuli for the decision motor report (Salinas et al., 2000; Lemus et al., 2010). This poses the question of where and how in the brain all these processes are implemented to solving this task. An obvious candidate in the ascending hierarchy is S2, and areas receiving inputs from S2 too.

3.7. Coding sensory stimuli in S2

Anatomical (Burton et al., 1995) and electrophysiological (Pons et al., 1987) evidence suggest that S1 and S2 are connected serially in monkeys (Iwamura, 1998). Lesions in the hand representation of S1 selectively deactivate responses of the hand representation in S2 (Pons et al., 1987). During the frequency discrimination task, S2 neurons respond ~10 ms after S1 neurons (Hernández et al., 2008; Salinas et al., 2000), a finding that is also consistent with a serial flow of information from S1 to S2 (a difference of ~10 ms between each processing stage has also been observed in the visual system; Fabre-Thorpe et al., 2001). In addition, the majority of the responses of S2 neurons are not "phase-locked" with the temporal structure of the stimuli and it has been shown that the temporal structure of spike trains of S2 neurons could not provide enough information to estimate the stimulus frequency (Romo et al., 2003; Salinas et al., 2000). As shown for S1, comparisons of activity during hit and error trials showed that only firing rate variations covaried with discrimination responses (Salinas et al., 2000).

How, then, is the stimulus frequency represented across the somatosensory cortices? The results reviewed suggest that the neural representation of the stimulus frequency be achieved by a two-step mechanism. First, the information of the number of pulses, the time intervals between them, and the total duration of the stimulus is represented in the spike trains produced by S1 neurons, particularly in QA neurons of S1 (Hernández et al., 2000; Luna et al., 2005; Mountcastle et al., 1969, 1990; Salinas et al.,

2000). This information is transmitted to S2, and it is transformed in such a way that the temporal structure of the stimulus is no longer represented in the response spike trains (Romo et al., 2003; Salinas et al., 2000). Second, almost half of the S2 neurons are preferentially activated by low stimulus frequencies: they show negative monotonic responses as a function of the increasing stimulus frequencies (Romo et al., 2002, 2003). Thus, in addition to the positive monotonic responses (like to those observed in S1); in S2 there is a complementary population of neurons with opposite responses (Fig. 15). This dual encoding has also been observed in S2 of monkeys trained in texture discrimination (Sinclair and Burton, 1991, 1993). As will be discussed later, the frequency representation based on two sets of neurons with opposite tuning properties (slopes), seems to have a beneficial effect for the stimulus encoding and for the discrimination performance (Fig. 16; Romo et al., 2003). The cellular and network properties responsible for the transformation observed between S1 and S2 are not known, but the existence of two complementary types of responses at early stages may also be useful for interfacing with more central structures to S2 involved in working memory, decision responses (Hernández et al., 2002, 2010; Romo et al., 1999, 2002, 2003, 2004) and in motor decision reports like those studied by Gold and Shadlen (2001).

3.8. Coding sensory stimuli in frontal cortex

During the first stimulus presentation, in addition to the activity in S1 and S2, sensory responses have been observed in the prefrontal (PFC), MPC, VPC and DPC (Barak et al., 2010; Hernández et al., 2002, 2010; Jun et al., 2010; Romo et al., 1999, 2004), with response latencies slightly higher than S2 and S1 (Fig. 17; Hernández et al., 2010). As for S2, neurons from these cortical areas encode the stimulus frequency by two classes of neurons, with opposite slopes (Fig. 18). In these cortical areas subtraction can also enhance information about the stimulus frequency (Romo et al., 2003).

What is, then, the role of these sensory representations located in areas central to S2? Current viewpoints on the cortical hierarchy of information processing propose that neuronal activity proximal to M1 can be related to the preparation and execution of motor commands. However, the role of sensory responses in the PFC, VPC, DPC and MPC cortices is difficult to explain in motor terms only because monkeys cannot make predictions about the direction of the response movement based on the f_1 stimulus information (Hernández et al., 1997). Crick and Kock (1995) have suggested that conscious perception of sensory stimuli require activation of frontal cortices. Moreover, it has been proposed that higher sensory representations need to be fed-back to lower-level sensory areas in order to be perceived (Meyer, 2011; Pascual-Leone and Walsh, 2001; Romo et al., 2002). According to this hypothesis, neural activation of frontal cortices during the f_1 stimulus presentation would be related to the conscious perception of the stimulus. However, this conjecture remains to be proved as for the detection task (de Lafuente and Romo, 2005, 2006).

3.9. Coding sensory stimuli during working memory

To solve the vibrotactile discrimination task, the frequency of f_1 , must be compared against the frequency of f_2 . The presence of this inter-stimulus delay requires the use of working memory mechanisms to hold in time f_1 . Unlike other psychophysical tasks in which certain features of a single stimulus must be evaluated according to a previously learned criterion (acquired during training and stored in long-term memory), in the discrimination task the reference value of f_1 changes every trial, forcing the monkeys to use working memory mechanisms (Hernández et al., 1997). Where and how is f_1 stored? The ability to retain

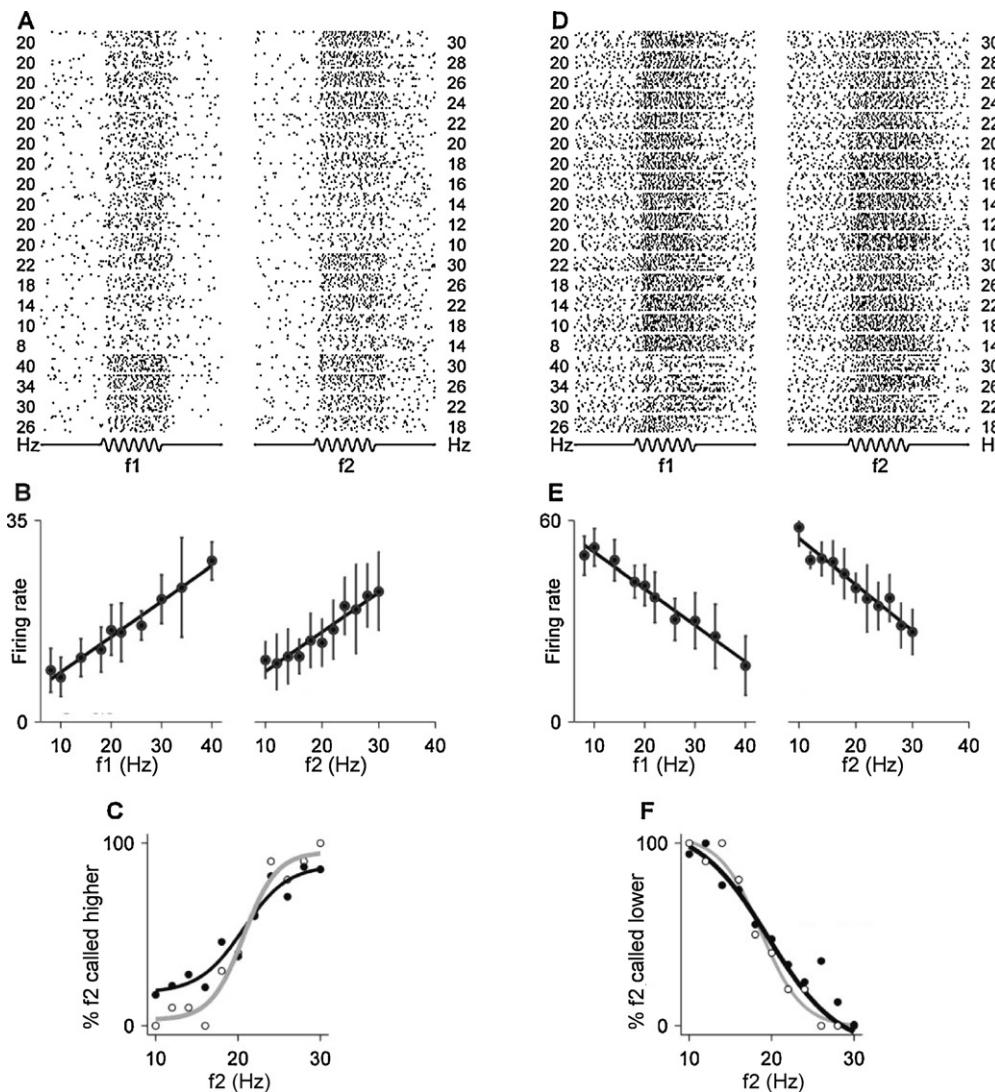


Fig. 15. Examples of neuronal responses in secondary somatosensory cortex (S2). (A) Raster plots of an S2 neuron with positive slope. Each row of ticks is a trial, and each tick is an action potential. Labels at left and right indicate f_1 and f_2 in Hz. (B) mean firing rate (\pm S.D.) as functions of f_1 and f_2 . (C) Psychometric and neurometric functions for the responses in (B). Continuous curves are sigmoidal fits to the data points for 11 pairs of stimulus frequencies in which f_1 was fixed at 20 Hz. Gray line is psychometric function; black line is neurometric function. (D–F) Same format as in panels on the left, but for a neuron with negative tuning.

Adapted from Romo et al. (2003).

behaviorally meaningful sensory information for a brief time interval has been associated with activation of PFC neurons (Fuster, 1997; Funahashi et al., 1989; Miller and Cohen, 2001).

Initially, Romo et al. (1999) studied the activity of neurons in the inferior convexity of the PFC. In addition to the sensory responses, neurons in this area manifested firing rate modulations during the delay period between the two stimuli (Fig. 19). Did the delay activity of these neurons carry information about f_1 ? To answer this question, Romo and colleagues (Barak et al., 2010; Brody et al., 2003; Hernández et al., 2010; Jun et al., 2010; Machens et al., 2005, 2010; Romo et al., 1999) calculated the delay period during which firing rates can be adequately modeled by a linear function of the first stimulus frequency; that is, the period of time in which delay activity carries sensory information. The activation patterns proved to be anything but static. Based on activation dynamics, most of the neurons in the PFC can be sorted into three categories. “Early” neurons provide stimulus frequency information during the first third of the delay period (Fig. 20). The dependence of firing rates to stimulus frequency is evident towards the end of the delay period in “late” neurons (Fig. 20).

Finally, neurons classified as “persistent” carry information about the stimulus frequency throughout the entire delay period (Fig. 20). During this period, approximately half of the neurons increased their firing rate as a positive monotonic function (positive slope) of the increasing stimulus frequency, while the other half of the neurons decreased their firing rate (negative slope) as a function of the increasing stimulus frequency (Fig. 18). Thus, the analysis of activation dynamics of PFC neurons revealed that during the delay period, stimulus frequency – an analog scalar value – seems to be coded directly in the firing rate (also a scaled analog value) of two complementary populations of neurons (Barak et al., 2010; Brody et al., 2003; Hernández et al., 2010; Jun et al., 2010; Machens et al., 2005, 2010; Romo et al., 1999).

Is PFC the only cortical area involved in working memory during vibrotactile discrimination? Certainly not, but the PFC may play a crucial role. This is evidenced when it was contrasted the neuronal activity of other cortical areas in the same task (Figs. 18 and 21). For example, S2 neurons retain information only during the early component of the delay period (Romo et al., 2002; Salinas et al., 2000). The MPC contains an important fraction of neurons that

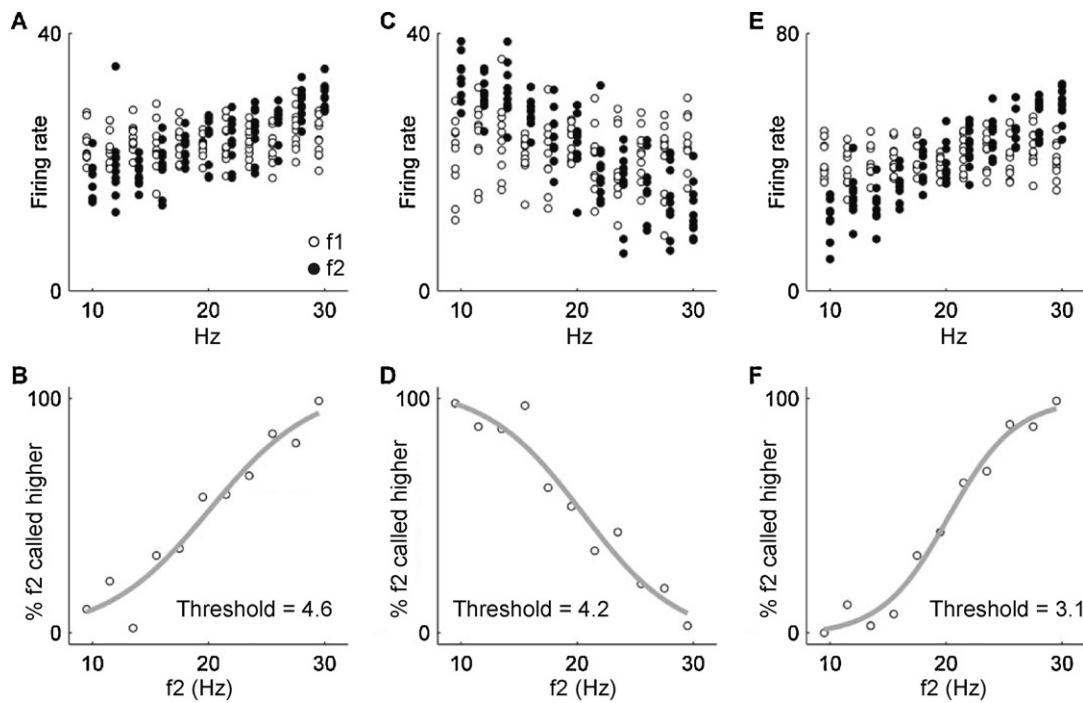


Fig. 16. Increase in discrimination capacity after subtraction of opposite S2 responses. (A) Firing rates of a neuron with positive slope. Open and filled circles indicate rates evoked during f1 (fixed at 20 Hz) and f2, respectively. (B) Neurometric function for the responses in (A). Y-axis corresponds to performance of an ideal observer. (C) Firing rates for a neuron with negative slope. (D) Neurometric function for the response in (C). (E) Responses obtained by subtracting the firing rates in (C) from those in (A), plus a constant. (F) Neurometric function computed from the data in (E). Note the increase in performance and the corresponding lower threshold.

Adapted from Romo et al. (2003).

encode the f1 stimulus frequency during the delay period (Hernández et al., 2002, 2010). Also, the VPC (Romo et al., 2004) neurons encode similarly f1 as during the working memory period as do PFC and MPC (Figs. 18 and 21). As in the PFC, neural activity in all these premotor areas, including DPC, was not static and could be sorted in early, late and persistent categories. In the premotor areas, however, approximately 60% of neurons code stimulus frequency during the final third of the delay (late responses; Fig. 21). Similar to S2 and PFC, approximately half of the premotor neurons are preferentially activated by low stimulus frequencies, and the other half by high stimulus frequencies. An interesting finding was that none of the S1 neurons studied during the vibrotactile discrimination task showed information of the first stimulus during the delay period (Hernández et al., 2010; Lemus et al., 2010; Romo et al., 2004; Salinas et al., 2000).

The temporal dynamics of frequency-encoding delay activity in S2, PFC, VPC, DPC and MPC is consistent with the cortical hierarchy of information processing: neurons in S2 encode the stimulus frequency during the early component of the delay period (Fig. 21). PFC and VPC neurons maintain this information during the entire delay period, allowing it to be fed-back to lower-level sensory areas or to be forwarded to movement related areas (Fig. 21). Finally, towards the end of the delay period, as the stimuli comparison operation and movement execution is imminent, neurons in DPC and MPC activate strongly (Fig. 21).

