Research report

From sensation to action

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Abstract

Key to understanding somatosensation is the form of how the mechanical stimuli are represented in the evoked neuronal activity of the brain. Here, we focus on studies that address the question of which components of the evoked neuronal activity in the somatosensory system represent the stimulus features. We review experiments that probe whether these neuronal representations are essential to somatosensation. We also discuss recent results that suggest how the somatosensory stimuli are represented in the brain during short-term memory. Finally, we review data that