Is the delay activity of PFC and premotor areas neurons coding the first stimulus frequency or, instead, reflects preparatory activity related to the forthcoming motor response? The stimuli sets used in the discrimination task were designed in such a way that the frequency of the first stimulus on its own did not allow prediction of the response movement beyond chance levels. Given that monkeys achieved 84–94% correct responses, significantly above the 50% chance level, it is possible to state that the delay activity observed in these neurons is not exclusively related to a motor plan (Hernández et al., 2010).

3.10. Comparison and decision-making processes

The f2 is presented after the delay period. Monkeys then have to compare it against the memory trace of f1 and decide whether it had a higher or lower frequency. Where and how is the neuronal operation of comparison and decision-making executed? Gold and Shadlen (2001) have shown that only a subtraction operation between the responses of two neurons tuned with opposite stimulus characteristics is necessary to generate a decision signal favoring a particular sensory hypothesis. Supporting this proposal, they have found decision-making neural activity that seems to be arising from responses of direction sensitive neurons in the parietal visual cortex of monkeys (Gold and Shadlen, 2000; Shadlen and Newsome, 2001).

Extending Gold and Shadlen's proposal to the vibrotactile discrimination task, the sign resulting from subtraction of the responses of neurons with opposite tuning curves may indicate whether f2 was of a higher or lower frequency than f1 (Romo et al., 2002, 2003). It is possible that the subtraction operation could be implemented between the sensory representation of f2 and the mnemonic reference of f1. Is there any evidence indicating that this operation is performed during the discrimination task? To answer this question, Romo and colleagues originally studied the responses of S2 (Romo et al., 2002), during the 500 ms period of f2 presentation; that is, during the period in which the comparison operation takes place.

What anatomic elements are required for the comparison process? In addition to the massive afferents originating in S1 areas (3a, 3b, 1 and 2), S2 is reciprocally connected with the insular cortex, with areas 5 and 7b in the parietal cortex, and with M1, DPC, PFC, VPC and MPC (Cipolloni and Pandya, 1999). This connectivity, in principle, allows S2 to integrate both, sensory information (bottom-up) and information fed-back from more central areas (top-down). For this reason, S2 may be well suited to participate in the comparison and decision-making process. Consistent with this

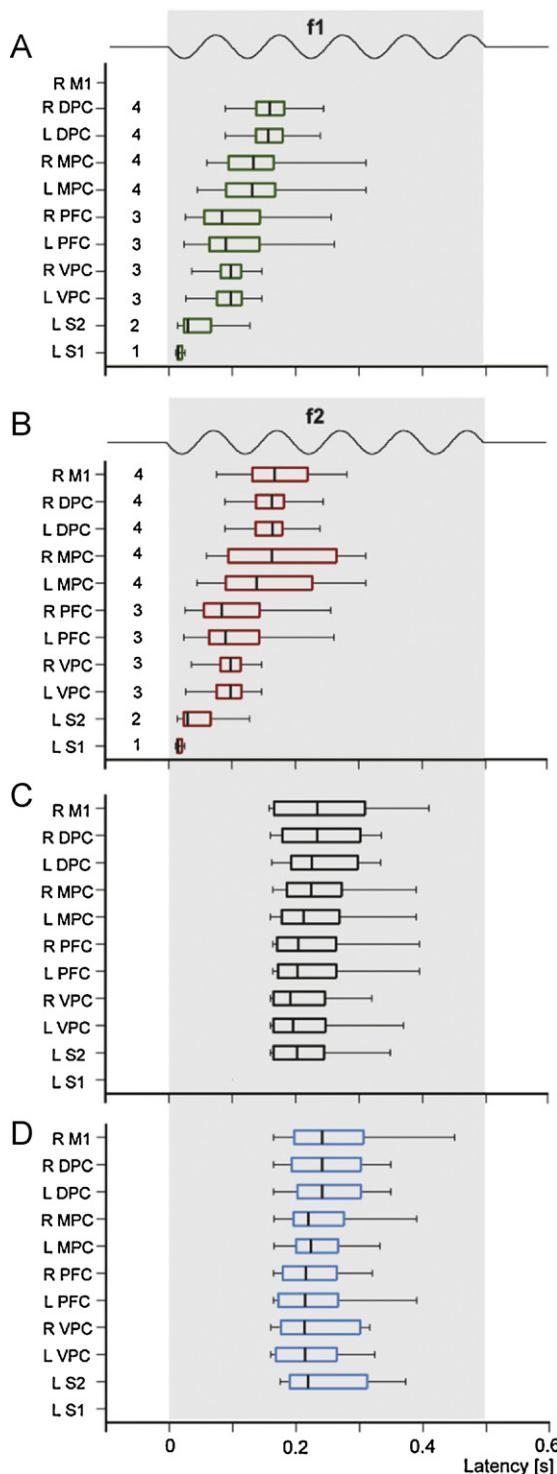


Fig. 17. Box plots illustrate response latency distributions for f_1 (green), f_2 (red), comparison signals (C, black) and differential signals (D, blue) across cortical areas. These boxes have lines at the lower quartile, median, and upper quartile values. Whiskers represent the data's range. A comparative analysis (Wilcoxon rank-sum test; Siegel and Castellan, 1988) of the response latencies between the cortical areas showed that f_1 and f_2 responses began earlier in S1 ($p < 0.01$) than in S2, PFC, VPC, MPC, DPC and M1 (f_1 was not present in M1). Responses for f_1 and f_2 in S2 ($p < 0.01$) began earlier than PFC, VPC, MPC, DPC and M1. Response latencies for f_1 and f_2 are shorter in PFC and VPC ($p < 0.01$) as compared to MPC, DPC and M1. There were no differences in response latencies for f_1 and f_2 between MPC, DPC and M1 ($p > 0.01$). f_1 and f_2 latencies, in all recorded areas, began earlier ($p < 0.01$) than comparison (C) and differential responses (D). No differences were found between comparison and differential responses across cortical areas. L, left hemisphere (contralateral to the stimulated hand); R, right hemisphere (ipsilateral to the stimulated hand). Recordings in primary somatosensory cortex (S1) and secondary somatosensory

hypothesis, Romo et al. (2002) found that the responses of some S2 neurons to f_2 were not only modulated by the frequency of the stimulus being presented, but also were modulated by the frequency of f_1 applied some seconds before. This fact is illustrated by the neural responses to the final 200 ms period of f_2 , where it can be observed that activity is not related to specific frequency values of f_2 or f_1 , instead, they indicate if $f_2 > f_1$ or $f_2 < f_1$ (Figs. 22 and 23; Romo et al., 2002).

To further show this quantitatively, Romo et al. (2002) analyzed the response of neurons by means of a multiple linear regression of the type: $\text{firing rate} = a_1 \times f_1 + a_2 \times f_2 + \text{constant}$ (Draper and Smith, 1966). The coefficients a_1 and a_2 measure the strength of the relationship between a neuron's firing rate and the frequency of f_1 and f_2 stimuli, respectively. Fitting this equation to neuronal responses in successive time windows and plotting a_2 as a function of a_1 allows to appreciate the time dynamics of the neuron's response dependence on the frequency of f_1 and f_2 (Figs. 18 and 23). Three lines on this graph are of particular interest. Points falling on the $a_2 = 0$ line illustrate neural responses that are function of f_1 only. Points on $a_1 = 0$ indicate responses that are exclusively a function of f_2 . Points along the diagonal $a_1 = -a_2$ illustrate neural responses that are the result of the difference between f_2 and f_1 . Applying multiple linear regression analysis through a sliding time window throughout the second stimulus period allowed to reveal the temporal dynamics of the dependence of the neuron's firing rate to the f_1 and f_2 stimuli. It was found that the temporal dynamics of individual neurons were highly variable, but the population showed a clear tendency. Initially, firing rates were mainly a function of f_1 or f_2 frequency. However, towards the end of the 500 ms of the second stimulus, firing rates were no longer a function f_1 or f_2 but only of the sign resulting from the subtraction of $f_2 - f_1$ (Figs. 18 and 23). Thus, the activity of the S2 neurons during f_2 reflected the comparison process between f_1 and f_2 . In principle, this operation could be generated by the subtraction of the mnemonic reference of f_1 (maintained by PFC or premotor areas) and the sensory representation of f_2 (originating in S1). The symmetrical point distribution in the first and fourth quadrants indicates the existence of two neuronal populations with opposite responses (Figs. 18 and 23). Points in the first quadrant are from neurons that prefer, i.e. fire strongly, during the condition $f_2 > f_1$, while points in the fourth quadrant come from $f_2 < f_1$ selective neurons. In this manner, decision signals resulting from the comparison operation are coded by means of two neuronal populations with opposite responses; that is, by means of a dual representation (Romo et al., 2003).

An important issue concerning the selective responses observed towards the end of f_2 is whether they arise from a comparison operation or, instead, are exclusively related to the preparation of a motor response. To answer this question, some neurons of area S2 were studied while monkeys performed a control task in which they executed the same response movements, but instead of being guided by the result of the comparison process they were visually instructed to press the illuminated button for reward. In this control task, the correct response button was illuminated at the beginning of the trial so that somatosensory information and the comparison process were unnecessary for reward. During this control experiment, most of the response's dependence on f_1 and f_2 was lost, suggesting that it be related to the comparison operation and not necessarily to the motor response (Romo et al., 2002).

cortex (S2) were made contralateral to the stimulated hand (left hemisphere) and in primary motor cortex (M1) contralateral to the responding hand/arm (right hemisphere). Recordings were made bilaterally in prefrontal cortex (PFC), ventral premotor cortex (VPC), medial premotor cortex (MPC) and dorsal premotor cortex (DPC).

Adapted from Hernández et al. (2010).

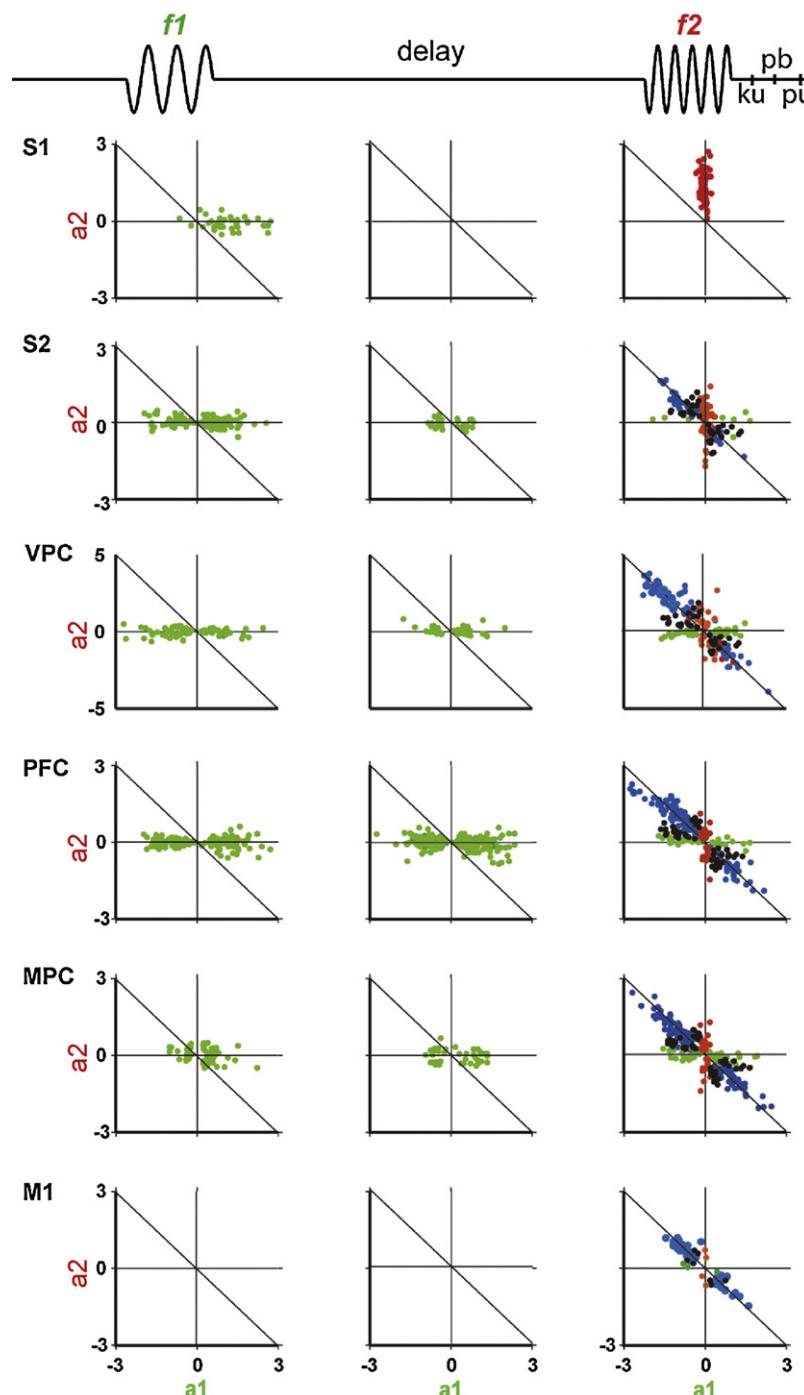


Fig. 18. Coefficients values across cortical areas during the different components of the discrimination task. Each point represents one neuron with at least one coefficient significantly different from zero. Three periods were analyzed: f_1 (500 ms), delay between f_1 and f_2 (3000 ms), f_2 (500 ms), delay between the end of f_2 and PU of (Fig. 1). Each neuron contributed with its largest coefficient evaluated by 200 ms bins. Green and red circles correspond, respectively, to neurons with significant a_1 coefficients only, or a_2 coefficients only. Black circles correspond to neurons with both significant a_1 and a_2 coefficients of opposite signs, but of significantly different magnitudes; these are partially differential responses. Blue circles correspond to neurons with both significant a_1 and a_2 coefficients, but of opposite signs and statistically equal magnitude; these are fully differential or categorical responses encoding $f_2 - f_1$. S1, primary somatosensory cortex; S2, secondary somatosensory cortex; VPC, ventral premotor cortex; PFC, prefrontal cortex; MPC, medial premotor cortex; M1, primary motor cortex.

Adapted from Hernández et al. (2000, 2002), Romo et al. (1999, 2002, 2003, 2004).

Evidence discussed up to this point suggests that S2 is involved in the comparison process. However, recent findings have shown that other structures may also be involved (Hernández et al., 2002, 2010; Romo et al., 2004; Kun et al., 2010). It is possible that the decision signals observed in S2 are only a copy of decision-making processes elaborated in other cortical areas. As we shall see below,

decision-related signals are observed in PFC, VPC, DPC, and MPC before they appear in S2.

It has consistently been found that PFC, VPC, MPC, DPC and M1 activity is related to movement preparation (Shima and Tanji, 2000; Matsuzaka et al., 1992). Given that the ultimate objective of the discrimination task is to generate a response movement

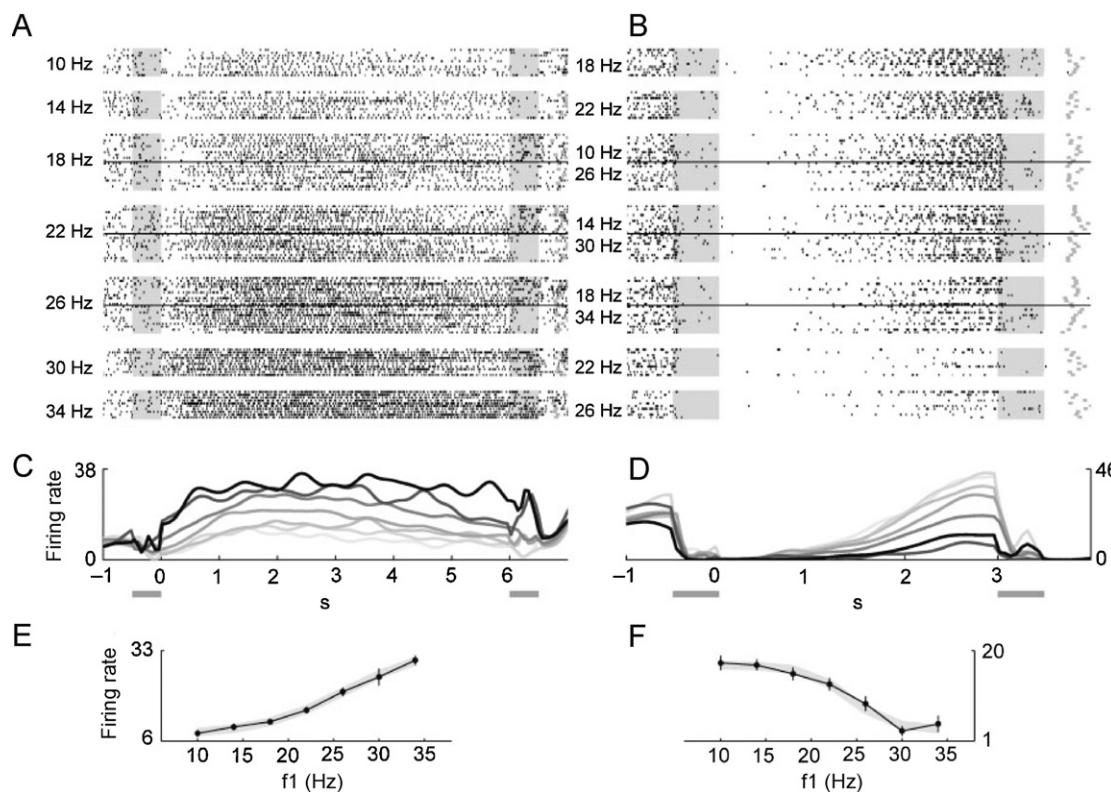


Fig. 19. Encoding of stimulus frequency in working memory by a positive (A, C, E) and a negative neuron (B, D, F). (A, B) Raster plots. Each row of ticks represents a trial, and each tick represents an action potential. Grey boxes and short horizontal lines in C and D indicate base and comparison stimulus periods; thick grey ticks after the comparison stimulus indicate the beginning of the motor response (KU in Fig. 9). Time axes for (A) and (B) are shown in (C) and (D), respectively. (C, D) Time-dependent spike densities sorted by base frequency. Light grey corresponds to 10 Hz, and dark grey line corresponds to 34 Hz. (E, F) Mean firing rates, averaged across the entire delay period. Adapted from Romo et al. (1999).

(to obtain a reward) and that this can only be correctly achieved only after comparing the f_1 and f_2 stimuli, is the activity of these premotor areas involved in the sensory-to-motor transformation achieved by the comparison operation? Romo and colleagues (Hernández et al., 2002; Kun et al., 2010; Machens et al., 2005; Romo et al., 2004) found that about half of the neurons recorded in PFC, VPC, DPC MPC and M1 during the discrimination task showed activity during f_2 (Fig. 18). Of these neurons, a vast majority showed selective responses that indicated whether $f_2 > f_1$ or $f_2 < f_1$. A ROC analysis, which estimates the probability of an ideal observer, looking at single neuron responses, of correctly distinguishing the $f_2 > f_1$ or $f_2 < f_1$ conditions was used to quantitatively study the strength of the selective responses. A 0.5 valued ROC index indicates that the response of the neuron is similar for both conditions and that is unable to indicate, beyond chance level, if $f_2 > f_1$ or $f_2 < f_1$ had occurred. In contrast, a 1.0 ROC index indicates that the neuron is able to indicate, on each trial, whether $f_2 > f_1$ or $f_2 < f_1$ had occurred. To study the temporal dynamics of this selective activity, ROC indices for each neuron were calculated in a 100 ms-wide sliding window, displaced in 20 ms steps, beginning one second before the second stimulus presentation and ending one second after the stimulus presentation. During the comparison process, approximately half of the neurons showed ROC indices that deviated above 0.5 (indicating selective activity for the $f_2 > f_1$ condition) while the other half deviated below 0.5 (indicating selective activity for the $f_2 < f_1$ condition). These results indicate that, just as the neural representation of sensory stimuli, decision signals indicating the result of the comparison process are coded by two complementary neuronal populations (Fig. 18).

To quantitatively measure the neural response's dependence on the frequency of the f_1 and f_2 stimuli, just as in S2 neurons, a

multiple linear regression analysis was carried. Romo et al. (2002) found that during the first 100 ms of the f_2 stimulus the activity of some neurons was mainly a function of f_1 frequency. This finding is consistent with a "memory recall" of the base stimulus frequency. However, what is typically observed in PFC, VPC, DPC and MPC is that, during the f_2 stimulus, some neurons initially code f_1 or f_2 frequency and, later, these and other neurons code whether $f_2 > f_1$ or $f_2 < f_1$ (Hernández et al., 2002, 2010; Romo et al., 2002, 2004; Kun et al., 2010). These results show that during the f_2 stimulus presentation, the dynamics of PFC, VPC, DPC, MPC and M1 neurons is very similar to that observed in S2 neurons, and it is consistent with a stimuli comparison operation (Hernández et al., 2010).

As in S2, a crucial question is whether the differential responses observed in these areas are exclusively related to motor planning or, instead, they arise from the stimuli comparison operation. Error trial analysis indicates that they code the decision motor output (Fig. 24). However, during the visual instruction task (discussed above), all neurons attenuated their responses (to ROC values close to 0.5), suggesting that the differential activity observed during the comparison period depended on the comparison operation and not merely reflected the planning of a motor response (Hernández et al., 2002; Romo et al., 2004).

These results suggest that the decision-making process is widely distributed through the cortex (Romo et al., 2004). To what extent the decision responses are generated de novo in each area, or arise by shared input, remains an open question that needs to be further explored. In agreement with our findings in the monkey cortex, recent functional imaging studies have found that human dorsolateral prefrontal cortex (dPFC) participates in decision making tasks that require evaluation of sensory information.

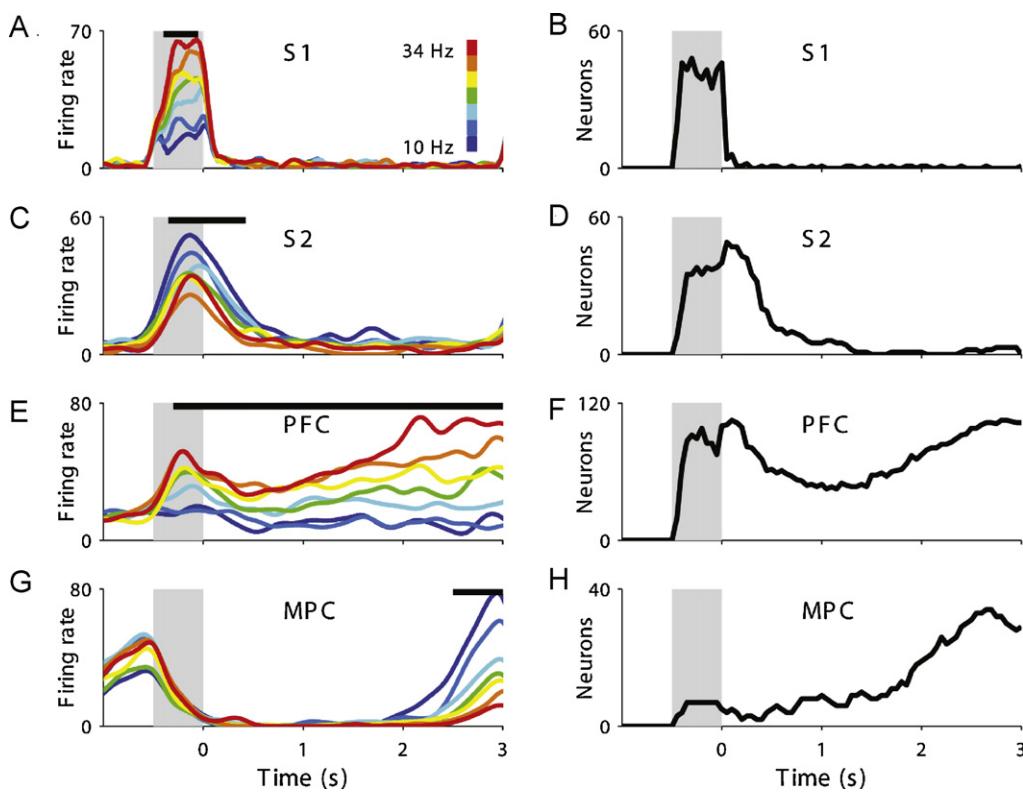


Fig. 20. Neuronal responses observed during the delay period in four areas. (A, C, E, G) Spike density functions from four single neurons. Dark bars above each plot indicate times during which the neuron's firing rate carried a significant ($P < 0.01$) monotonic signal about the base stimulus. Color densities are used to sort responses according to base frequency, as indicated by the scale gradient. (A, E) These neurons fired most strongly with high stimulus frequencies. (C, G) These neurons fired most strongly with low frequencies. (B, D, F, H) Number of recorded neurons carrying a significant signal about the base stimulus, as a function of time relative to the beginning of the delay period. Only data collected from runs with a fixed delay of 3 s are included. S1, primary somatosensory cortex; S2, secondary somatosensory cortex; MPC, medial premotor cortex; PFC, prefrontal cortex.

Adapted from Hernández et al. (2000, 2002), Romo et al. (1999, 2002), Salinas et al. (2000).

Importantly, these studies found that dPFC is recruited by decision making tasks irrespective of the sensory modality upon which decisions are based, and also irrespective of the particular motor commands used to communicate the decisions (Heekeren et al., 2006).

3.11. Decision-making in the motor cortex

As reviewed above, it has been shown that both S2 and frontal lobe areas show neural activity dynamics consistent with a frequency comparison operation. What is the role of the primary motor cortex (M1)? It has been shown that M1 neurons code parameters such as the strength and direction of movements (Georgopoulos et al., 1988). This might lead us to think that M1 receives neural signals resulting from the comparison operation (binary signals that should trigger arm movements to either of the response buttons). However, recordings of M1 neurons in monkeys performing the frequency discrimination task showed that these neurons are activated during the second stimulus presentation ~ 600 ms before response movement initiation. In addition, multiple linear regression analysis (discussed above) showed that these responses are grouped very close to the diagonal $a_2 = -a_1$, indicating that this activity depends on the result of the comparison of the stimuli (Fig. 18). The pattern of M1 activity is quite similar to the differential responses observed in S2 and the other frontal lobe area. This observation opens the possibility that the differential responses observed in these cortical areas could be just a copy of the activity generated in M1. To test this hypothesis, Romo et al. (2002) compared response latencies in these three areas. Results showed that differential responses in M1 are the last

to appear (295 ± 20 ms), and that comparison and decision-making activity in S2 (236 ± 21) and in MPC (201 ± 66) preceded the activity of M1 neurons (Fig. 17B).

Just as in S2, PFC, DPC, VPC and MPC neurons with selective activity in M1 can be sorted into two populations: Those that activate more when $f_2 > f_1$ are plotted by in the first quadrant (regression analysis), and those that activate maximally when $f_2 < f_1$ are plotted in the fourth quadrant (Fig. 18). We should not forget that it has been observed this dual coding in all the cortical areas studied central to S1, and in all the operations required to solve the discrimination task (Fig. 18).

What is the role of the differential activity observed in M1? Does it constitute only a mirror image of decision signals originated in other areas, or instead, does it play an active role in information processing? To study the role of M1 in decision-making processes, Salinas and Romo (1998) studied responses of M1 neurons in monkeys trained to categorize the speed of a mechanical probe moving along one of their fingertips. By pressing one of the two response buttons, monkeys had to indicate whether movement speed was high or low, based on arbitrary categories learned during training (Romo et al., 1993, 1996, 1997). Movement speed was systematically varied in order to produce psychophysical categorization curves. As expected, the majority of M1 neurons showed movement related activity that did not indicate the stimulus speed of motion. However, one-fifth of these neurons showed selective activity that was a function of both, stimulus speed and the stimulus category (high or low). One important observation is that the differences in firing rates of these neurons (that indicated the selectivity for one category or the other) are not explained exclusively by the differences in the direction of

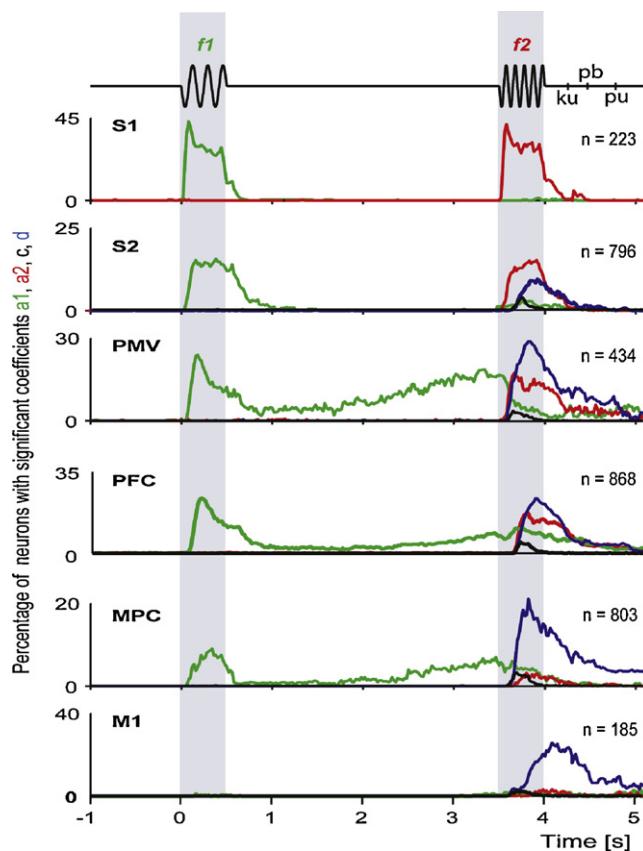


Fig. 21. Dynamics of population responses of five cortical areas during the discrimination task. The number of neurons with significant coefficients is plotted as a function of time. Green traces correspond to a_1 sensory tuning (f_1), and red traces to a_2 sensory tuning (f_2) (see Fig. 18). Blue traces indicate the number of neuron with coefficients a_1 and a_2 of opposite sign but similar magnitude; these produce a differential signal. Black traces indicate the number of neurons whose coefficient a_1 during the comparison period combines with a_2 , then switch to a differential response. The number of differential responses increases during f_2 and decreases during the actual motor report.

Adapted from Romo et al. (2004).

response movement. This conclusion is supported by results obtained by Schwartz et al. (1988), which implicated that the 11° response button separation would only produce a 1 spike/second difference in the response of a movement direction-selective neuron. The selectivity of M1 neurons and their ability to code (through two complementary populations) the sensory component of the stimuli (velocity of movement) suggests the existence of sub-populations of M1 neurons that may be involved in the conversion of sensory information into response movements (Salinas and Romo, 1998).

3.12. Is there any coding scheme across cortex for decision-making?

The data obtained in this combined neurophysiological/psychophysical experiment provide evidence that the neural dynamics in these frontal lobe areas involve 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 into a decision signal that is consistent with the subject's motor report. 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 f_1 regardless of subsequent movements, (2) differential responses developed gradually, often depending exclusively on f_2 or f_1 early

in the comparison, (3) choice probability indices depended on $|f_2 - f_1|$, and (4) when the same movements were guided by visual cues the differential activity disappeared.

Previous observations suggest that some neurons particularly those from VPC transform the perception of complex visual objects or actions into body movements (Rizzolatti and Luppino, 2001). This may apply for practically all frontal lobe circuits. However, how exactly is the neuronal operation of this cognitive operation? It is not clear, for example, whether frontal lobe neurons encode the stimulus features. If there is an encoding of the stimulus feature, how then is it transformed into an action? Also, actions depend on the interaction between internal and external factors as well. In the vibrotactile discrimination task, a voluntary motor action is triggered by the interaction between current and recalled sensory information, and the dynamics of the frontal lobe neurons showed this cognitive operation. It is also worth emphasizing that in the vibrotactile task, frontal lobe neurons encode in their firing rate the stimulus parameter both during the sample stimulus and working memory periods. Thus these observations are consistent with the fact that sensory, motor and memory-related areas of the brain are anatomically inter-connected with prefrontal and premotor areas (Rizzolatti and Luppino, 2001). This further supports the idea that prefrontal and premotor cortices are well situated for linking sensory (Hernández et al., 2002, 2010; Romo et al., 2004; Romo and Salinas, 2003) and memory (Miller and Cohen, 2001; Ohbayashi et al., 2003; Romo and Salinas, 2003) events with motor actions (Wise et al., 1992; Rizzolatti and Luppino, 2001; Schall, 2001; Romo et al., 2004; Romo and Salinas, 2003).

One crucial question emerges from these results: is the activity of neuronal populations in each frontal lobe area sufficient to generate the entire perceptual decision process studied here? Considering the activity observed in each cortical area during the same task, it would seem that this process involves the conjoined responses of many areas (Chow et al., 2009; Brody et al., 2003; Hernández et al., 2000, 2002, 2010; Kun et al., 2010; Romo et al., 1999, 2002, 2004; Salinas et al., 2000). Although this is unknown, a comparison between the responsive cortical areas could suggest their relative contributions in each component of the discrimination task. For example, f_1 is encoded in several cortical areas (Fig. 18). Such encoding seems to proceed in a serial fashion from S1 (Salinas et al., 2000) to S2 (Salinas et al., 2000), then to VPC, PFC, DPC and MPC (Hernández et al., 2010). Thus several cortical areas central to S1 are involved in the sensory component of this task. All these cortical areas, except S1 (Salinas et al., 2000), encode the storage of f_1 at different times during the working memory component of the task (Hernández et al., 2002, 2010; Romo et al., 1999, 2002, 2004; Romo and Salinas, 2003; Salinas et al., 2000). This is consistent with the proposal that there is a cortical network that stores sensory information (Fuster, 1997). During the comparison period, f_2 is mainly processed in S1 and S2 (Salinas et al., 2000). Except for S1, the comparison of the stored and ongoing sensory information is observed in S2 (Romo et al., 2002), MPC (Hernández et al., 2002), VPC (Romo et al., 2004) PFC (Brody et al., 2003; Machens et al., 2005; Jun et al., 2010; Romo et al., 1999) and DPC (Hernández et al., 2010). The resulting comparison signal evolves in these areas into a signal, which is consistent with the motor choice. In M1, the resulting motor signal expressing the motor choice is also observed (Romo et al., 2004), but it does not participate in the sensory, memory, and comparison processes of the task (Hernández et al., 2010; Romo et al., 2002). Thus, it seems that in this task the comparison between stored and ongoing information takes place in those areas between S1 and M1. However, it is remarkable that the entire chain of events related to the temporal evolution of a perceptual process can be represented in the activity of a localized neuronal population, except for S1 and

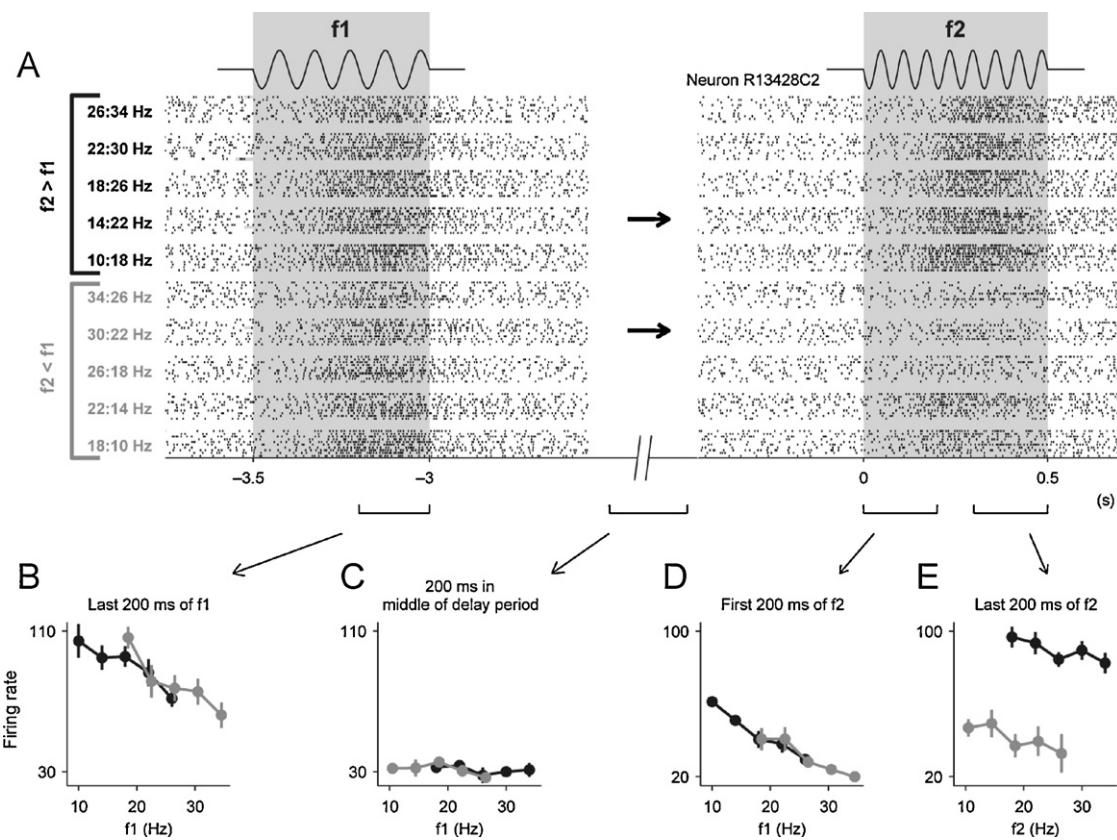


Fig. 22. A secondary somatosensory (S2) cortex neuron with a response to the second stimulus (f_2) that shifted to reflect ($f_2 - f_1$) comparison. (A) Raster plots of responses to stimuli f_1 and f_2 . Labels at left indicate ($f_1:f_2$) stimulus frequencies. (B) Average firing rates during the last 200 ms of f_1 . Black indicates $f_2 > f_1$ ($f_2 = f_1 + 8$ Hz); grey indicates $f_2 < f_1$ ($f_2 = f_1 - 8$ Hz). (C) Information of f_1 is not present during the delay period between f_1 and f_2 . (D) First 200 ms of f_2 , plotted as function of f_1 ; information of f_1 is therefore present during f_2 . (E) Last 200 ms of f_2 , plotted as function of f_2 : the main determinant of firing rate was whether $f_2 > f_1$ or $f_2 < f_1$.

Adapted from Romo et al. (2002).

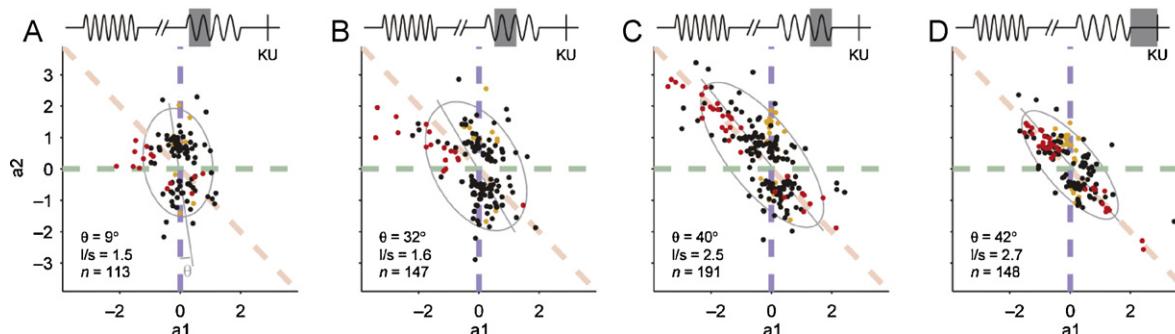


Fig. 23. Population responses of second somatosensory (S2) neurons gradually become aligned to the $a_2 = -a_1$ axis. Responses to f_2 depend on the previously applied first stimulus (f_1). Each point shows the result of fitting the equation $\text{firing rate} = a_1 \times f_1 + a_2 \times f_2 + \text{constant}$ averaged over different periods of f_2 . Points that fall on the $a_1 = 0$ axis (blue dashes) represent responses that depend on f_2 only; points that fall on the $a_2 = 0$ axis (green dashes) represent responses on f_1 only; points that fall on the $a_2 = -a_1$ line (red dashes) represent responses that are function of ($f_2 - f_1$). Grey boxes indicate the time window for each panel. (A) 25–225 ms; (B) 90–290 ms; (C) 300–500 ms after stimulus onset. (D) Window from f_2 offset until start of motor responses. Ellipses are the 2σ -contour for a two-dimensional Gaussian fit to the data point distribution. Colors refer to data sets of neurons analyzed in Fig. 24.

Adapted from Romo et al. (2002).

M1, where the responses are mainly sensory (S1) and/or associated very likely with the decision motor report in M1 only. We suggest that this must not be unique to the evaluation of somatosensory information. For example, VPC and MPC in addition to somatosensory processing process auditory (Graziano et al., 1999; Lemus et al., 2009) and visual information (Rizzolatti et al., 1988; Graziano et al., 1997) too, so it may participate in transforming sensation into action in these modalities as well.

In conclusion, frontal lobe circuits during the vibrotactile discrimination task show the neuronal processing path that links

sensory information with an action. This processing path proceeds in a hierarchical or serial fashion: (1) encoding f_1 both during the stimulus presentation and working memory periods, (2) encoding the interaction between the current sensory input (f_2) and the memory trace of f_1 , and (3) encoding the animal's decision report. Although this processing path is represented in the activity of frontal lobe and posterior parietal areas, however, other cortical and subcortical areas must be also engaged in this cognitive operation. Thus, further studies are needed to establish the cortical and subcortical network that underlies the link between sensory

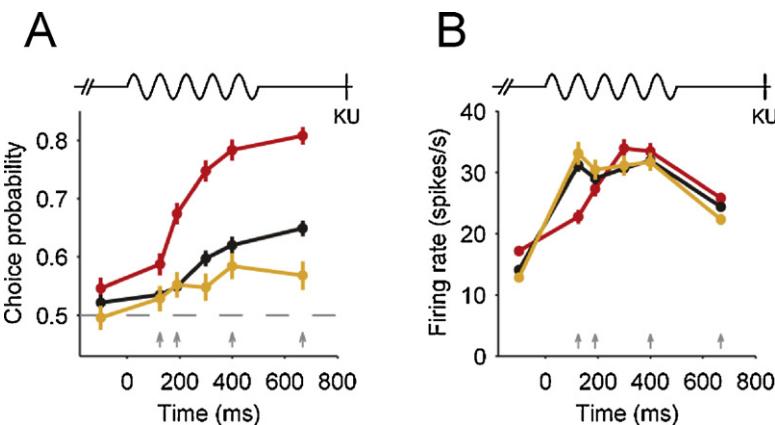


Fig. 24. Error trial analysis of S2 neurons. Neurons that are ($f_2 - f_1$)-dependent in response to correct trials are highly correlated with the monkey's choice of button to press. (A) Choice probabilities, averaged over f_2 for three different groups of neurons. Red ($f_2 - f_1$)-dependent neurons; black, intermediate/ambiguous neurons; orange, f_2 -dependent neurons. The sensory stimulus runs from time 0 to 500 ms. Dashed line indicates 0.5 chance level, and arrows indicate the four time windows of Fig. 23. (B) Overall average of firing rates for the same time windows and neuronal groups as in (A).

Adapted from Romo et al. (2002).

information and action (de Lafuente and Romo, 2011). This is fundamental to understand how this decision-making network generates a perceptual process, as the one studied in the reviewed experiments.

3.13. Decoding postponed decision reports across cortex

The task used in above reviewed studies simulates the behavioral condition in which the decision based on a sensory evaluation is immediately reported through a voluntary movement (Hernández et al., 1997). There are, however, behavioral conditions in which a perceptual decision can be postponed for later report. But, in theory, once the subject reaches a decision, this becomes categorical, no matter whether it must be reported immediately or reported later (Shadlen and Newsome, 1996). If postponed, memory circuits may store the categorical decision for later report. However, an alternative could be that the memory

circuits store not only the categorical decision, but also the information on which the decision is based (Lemus et al., 2007). This last possibility could be extremely advantageous since it gives flexibility for the decision-making process. In this case, it is possible that the decision is revised or updated as long as there is time for it to be reconsidered.

In a variant of the vibrotactile discrimination task (Fig. 25), in which monkeys were asked to postpone their decision report, Romo and colleagues found that the activity of MPC neurons during this period encodes both the result of the sensory evaluation (which corresponds to the monkey's two possible choices) and past information on which the decision is based (Lemus et al., 2007). These responses could switch back and forth with remarkable flexibility across the postponed decision report period. Moreover, these responses covaried with the animal's decision report. Thus, the MPC circuits appear critically suited to integrate and reorganize all of the elements associated with

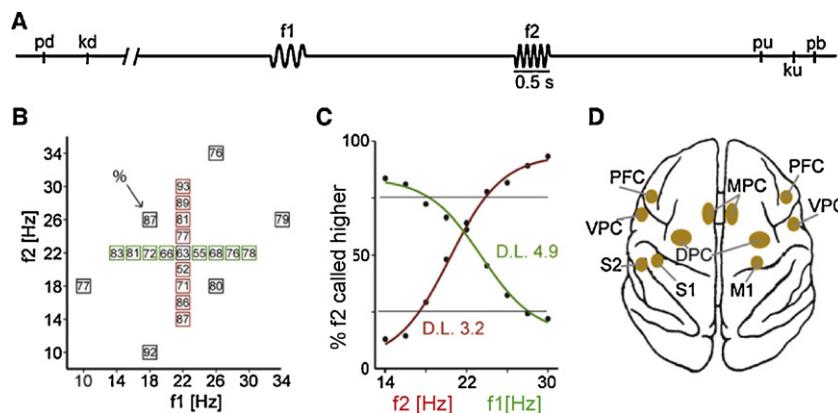


Fig. 25. Postponed discrimination report. (A) Sequence of events during discrimination trials. The mechanical probe is lowered, indenting the glabrous skin of one digit of the restrained hand (pd); the monkey places its free hand on an immovable key (kd); the probe oscillates vertically, at the base stimulus frequency (f_1); after a fixed delay (3 s), a second mechanical vibration is delivered at the comparison frequency (f_2); after another fixed delay (3 s) between the end of f_2 and probe up (pu), 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, respectively. (B) Stimulus set used during recordings. Each box indicates a base/comparison frequency stimulus pair. The number inside the box indicates overall percentage of correct trials for each (f_1 , f_2) stimulus pair, except when the pair was identical (22 Hz; here it was plotted the percentage of trials in which the animal pressed the lateral push button). (C) Psychophysical performance when f_1 was maintained fixed at 22 Hz and f_2 was variable (red curve), and when f_2 was fixed at 22 Hz and f_1 was variable (green curve). D.L. is the discrimination threshold in Hz. (D) Top view of the monkey brain and the cortical areas recorded during perceptual discrimination (orange spots). Recordings were made in primary somatosensory cortex (S1) and secondary somatosensory cortex (S2) contralateral to the stimulated hand (left hemisphere) and in primary motor cortex (M1) contralateral to the responding hand/arm (right hemisphere). Recordings were made contralateral and ipsilateral to the stimulated fingertip prefrontal cortex (PFC), ventral premotor cortex (VPC), medial premotor cortex (MPC) and dorsal premotor cortex (DPC).

Adapted from Hernández et al. (2010).

decision making in this task. Furthermore, they reflect the flexibility that is needed when a perceptual decision must be either immediately reported (Hernández et al., 2002) or postponed for later report (Lemus et al., 2007).

Romo and colleagues explored whether the neuronal responses recorded during the postponed decision period are a unique property of the MPC circuit (Lemus et al., 2007) or whether similar processes are also present in other cortical areas of the parietal and frontal lobes during this variant of the task (Hernández et al., 2010). To further investigate this question, these authors recorded the neuronal activities of diverse cortical areas while trained

monkeys reported a postponed decision based on previous sensory evaluation (Fig. 25D). As in the task reviewed in the above section, monkeys must hold f_1 in working memory and must compare it to the current sensory stimulus (f_2) and must postpone the decision report until a cue triggers the motor report, i.e., whether $f_2 > f_1$ or $f_2 < f_1$. Clearly, the neuronal processes associated with the postponed decision report and the task components that precede it can be analyzed across diverse cortical areas (Fig. 26).

Romo and colleagues (Hernández et al., 2010) found that the encoding of f_1 and f_2 through all task periods is widely distributed across cortical areas (Figs. 26 and 27A). They also found that the

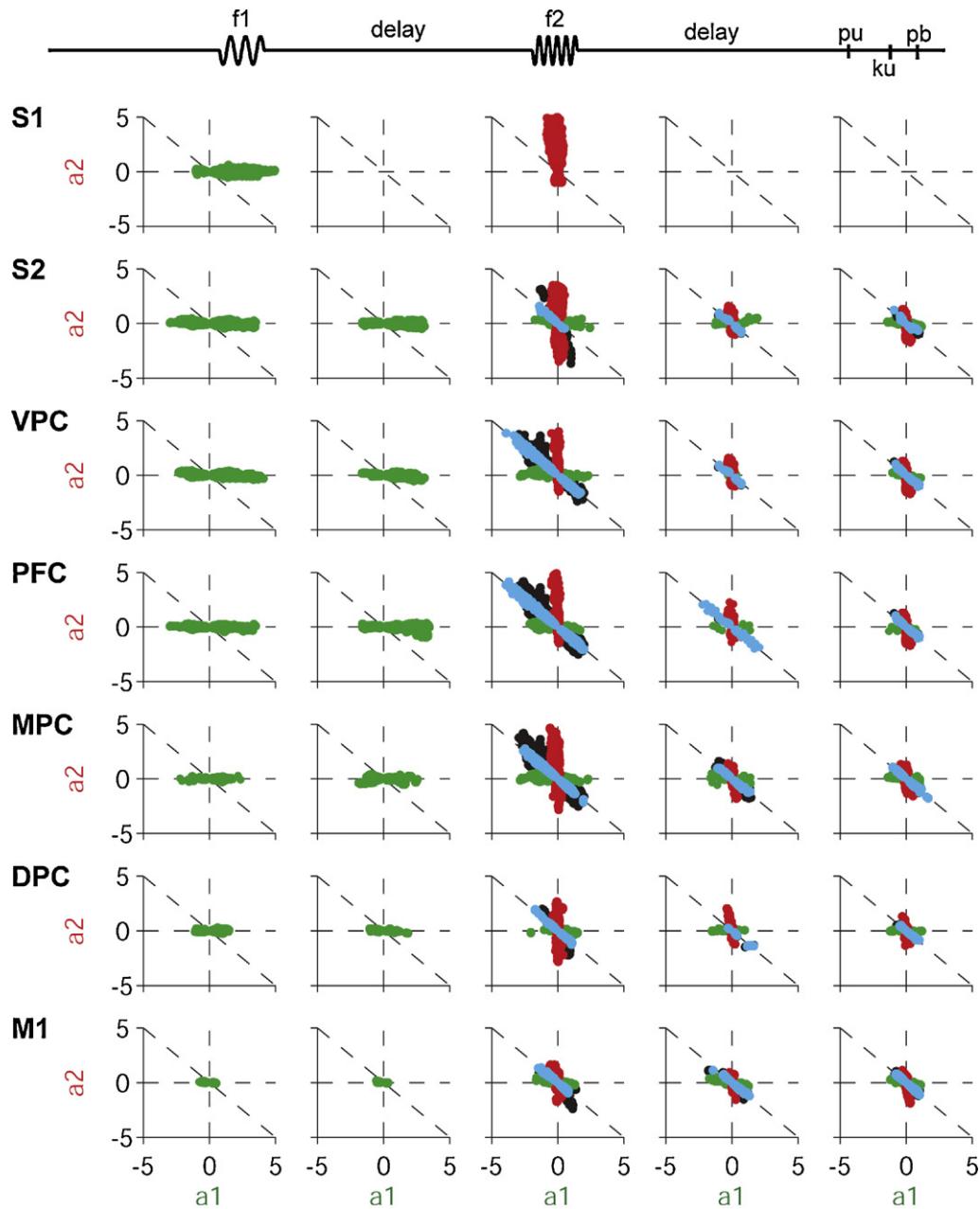


Fig. 26. Population coefficients values across cortical areas during the different components of the postponed discrimination task report. Each point represents one neuron with at least one coefficient significantly different from zero. We analyzed five periods: f_1 (500 ms), delay between f_1 and f_2 (3000 ms), f_2 (500 ms), delay between the end of f_2 and pu (3000 ms) and during a period posterior to pu (1000 ms). For each neuron, we identified a 200 ms bin with the highest modulation during each period. Green and red circles correspond, respectively, to neurons with significant a_1 coefficients only or a_2 coefficients only. Black circles correspond to neurons with both significant a_1 and a_2 coefficients of opposite signs, but of significantly different magnitudes; these are partially differential responses. Blue circles correspond to neurons with both significant a_1 and a_2 coefficients, but of opposite signs and statistically equal magnitude; these are fully differential or categorical responses encoding $f_2 - f_1$. S1, primary somatosensory cortex; S2, secondary somatosensory cortex; VPC, ventral premotor cortex; PFC, prefrontal cortex; MPC, medial premotor cortex; DPC, dorsal premotor cortex; M1, primary motor cortex.

Adapted from Hernández et al. (2010).

activity of frontal lobe circuits encodes both the result of the sensory evaluation and past information on which those choices are based. Notably, the activity of M1 showed processes similar to those observed in the premotor areas (VPC, DPC, and MPC) and PFC, both during the comparison and postponed decision report periods. These results suggest that frontal lobe neurons have the capacity to encode during the comparison and postponed decision report periods both the final result of the sensory evaluation and past information about it.

3.14. Context dependent responses across cortex

Romo and colleagues (Hernández et al., 2010) also documented the nature of the neuronal responses during the stimuli and their interactions. In addition to the standard discrimination test, the neuronal activity of all cortical areas was studied when the stimuli were delivered but monkeys were not requested to perform the task (Fig. 27B). Under this condition, most neurons across the cortical areas no longer encoded information about the stimuli and their interactions during these trials. The only areas that responded in this case were S1 and S2. This would suggest that those cortical areas central to S1 that encoded information about the stimuli are more likely associated with the sensory evaluation, than engaged simply in encoding the sensory stimulus (Fig. 28A). They also tested each neuron in a simpler task, in which trials proceeded exactly as in the vibrotactile task, but the stimuli were not delivered to the skin and the movements were guided by visual

cues. Neurons responded during movement execution but not during the periods preceding it (Fig. 28B). These control tests show that the neuronal responses from all the cortical areas studied, except for S1, reflect both the active comparisons between f1 and f2 and the execution of the motor choice that is specific to the context of the vibrotactile discrimination task (Fig. 28A).

3.15. Further comments on the neural mechanisms of sensory discrimination

To understand perceptual discrimination, we need to know where in the brain are the physical relevant variables encoded, and what are their relative contributions to the final percept. The studies reviewed above focused on this problem using highly simplified stimuli, in which the neuronal responses from diverse cortical areas can be examined while trained monkeys executed the same task. Although not sufficiently exhaustive, these studies show how cortical circuits are associated with perceptual discrimination. For example, the results show that S1 is essentially sensory and M1 is not necessarily primarily associated with motor outputs only. Also, those cortical areas that receive the S1 inputs combine the sensory representations of S1 with other types of stored signals representing, for example, past experience. Notably, these cortical areas encode at various strengths and times the stimulus parameters of both past and current sensory information on which the perceptual decision report is based. Moreover, the sensory, memory and comparison signals are gradually conveyed

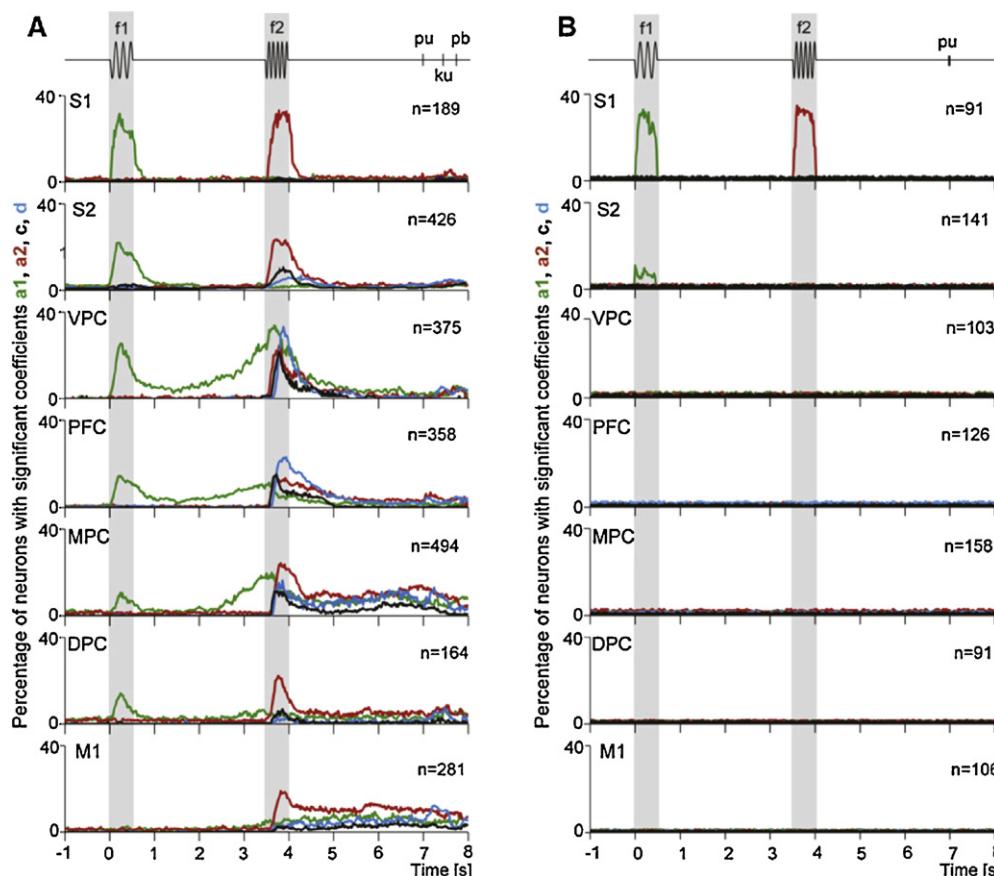


Fig. 27. Cortical population dynamics during the postponed discrimination task report. (A) Percentage of neurons with significant coefficients as a function of time. Green and red traces correspond to a_1 and a_2 coefficients, respectively. Black traces indicate percentage of neurons with a_1 and a_2 coefficients of opposite sign but of different magnitudes. These neurons combine differential response with a sensory component. Blue traces indicate percentage of neurons with coefficients a_1 and a_2 of opposite sign but similar magnitude; these produce a differential signal. (B) Percentage of neurons that responded during passive stimulation. These neurons constitute a subpopulation of those studied in A. S1, primary somatosensory cortex; S2, secondary somatosensory cortex; VPC, ventral premotor cortex; PFC, prefrontal cortex; MPC, medial premotor cortex; DPC, dorsal premotor cortex; M1, primary motor cortex. n = number of neurons.

Adapted from Hernández et al. (2010).

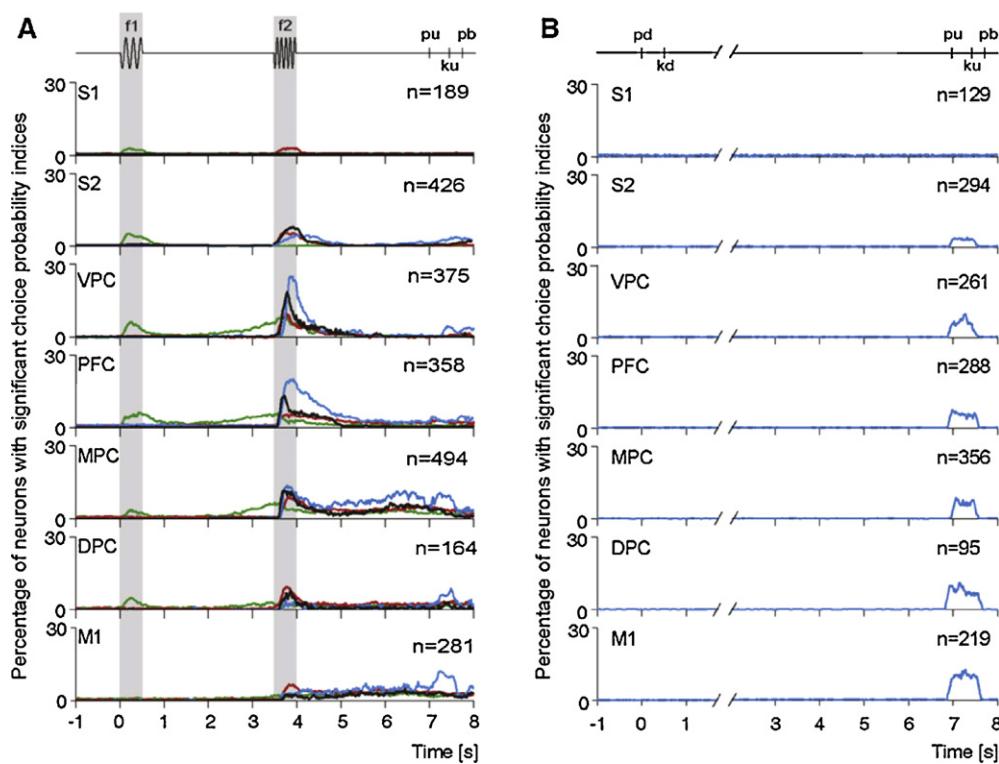


Fig. 28. Correlation between neuronal responses and behavioral choice. (A) Percentage of neurons that had significant choice probability indices as a function of time. Green trace: neurons that encoded information about f_1 ; red trace: neurons that carried information about f_2 ; black trace: partially differential neurons that carried information about f_1 and f_2 ; blue trace: fully differential neurons that carried information specifically about $f_2 - f_1$ only. (B) Percentage of the neurons in panel A that showed significant choice probability indices during the visual control task. In this test, animals had to follow a visual cue to produce the motor response. S1, primary somatosensory cortex; S2, secondary somatosensory cortex; PFC, prefrontal cortex; VPC, ventral premotor cortex; MPC, medial premotor cortex; DPC, dorsal premotor cortex; M1, primary motor cortex. n = number of neurons.

Adapted from Hernández et al. (2010).

to the frontal lobe circuits that in turn drive the motor circuits for a movement execution. Although this suggests a feed-forward processing beginning in S1 and ending in M1 this seems unlikely given feedback/recurrent communications between cortical and subcortical areas (Lamme and Roelfsema, 2000). This problem is currently addressed by recording the simultaneous activity of neurons distributed across cortical circuits engaged in the task reviewed here (Hernández et al., 2008).

The studies reviewed above show how distinct cortical areas contribute to the entire sequence of the processing steps that link sensation and decision making. One could argue that the neuronal events recorded in frontal lobe circuits during this task reflect other processes, such as preparation for a future action, particularly during the postponed decision report. This seems unlikely, however, because (1) delay responses between f_1 and f_2 depended on f_1 regardless of subsequent movements; (2) responses during the postponed decision period often reflected f_1 or f_2 information; (3) choice probability indices indicated that there were significant differences between correct versus error trials—except for S1, variability in the responses of those S2 and frontal neurons associated with encoding the stimuli correlates with the behavioral choice, although less strong than for the differential responses; (4) when the same movements were guided by visual cues the differential activity disappeared, except for some neurons that maintained their differential activity during movement execution; and (5) except for S1, all these processes are dependent on active stimulus comparisons, because they disappeared when subjects were not engaged in solving the task. It is surprising that during the comparison and postponed decision period some M1 neurons encoded information on which the decision is based. This result could suggest that M1 is engaged in

the readout of sensory information from working memory, when it is required to be compared with other sensory inputs, than engaged simply in a motor response in this task. However, considering the activity observed in other cortical areas notably in PFC, VPC, MPC and DPC during the same task, it would seem that this process involved conjoined activity of these cortical areas, not only during the postponed decision report, but also during the task components preceding it. Thus, a comparison of the strengths, dynamics and latencies of the f_1 and f_2 responses and their interactions across cortical areas is instructive.

The results show that the amplitude of the f_1 responses during the stimulus period is larger in S1, and gradually decreasing in S2, PFC, VPC, MPC and DPC. Also, more neurons with f_1 responses were recorded in S1, S2, PFC and VPC than in MPC and DPC. This suggests that f_1 is preferentially encoded in some of the cortical areas studied during this task. Accurate performance of the task can be consistent only with a sensory percept elicited during the f_1 period. The lifetime of the percept directly induced by f_1 could not be measured, if it were not kept in working memory. It therefore remained possible that the lifetime of a quantitative, induced percept was confined to the period of stimulation. The results reviewed show that the induced percept can be quantitatively memorized as illustrated by the microstimulation and decoding experiments. Although the strength of this signal varies across areas, all of them except S1 and M1 store the value of f_1 at different strengths and times during the working memory component of the task. These results are in accord with the proposal that there is a large cortical network that dynamically stores sensory information during working memory.

During the comparison period, f_2 is processed similarly by the same cortical areas and also in M1. Again, accurate performance of the task can be consistent only with a sensory percept elicited

during the f_2 period. But, it is during the f_2 period that the comparison between stored (f_1) and ongoing sensory information (f_2) takes place. During this period, f_2 must not only be present, but f_1 too. The comparison between f_1 and f_2 is observed in S2, VPC, PFC, MPC, DPC and M1, again at various strengths across these cortical areas. Some of these comparison signals evolve into a signal that is consistent with the animal's motor choice. During the postponed report period, the activity of all cortical areas except S1 encodes both the result of the comparison and past information on which the decision is based, and covaried with the animal's decision report. During the comparison and postponed delay periods, more neurons in MPC, DPC and M1 encoded f_2 than information about f_1 and comparison signals. This would suggest that these frontal circuits are more likely to store recent sensory information (f_2) than immediately-preceding sensory information (f_1) during this task. Consistent with this observation is the fact that the lifetime of the percept kept in working memory seems to impact the decision report. These results suggest that frontal lobe circuits do not simply wait for the result of a sensory evaluation to be communicated, but that actively participate in this process. Although highly speculative, we suggest that maintaining in working memory the original stimulus information on which the decision is based could serve to continuously update the postponed decision report in this task, and that very likely depends on the conjoined activity of these cortical areas.

Assuming that neurons from distinct cortical circuits coordinate their activities to solve this perceptual discrimination task, we wonder how these events evolve in time. The comparative analysis of the response latencies of f_1 , f_2 , and comparison signals could shed some light on this problem. For instance, compare S1 and S2: their response latencies were significantly different ($p < 0.01$), with the f_1 and f_2 signals beginning earlier in S1 than in S2. This type of comparative analysis also shows that the response latencies of S2 began significantly earlier ($p < 0.01$) than in VPC, PFC, MPC and DPC. This would suggest that S2 could send information about the stimuli to these frontal lobe circuits because their response types are quite similar to S2. The question is whether frontal lobe circuits receive at the same time S2 inputs or at different times. An analysis of the response latencies for f_1 and f_2 showed that the PFC and VPC respond significantly earlier ($p < 0.01$) than DPC, MPC and M1 (f_1 was not present in M1), with no significant differences between PFC and VPC ($p > 0.01$). This would suggest that the PFC and VPC receive the S2 inputs and that very likely distribute them to DPC, MPC and M1. However, further studies are needed to establish whether the functional connectivity between these cortical circuits proceeds in such order in the task used here.

The comparative analysis of the response latencies shows, in this task, that sensory information processing proceeds in a serial order. An important observation is that it was not found significant differences in the response latencies between the comparison and differential signals in the cortical areas that showed these responses (Hernández et al., 2010). The response latencies for the comparison and differential signals were all significantly ($p < 0.01$) delayed in comparison to the f_1 and f_2 signals. These findings suggest that S1 generates first a neural representation of the stimulus (positive monotonic encoding) and that then the S2 circuit transforms it into a dual representation (positive and negative monotonic encoding). The S2 representations could be then used by the frontal lobe circuits to not only encode the sensory information but also for the decision process (Romo et al., 2003). Also, these findings suggest that frontal lobe circuits coordinate the sensory, memory and decision components of the task, but that these processes are first coordinated in PFC and VPC (Hernández et al., 2010; Romo et al., 2004). These interpretations, however, need further support by analyzing the neuronal

responses simultaneously recorded across cortical areas during this task (Hernández et al., 2008).

A fundamental problem posed by the results obtained in this study is whether the neuronal signals across the task components are associated with decision making or motor planning. But, is there any difference between making a decision and planning a motor action that can be also postponed? In this respect, the study by Gold and Shadlen (2000) is particularly revealing. They recorded neural activity and injected microstimulation current in the frontal eye field of monkeys performing a two-alternative visual motion discrimination task. They found that this area gradually accumulates evidence for motion in one or another direction, such that the process of forming a decision and motor preparation seem to be indistinguishable. The decision process studied here seems to proceed as if it were part of an encompassing, established plan. In this respect, decision making could be conceived as the creation of a highly flexible motor plan that can be delayed (if the action requires a go signal to be triggered) or rapidly reconfigured (if the motor output is not specified ahead of time), for example (Hernández et al., 2002; Lemus et al., 2007; Romo et al., 2002, 2004). In fact, the stronger signals that come closest to encoding the output of a decision making process in our task have been found in areas involved in motor actions: PFC, VPC, MPC, DPC and M1. These results fit quite well with the interpretation that those frontal lobe circuits that show preparatory activity during delay periods not only encode the planning of motor actions, but encode also information on which the motor action is based (Carpenter et al., 1999; Hoshi and Tanji, 2004; Mushiake et al., 2006; Ohbayashi et al., 2003; Shima et al., 2006).

Intuitively, the circuits that generate motor commands should stand at the other end of the decision making processes because their output needs to be expressed physically.

Consistent with this conjecture is the fact that some neurons from the frontal lobe circuits respond differentially during the movement execution in the light instruction task, but not during the periods that preceded it. This result is very similar to that reported by Salinas and Romo (1998) in a categorization task. Another possibility is that motor planning in this task is maintained in other circuits, for example, in the spinal cord (Prut and Fetz, 1999). In this case weak signals sent from the cortical lobe circuits could activate the execution of the motor plan in this task. This conjecture is supported by the fact that the frontal lobe circuits studied in our task send projections to the motor circuits of the spinal cord (Dum and Strick, 1991; He et al., 1993). However, few studies have explored the functional role of frontal lobe neurons that project to the spinal cord during cognitive tasks (Kraskov et al., 2009). Thus, further studies are needed to explore the functional roles of frontal lobe circuit neurons that send projections to the spinal cord, and whether spinal motor circuits receive an instruction signal to execute the motor plan in this task.

The studies reviewed above are different from other paradigms used to investigate perceptual discrimination processes (de Lafuente and Romo, 2005; Newsome et al., 1989). They have shown how neurons from distinct cortical areas vary their discharges as a function of varying a sensory stimulus and of the behavioral responses (de Lafuente and Romo, 2006; Gold and Shadlen, 2007). The vibrotactile discrimination studies focused on how neurons from several cortical areas respond during decision making based on the evaluation of two stimuli. In the discrimination task, decision making arises from the interaction between stored information of f_1 and current f_2 . Thus, the fundamental mechanism behind decision making based on the evaluation of one single stimulus or about two stimuli resides on understanding the contribution of memory: how is it combined with the current sensory input to produce a decision? Although quite speculative, it is very likely that the working memory signals associated with the

delay period of the task is a reflection of the stimulus recall triggered by the sensory inputs. In this vein, it could be possible that the synapses of the neuronal networks associated with the discrimination task store the “task rule” (Deco et al., 2010; Mongillo et al., 2008), in which case the scalar analogue stimuli trigger synaptic graded responses, which are then reflected in the neuronal firing rates. This mechanism could be responsible for encoding the stimuli during the stimulus periods, working memory and decision periods in cortical areas central to S1.

In brief, we reviewed the available literature of how the dynamics of distinct cortical circuits contribute to perceptual discrimination. However, to reveal the flow of information between these circuits and the operations described in our task, it would be desirable to simultaneously record the neuronal events (Hernández et al., 2008; Haegens et al., 2011a,b). Experiments of this type would reveal how neuronal populations of distinct brain circuits joint efforts, in real time, to solve perceptual discrimination.

An important question deserving further research is whether the neuronal circuits that we studied arise as a consequence of training, or whether such circuits exist in naïve monkeys as well. A way to address this question would be to study those same circuits under different behavioral tasks. Additionally, it would be of much interest to study the same cortical areas in natural settings in monkeys carrying out natural behaviors. One possibility is that specialized circuits exist for each different behavior, and there is already experimental evidence for this hypothesis (Graziano and Aflalo, 2007). Alternatively, the cortical circuits we recorded could be participating in a wide range of behavioral tasks requiring the analysis of tactile information. In any case, recent experiments have shown that learning modulates the mechanisms by which sensory activity is read by upstream cortical areas (Imai et al., 2003; Law and Gold, 2008).

Insight into the neuronal operations underlying detection and discrimination of sensory information has emerged recently from computational modeling of neuronal circuits. These studies demonstrate that coding, maintenance and comparison of sensory information could be carried by attractor neuronal networks (Beck

et al., 2008; Machens and Brody, 2008; Wang, 2008; Barak et al., 2010). Under this assumption, the activity provided by sensory neurons, in conjunction with modulatory signals, shifts the neuronal networks through different stable states. These attractors maintain recurrent patterns of spiking activity, allowing the coding and maintenance of sensory information through delay periods in which no sensory inputs are provided to the network. The arrival of new modulatory and sensory activity can then take the network out of the memory state and set it into a winner take-all-mode. In this mode, one population of neurons inhibits its competitors and settles into a final attractor encoding the network output (Deco et al., 2010; Rolls et al., 2010). In agreement with physiological findings, these computational models propose that decisions are encoded by discrete neuronal populations whose activity selectively represent each decision outcome, i.e., whether a stimulus was present or not in the case of a detection task (Deco et al., 2007), and whether the f_1 or the f_2 stimuli had the higher frequency in the case of a comparison task (Machens et al., 2005; Martínez-García et al., 2011).

4. Conclusions

We review the available evidence on how a sensory stimulus is represented in the brain and how such representation relates to sensation, memory and decision reports. We showed that the stimulus-locked response of S1 neurons is transformed by downstream areas into a simple firing rate code representing the stimulus frequency during presentation, working memory and decision components of the tasks. The experimental results reviewed above show that detecting and discriminating sensory stimuli engages a large number of cortical areas of the parietal and frontal lobes. This representation progressively becomes associated with the subjects' perceptual decision reports. This suggests that multiple cortical areas, and very likely subcortical structures (de Lafuente and Romo, 2011; Merchant et al., 1997; Romo et al., 1995), are needed to generate a decision report. This should not be different in other sensory modality tasks, and comparative studies are required to uncover principles of brain organization of how

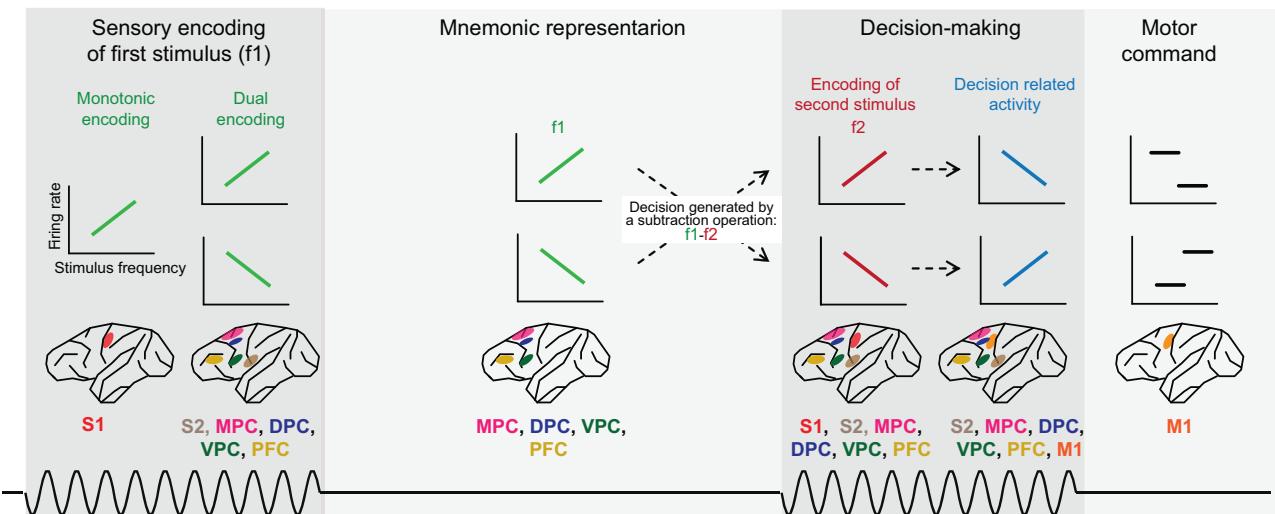


Fig. 29. The discrimination task engages multiple cortical areas on the parietal and frontal lobes. The two stimuli (f_1 and f_2) separated by a delay are depicted at the bottom (not drawn to scale). Diagrams of the macaque brain depict cortical areas with task-related activity. The primary somatosensory cortex (S1) encodes f_1 only through positive monotonic responses. This sensory information is distributed to other cortical areas and transformed in such a way that during the second half of the stimulus opposite representations (dual encoding) arise in S2, MPC, DPC, VPC and PFC. These dual neuronal representations of f_1 are encoded during the delay period by the sustained activity of cortical areas on the frontal lobe. After the delay period, the frequency of the second stimulus (f_2) is encoded in all recorded areas of the frontal and parietal lobes. Importantly, neurons with decision-related activity (i.e., reflecting the comparison of f_1 and f_2) emerge in frontal and parietal cortical areas around 220 ms into the second stimulus. These decision signals indicate the difference in frequency between the two stimuli, and could arise by subtracting the activity of neurons encoding f_1 and f_2 with opposite tuning. This decision activity could then be used to generate the binary-valued signals associated with motor commands to push the response buttons. Note that with the exception of S1, neurons with opposite tuning are observed across cortex.

sensory inputs are converted in memories and decision motor reports.

The vibrotactile discrimination task in conjunction with recordings of multiple cortical areas has proved to be a valuable tool to study how behavioral actions are selected according to current and past sensory information. By requiring the monkeys to compare two stimuli separated by a delay period, the discrimination task allowed uncovering the neuronal mechanism underlying the comparison of working memory information with incoming sensory stimuli.

As depicted in Fig. 29, the presentation of f1 activates a large network of cortical areas, from S1 to PFC. It is worth noting that with the exception of S1, activated neurons segregate into two populations with opposite tuning: one that is active for higher stimulus frequencies, and one that generates more activity with low frequency stimulation. This is suggestive of a specialized circuit that from early on the processing hierarchy is devoted to solve the discrimination task. How this circuit emerges or is shaped by learning is a subject of much interest that we think should be pursued in the future.

After the widespread activation elicited by f1 (Fig. 29), the neuronal representation of the vibration frequency is stored by the sustained activity of frontal lobe areas. We would like to emphasize that not only the PFC, but also the premotor areas participate in the encoding of sensory information into working memory.

The emerging picture shows that the comparison operation underlying a decision is widely distributed across cortex. With the exception of S1, decision-related activity could be observed in S2, MPC, VPC, DPC, PFC and M1. Response latencies indicate that decision-related activity emerges almost simultaneously in these cortical areas. This suggests that decision-making is a distributed function arising not from serial processing but from the joined activity of many cortical areas.

Acknowledgments

The research of R.R. was partially supported by an International Research Scholars Award from the Howard Hughes Medical Institute, El Colegio Nacional, and grants from the Dirección del Personal Académico de la Universidad Nacional Autónoma de México and the Consejo Nacional de Ciencia y Tecnología. V. de L. was supported by Dirección del Personal Académico de la Universidad Nacional Autónoma de México, grant number IA201011-22, and by Consejo Nacional de Ciencia y Tecnología.

References

- Adrian, E.D., 1928. The Basis of Sensation. The Action of the Sense Organs. London, Christopers.
- Axel, R., 2005. Scents and sensibility: a molecular logic of olfactory perception (Nobel lecture). *Angew. Chem. Int. Ed. Engl.* 44, 6110–6127.
- Bair, W., Zohary, E., Newsome, W.T., 2001. Correlated firing in macaque visual MT: time scales and relationship to behavior. *J. Neurosci.* 21, 1676–1697.
- Barak, O., Tsodyks, M., Romo, R., 2010. Neuronal population coding of parametric working memory. *J. Neurosci.* 30, 9424–9430.
- Barlow, H.B., 1957. Increment thresholds at low intensities considered as signal/noise discriminations. *J. Physiol.* 136, 469–488.
- Beck, J.M., Ma, W.J., Kiani, R., Hanks, T., Churchland, A.K., Roitman, J., Shadlen, M.N., Latham, P.E., Pouget, A., 2008. Probabilistic population codes for Bayesian decision making. *Neuron* 60, 1142–1152.
- Britten, K.H., van Wezel, R.J., 1998. Electrical microstimulation of cortical MST biases heading perception in monkeys. *Nat. Neurosci.* 1, 59–63.
- Britten, K.H., Newsome, W.T., Shadlen, M.N., Celebrini, S., Movshon, J.A., 1996. A relationship between behavioral choice and the visual responses of neurons in macaque MT. *Vis. Neurosci.* 13, 87–100.
- Brody, C.D., Hernández, A., Zainos, A., Romo, R., 2003. Timing and neural encoding of somatosensory parametric working memory in macaque monkey. *Cereb. Cortex* 13, 1196–1207.
- Buck, L.B., 2005. Unraveling the sense of smell (Nobel lecture). *Angew. Chem. Int. Ed. Engl.* 44, 6128–6140.
- Burton, H., Fabri, M., 1995. Ipsilateral intracortical connections of physiologically defined cutaneous representations in areas 3b and 1 of macaque monkeys. *J. Comp. Neurol.* 355, 508–538.
- Burton, H., Fabri, M., Alloway, K., 1995. Cortical areas within the lateral sulcus connected to cutaneous representations in areas 3b and 1: a revisited interpretation of the second somatosensory area in macaque monkeys. *J. Comp. Neurol.* 355, 539–562.
- Carpenter, A.F., Georgopoulos, A.P., Pellicer, G., 1999. Motor cortical encoding of serial order in a context-recall task. *Science* 283, 1752–1757.
- Chow, S.S., Romo, R., Brody, C.D., 2009. Context-dependent modulation of functional connectivity: S2 to PFC connections in two-stimulus-interval discrimination task. *J. Neurosci.* 29, 7238–7245.
- Cipolloni, P.B., Pandya, D.N., 1999. Cortical connections of the frontoparietal opercular areas in the rhesus monkey. *J. Comp. Neurol.* 403, 431–458.
- Connor, C.E., Hsiao, S.S., Phillips, J.R., Johnson, K.O., 1990. Tactile roughness: neural codes that account for psychophysical magnitude estimates. *J. Neurosci.* 10, 3823–3836.
- Creutzfeldt, O.D., Nothdurft, H.C., 1978. Representation of complex stimuli in the brain. *Naturwissenschaften* 65, 307–318.
- Crick, F., Koch, C., 1995. Are we aware of neural activity in primary visual cortex? *Nature* 375, 121–123.
- Daniel, W.W., 2009. Biostatistics: a foundation for analysis in the health sciences. J. Wiley & Sons, Hoboken, NJ.
- de Lafuente, V., Romo, R., 2005. Neuronal correlates of subjective sensory experience. *Nat. Neurosci.* 12, 1698–1703.
- de Lafuente, V., Romo, R., 2006. Neural correlate of subjective sensory experience gradually builds up across cortical areas. *Proc. Natl. Acad. Sci. U.S.A.* 10, 1266–1271.
- de Lafuente, V., Romo, R., 2011. Midbrain brain dopamine neurons code subjective sensory experience and uncertainty of perceptual decisions. *Proc. Natl. Acad. Sci. U.S.A.* 2011, <http://dx.doi.org/10.1073/pnas.1117636108>.
- Deco, G., Pérez-Sanagustín, M., de Lafuente, V., Romo, R., 2007. Perceptual detection as a dynamical bistability phenomenon: a neurocomputational correlate of sensation. *Proc. Natl. Acad. Sci. U.S.A.* 104, 20073–20077.
- Deco, G., Rolls, E.T., Romo, R., 2010. Synaptic dynamics and decision making. *Proc. Natl. Acad. Sci. U.S.A.* 107, 7545–7549.
- Draper, N., Smith, H., 1966. Applied Regression Analysis, second edition. New York, John Wiley and Sons.
- Dum, R.P., Strick, P.L., 1991. The origin of corticospinal projections from the premotor areas in the frontal lobe. *J. Neurosci.* 11, 667–689.
- Fabre-Thorpe, M., Delorme, A., Marlot, C., Thorpe, S., 2001. A limit to the speed of processing in ultra-rapid visual categorization of novel natural scenes. *J. Cogn. Neurosci.* 13, 171–180.
- Fries, P., Neueschwander, S., Engel, A.K., Goebel, R., Singer, W., 2001a. Rapid feature selective neuronal synchronization through correlated latency shifting. *Nat. Neurosci.* 4, 194–200.
- Fries, P., Reynolds, J.H., Rorie, A.E., Desimone, R., 2001b. Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* 291, 1560–1563.
- Funahashi, S., Bruce, C.J., Goldman-Rakic, P.S., 1989. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J. Neurophysiol.* 331–349.
- Fuster, J.M., 1997. Network memory. *Trends Neurosci.* 20, 451–459.
- Georgopoulos, A.P., Schwartz, A., Kettner, R.E., 1988. Primate motor cortex and free arm movements to visual targets in three-dimensional space. II. Coding of direction of movement by a neuronal population. *J. Neurosci.* 8, 2928–2937.
- Gold, J.I., Shadlen, M.N., 2000. Representation of a perceptual decision in developing oculomotor commands. *Nature* 404, 390–394.
- Gold, J.I., Shadlen, M.N., 2001. Neural computations that underlie decisions about sensory stimuli. *Trends Cogn. Sci. (Regul. Ed.)* 5, 10–16.
- Gold, J.I., Shadlen, M.N., 2007. The neural basis of decision making. *Annu. Rev. Neurosci.* 30, 535–574.
- Graziano, M.S.A., Aflalo, T.N., 2007. Mapping behavioral repertoire onto the cortex. *Neuron* 56, 239–251.
- Graziano, M.S., Hu, X.T., Gross, C.G., 1997. Visuospatial properties of ventral premotor cortex. *J. Neurophysiol.* 77, 2268–2292.
- Graziano, M.S., Reiss, L.A., Gross, C.G., 1999. A neuronal representation of the location of nearby sounds. *Nature* 397, 428–430.
- Green, D.M., Swets, J.A., 1966. Signal Detection Theory and Psychophysics. Wiley, New York.
- Haegens, S., Nácher, V., Hernández, A., Luna, R., Jensen, O., Romo, R., 2011a. Beta oscillations in monkey sensorimotor network reflect decision making. *Proc. Natl. Acad. Sci. U.S.A.* 108, 10708–10713.
- Haegens, S., Nácher, V., Luna, R., Romo, R., Jansen, O., 2011b. Alpha oscillations in the monkey sensorimotor network influence discrimination performance by rhythmical inhibition of neuronal spiking. *Proc. Natl. Acad. Sci. U.S.A.* 108, 19377–19382.
- Harris, J.A., Miniussi, C., Harris, I.M., Diamond, M.E., 2002. Transient storage of a tactile memory trace in primary somatosensory cortex. *J. Neurosci.* 22, 8720–8725.
- Harris, J.A., Arabzadeh, E., Fairhall, A.L., Benito, C., Diamond, M.E., 2006. Factors affecting frequency discrimination of vibrotactile stimuli: implications for cortical encoding. *PLoS ONE* 1, e100.
- Hartline, H.K., Wagner, H.G., Ratliff, F., 1956. Inhibition in the eye of limulus. *J. Gen. Physiol.* 39, 651–673.

- He, S.Q., Dum, R.P., Strick, P.L., 1993. Topographic organization of corticospinal projections from the frontal lobe: motor areas in the lateral surface of the hemisphere. *J. Neurosci.* 13, 952–980.
- Heekeren, H.R., Marrett, S., Ruff, D.A., Bandettini, P.A., Ungerleider, L.G., 2006. Involvement of human left dorsolateral prefrontal cortex in perceptual decision making is independent of response modality. *Proc. Natl. Acad. Sci. U.S.A.* 103, 10023–10028.
- Hernández, A., Salinas, E., García, R., Romo, R., 1997. Discrimination in the sense of flutter: new psychophysical measurements in monkeys. *J. Neurosci.* 17, 6391–6400.
- Hernández, A., Zainos, A., Romo, R., 2000. Neuronal correlates of sensory discrimination in the somatosensory cortex. *Proc. Natl. Acad. Sci. U.S.A.* 97, 6091–6096.
- Hernández, A., Zainos, A., Romo, R., 2002. Temporal evolution of a decision-making process in medial premotor cortex. *Neuron* 33, 959–972.
- Hernández, A., Nácher, V., Luna, R., Alvarez, M., Zainos, A., Cordero, S., Camarillo, L., Vázquez, Y., Lemus, L., Romo, R., 2008. Procedure for recording the simultaneous activity of single neurons distributed across cortical areas during sensory discrimination. *Proc. Natl. Acad. Sci. U.S.A.* 105, 16785–16790.
- Hernández, A., Nácher, V., Luna, R., Zainos, A., Lemus, L., Alvarez, M., Vázquez, Y., Camarillo, L., Romo, R., 2010. Decoding a perceptual decision process across cortex. *Neuron* 66, 300–314.
- Hoshi, E., Tanji, J., 2004. Differential roles of neural activity in the supplementary and presupplementary motor areas: from information retrieval to motor planning and execution. *J. Neurophysiol.* 92, 3482–3489.
- Hubel, D.H., Wiesel, T.N., 1998. Early exploration of the visual cortex. *Neuron* 20, 401–412.
- Imai, T., Kamping, S., Breitenstein, C., Pantev, C., Lutkenhoner, B., Knecht, S., 2003. Learning of tactile frequency discrimination in humans. *Human Brain Mapping* 18, 260–271.
- Iwamura, Y., 1998. Hierarchical somatosensory processing. *Curr. Opin. Neurobiol.* 8, 522–528.
- Johnson, K.O., 1980. Sensory discrimination: neural processes preceding discrimination decision. *J. Neurophysiol.* 43, 1793–1815.
- Johnson, K.O., Hsiao, S.S., 1992. Neural mechanism of tactful form and texture perception. *Annu. Rev. Neurosci.* 15, 227–250.
- Jun, J.K., Miller, P., Hernández, A., Zainos, A., Lemus, L., Brody, C.D., Romo, R., 2010. Heterogenous population coding of a short-term memory and decision task. *J. Neurosci.* 30, 916–929.
- Jung, R., 1984. Sensory research in historical perspective: some philosophical foundations of perception. In: Brookhart, J.M., Mountcastle, V.B. (Eds.), *Handbook of Physiology. Section 1: The Nervous System, Vol. III. Sensory Process, Part 1* (Vol. Ed. Darian-Smith, I.) American Physiological Society, Bethesda, M.D., pp. 1–74.
- Kepcs, A., Wang, X.J., Lisman, J., 2002. Bursting neurons signal input slope. *J. Neurosci.* 22, 9053–9062.
- Krahe, R., Gabbiani, F., 2004. Burst firing in sensory systems. *Nat. Rev. Neurosci.* 5, 13–24.
- Kraskov, A., Dancause, N., Quallo, M.M., Shepherd, S., Lemon, R.N., 2009. Corticospinal neurons in macaque ventral premotor cortex with mirror properties: a potential mechanism for action suppression? *Neuron* 64, 922–930.
- Kun, J.K., Miller, P., Hernández, A., Zainos, A., Lemus, L., Brody, C.D., Romo, R., 2010. Heterogenous population of a short-term memory and decision task. *J. Neurosci.* 30, 916–929.
- Lamme, V.A., Roelfsema, P.R., 2000. The distinct modes of vision offered by feedforward and recurrent processing. *Trends Neurosci.* 23, 571–579.
- LaMotte, R.H., Mountcastle, V.B., 1975. Capacities of humans and monkeys to discriminate between vibratory stimuli of different frequency and amplitude: correlation between neural events and psychophysical measurements. *J. Neurophysiol.* 38, 539–559.
- Law, C.T., Gold, J.I., 2008. Neural correlates of perceptual learning in a sensory-motor but not a sensory, cortical area. *Nat. Neurosci.* 11, 505–513.
- Lemus, L., Hernández, A., Luna, R., Zainos, A., Nácher, V., Romo, R., 2007. Neural correlates of a postponed decision report. *Proc. Natl. Acad. Sci. U.S.A.* 104, 17174–17179.
- Lemus, L., Hernández, H., Romo, R., 2009. Neural encoding of auditory discrimination in ventral premotor cortex. *Proc. Natl. Acad. Sci. U.S.A.* 106, 14640–14645.
- Lemus, L., Hernández, A., Luna, R., Zainos, A., Romo, R., 2010. Do sensory cortices process more than one sensory modality during perceptual judgments? *Neuron* 67, 335–348.
- Leopold, D.A., Logothetis, N.K., 1996. Activity changes in early visual cortex reflect monkeys' percepts during binocular rivalry. *Nature* 379, 549–553.
- Luna, R., Hernández, A., Brody, C.D., Romo, R., 2005. Neural codes for perceptual discrimination in primary somatosensory cortex. *Nat. Neurosci.* 8, 1210–1219.
- Macefield, G., Gandevia, S.C., Burke, D., 1990. Perceptual responses to microstimulation of single afferents innervating joints, muscles and skin of the human hand. *J. Physiol.* 429, 113–129.
- Machens, C.K., Brody, C.D., 2008. Design of continuous attractor networks with monotonic tuning using a symmetry principle. *Neural. Comput.* 20, 452–485.
- Machens, C.K., Romo, R., Brody, C.D., 2005. Flexible control of mutual inhibition: a neural model of two-interval discrimination. *Science* 307, 1121–1124.
- Machens, C.K., Romo, R., Brody, C.D., 2010. Functional, but not anatomical, separation of "what" and "when" in prefrontal cortex. *J. Neurosci.* 30, 350–360.
- Martínez-Conde, S., McKinik, S.L., Hubel, D.H., 2000. The function of bursts of spikes during visual fixation in the awake primate lateral geniculate nucleus and primary visual cortex. *Proc. Natl. Acad. Sci. U.S.A.* 99, 13920–13925.
- Martínez-García, M., Rolls, E.T., Deco, G., Romo, R., 2011. Neural and computational mechanisms of postponed decisions. *Proc. Natl. Acad. Sci. U.S.A.* 108, 11626–11631.
- Matsuzaka, Y., Aizawa, H., Tanji, J., 1992. A motor area rostral to the supplementary motor areas (presupplementary motor area) in the monkey: neuronal activity during a learned motor task. *J. Neurophysiol.* 68, 653–662.
- Merchant, H., Zainos, A., Hernández, A., Salinas, E., Romo, R., 1997. Functional properties of primate putamen neurons during the categorization of tactile stimuli. *J. Neurophysiol.* 77, 1132–1154.
- Merzenich, M.M., Brugge, J.F., 1973. Representation of the cochlear partition of the superior temporal plane of the macaque monkey. *Brain Res.* 50, 275–296.
- Meyer, K., 2011. Primary sensory cortices, top-down projections and conscious experience. *Prog. Neurobiol.* 94, 408–417.
- Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* 24, 167–202.
- Mishkin, M., 1979. Analogous neural models for tactial and visual learning. *Neuropsychologia* 17, 139–151.
- Mongillo, G., Barak, O., Tsodyks, M., 2008. Synaptic theory of working memory. *Science* 319, 1543–1546.
- Mountcastle, V.B., 1957. Modality and topographic properties of single neurons of cat's somatic sensory cortex. *J. Neurophysiol.* 20, 408–434.
- Mountcastle, V.B., Talbot, W.H., Darian-Smith, I., Kornhuber, H.H., 1967. Neural basis of the sense of flutter-vibration. *Science* 155, 597–600.
- Mountcastle, V.B., Talbot, W.H., Sakata, H., Hyvärinen, J., 1969. Cortical neuronal mechanisms in flutter-vibration studied in unanesthetized monkeys. *Neuronal periodicity and frequency discrimination*. *J. Neurophysiol.* 32, 452–484.
- Mountcastle, V.B., LaMotte, R.H., Carli, G., 1972. Detection thresholds for stimuli in humans and monkeys: comparison with thresholds events in mechanoreceptive afferent nerve fibers innervating the monkey hand. *J. Neurophysiol.* 25, 122–136.
- Mountcastle, V.B., Steinmetz, M.A., Romo, R., 1990. Frequency discrimination in the sense of flutter: psychophysical measurements correlated with postcentral events in behaving monkeys. *J. Neurosci.* 10, 3032–3044.
- Mushiake, H., Saito, N., Sakamoto, K., Itoyama, Y., Tanji, J., 2006. Activity in the lateral prefrontal cortex reflects multiple steps of future events in action plans. *Neuron* 50, 631–641.
- Nácher, V., Ojeda, S., Cardoso-Suárez, C., Roca-Pardinas, J., Acuña, C., 2006. Neural correlates of memory retrieval in the prefrontal cortex. *Eur. J. Neurosci.* 24, 925–936.
- Newsome, W.T., Britten, K.H., Movshon, J.A., 1989. Neural correlates of a perceptual decision. *Nature* 341, 52–54.
- Ochoa, J., Torebjörk, E., 1983. Sensations evoked by intraneuronal microstimulation of single mechanoreceptor units innervating the human hand. *J. Physiol.* 342, 633–654.
- Ohbayashi, M., Ohki, K., Miyashita, Y., 2003. Conversion of working memory to motor sequence in the monkey premotor cortex. *Science* 301, 233–236.
- Pascual-Leone, A., Walsh, V., 2001. Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science* 292, 510–512.
- Pons, T.P., Garraghty, P.E., Friedman, D.P., Mishkin, M., 1987. Physiological evidence for serial processing in somatosensory cortex. *Science* 237, 417–420.
- Powell, T.P.S., Mountcastle, V.B., 1959. Some aspects of the functional organization of the cortex of the postcentral gyrus of the monkey: a correlation of findings obtained in a single unit analysis with cytoarchitecture. *Bull. Johns Hopkins Hosp.* 105, 133–162.
- Prut, Y., Fetz, E.E., 1999. Primate spinal interneurons show premovement instructed delay activity. *Nature* 401, 590–594.
- Recanzone, G.H., Merzenich, M.M., Schreiner, C.E., 1992. Changes in the distributed temporal response properties of SI cortical neurons reflect improvements in performance on a temporally based tactile discrimination task. *J. Neurophysiol.* 67, 1071–1091.
- Reinagel, P., Godwin, D., Sherman, M., Koch, C., 1999. Encoding of visual information by LGN bursts. *J. Neurophysiol.* 81, 2558–2569.
- Ress, D., Heeger, D.J., 2003. Neuronal correlates of perception in early visual cortex. *Nat. Neurosci.* 6, 414–420.
- Rizzolatti, G., Luppino, G., 2001. The cortical motor system. *Neuron* 31, 889–901.
- Rizzolatti, G., Camarda, R., Fogassi, L., Gentilucci, M., Luppino, G., Matelli, M., 1988. Functional organization of inferior area 6 in the macaque monkey. II. Area F5 and the control of distal movements. *Exp. Brain Res.* 71, 491–507.
- Robinson, C.J., Burton, H., 1980. Organization of somatosensory fields in cortical areas 7b, retroinsular, postauditory, and granular insular cortical areas of the M. Fascicularis. *J. Comp. Neurol.* 192, 93–108.
- Rolls, E.T., Grabenhorst, F., Deco, G., 2010. Decision-making, errors, and confidence in the brain. *J. Neurophysiol.* 104, 2359–2374.
- Romo, R., Salinas, E., 2001. Touch and go: decision-making mechanisms in somatosensation. *Annu. Rev. Neurosci.* 24, 107–137.
- Romo, R., Salinas, E., 2003. Flutter discrimination: neural codes, perception, memory and decision making. *Nat. Rev. Neurosci.* 4, 203–218.
- Romo, R., Ruiz, S., Crespo, P., Zainos, A., Merchant, H., 1993. Representation of tactile signals in primate supplementary motor area. *J. Neurophysiol.* 70, 2690–2694.
- Romo, R., Merchant, H., Ruiz, S., Crespo, P., Zainos, A., 1995. Neuronal activity in primate putamen during categorical perception of somaesthetic stimuli. *NeuroReport* 6, 120–124.
- Romo, R., Merchant, H., Zainos, A., Hernández, A., 1996. Categorization of somaesthetic stimuli: sensorimotor performance and neuronal activity in primary somatic sensory cortex of awake monkeys. *NeuroReport* 7, 1273–1279.

- Romo, R., Merchant, H., Zainos, A., Hernández, A., 1997. Categorical perception of somesthetic stimuli: psychophysical measurements correlated with neuronal events in primate medial premotor cortex. *Cereb. Cortex* 7, 317–326.
- Romo, R., Hernández, A., Zainos, A., Salinas, E., 1998. Somatosensory discrimination based on cortical microstimulation. *Nature* 392, 387–390.
- Romo, R., Brody, C.D., Hernández, A., Lemus, L., 1999. Neuronal correlates of parametric working memory in the prefrontal cortex. *Nature* 399, 470–473.
- Romo, R., Hernández, A., Zainos, A., Brody, C.D., Lemus, L., 2000. Sensing without touching: psychophysical performance based on cortical microstimulation. *Neuron* 26, 273–278.
- Romo, R., Hernández, A., Zainos, A., Brody, C.D., 2002. Neuronal correlates of decision-making in secondary somatosensory cortex. *Nat. Neurosci.* 5, 1217–1225.
- Romo, R., Hernández, A., Zainos, A., Salinas, E., 2003. Correlated neuronal discharges that increase coding efficiency during perceptual discrimination. *Neuron* 38, 649–657.
- Romo, R., Hernández, A., Zainos, A., 2004. Neuronal correlates of a perceptual decision in ventral premotor cortex. *Neuron* 41, 165–173.
- Ruiz, S., Crespo, P., Romo, R., 1995. Representation of moving tactile stimuli in the somatic sensory cortex of awake monkeys. *J. Neurophysiol.* 73, 525–537.
- Salinas, E., Romo, R., 1998. Conversion of sensory signals into motor commands in primary motor cortex. *J. Neurosci.* 18, 499–511.
- Salinas, E., Hernández, A., Zainos, A., Romo, R., 2000. Periodicity and firing rate as candidate neural codes for the frequency of vibrotactile stimuli. *J. Neurosci.* 20, 5503–5515.
- Salzman, D., Britten, K.H., Newsome, W.T., 1990. Cortical microstimulation influences perceptual judgements of motion direction. *Nature* 346, 174–177.
- Schall, J.D., 2001. Neural basis of deciding, choosing and acting. *Nat. Rev. Neurosci.* 2, 583–591.
- Schwartz, A., Kettner, R.E., Georgopoulos, A.P., 1988. Primate motor cortex and free arm movements to visual targets in three-dimensional space. I. Relations between single cell discharge and direction of movement. *J. Neurosci.* 8, 2913–2927.
- Shadlen, M.N., Newsome, W.T., 1996. Motion perception: seeing and deciding. *Proc. Natl. Acad. Sci. USA* 93, 628–633.
- Shadlen, M.N., Newsome, W.T., 2001. Neural basis of a perceptual decision in the parietal cortex (area LIP) of the rhesus monkey. *J. Neurophysiol.* 86, 1916–1936.
- Shima, K., Tanji, J., 2000. Neuronal activity in the supplementary and presupplementary motor areas for temporal organization of multiple movements. *J. Neurophysiol.* 84, 2148–2160.
- Shima, K., Isoda, M., Mushiake, H., Tanji, J., 2006. Categorization of behavioral sequences in the prefrontal cortex. *Nature* 445, 315–318.
- Siegel, S., Castellan, N.J., 1988. Nonparametric statistics for the behavioral sciences. McGraw-Hill, New York.
- Sinclair, R.J., Burton, H., 1991. Tactile discrimination of gratings: psychophysical and neural correlates in human and monkey. *Somatosens. Mot. Res.* 8, 241–248.
- Sinclair, R.J., Burton, H., 1993. Neuronal activity in the second somatosensory cortex of monkeys (*Macaca mulatta*) during active touch of gratings. *J. Neurophysiol.* 70, 331–350.
- Stettler, D.D., Axel, R., 2009. Representations of odor in the piriform cortex. *Neuron* 63, 854–864.
- Sur, M., Wall, J.T., Kaas, J.H., 1984. Modular distribution of neurons with slowly adapting and rapidly adapting responses in area 3b of somatosensory cortex in monkeys. *J. Neurophysiol.* 51, 724–744.
- Talbot, W.H., Darian-Smith, I., Kornhuber, H.H., Mountcastle, V.B., 1968. The sense of flutter-vibration: comparison of the human capacity response patterns of mechanoreceptive afferents from the monkey hand. *J. Neurophysiol.* 31, 301–334.
- Thompson, K.G., Schall, J.D., 1999. The detection of visual signals by macaque frontal eye field during masking. *Nat. Neurosci.* 2, 283–288.
- Thompson, K.G., Schall, J.D., 2000. Antecedents and correlates of visual detection and awareness in macaque prefrontal cortex. *Vision Res.* 40, 1523–1528.
- Vallbo, A.B., 1995. Single-afferent neurons and somatic sensation in humans. In: Gazzaniga, M.S. (Ed.), *The Cognitive Neurosciences*. MIT Press, Oxford, pp. 237–252.
- Vallbo, A.B., Johansson, R.S., 1984. Properties of cutaneous mechanoreceptors in the human hand related to touch sensations. *Human Neurobiol.* 3, 3–14.
- Vázquez, P., Cano, M., Acuña, C., 2000. Discrimination of line orientation in humans and monkeys. *J. Neurophysiol.* 83, 2639–2648.
- Vogel, R., Orban, G., 1990. How well do response changes of striate neurons signal differences in orientation? A study in the discriminating monkey. *J. Neurosci.* 10, 3543–3558.
- von Heimendahl, M., Itskov, P.M., Arabzadeh, E., Diamond, M.E., 2007. Neuronal activity in rat barrel cortex underlying texture discrimination. *PLoS Biol.* 5, e305.
- Wang, X.J., 2008. Decision making in recurrent neuronal circuits. *Neuron* 60, 215–234.
- Werner, G., Mountcastle, V.B., 1965. Neural activity in mechanoreceptive cutaneous afferents: stimulus-response relations, weber functions, and information transmission. *J. Neurophysiol.* 28, 359–397.
- Wise, S.P., Di Pellegrino, G., Boussaoud, D., 1992. Primate premotor cortex: dissociation of visuomotor from sensory signals. *J. Neurophysiol.* 68, 969–972.
- Zainos, A., Merchant, H., Hernández, A., Salinas, E., Romo, R., 1997. Role of primary somatic sensory cortex in the categorization of moving tactile stimuli: effects of lesions. *Exp. Brain Res.* 115, 357–360.
- Zohary, E., Shadlen, M.N., Newsome, W.T., 1994. Correlated neuronal discharge rate and its implications for psychophysical performance. *Nature* 370, 140–143.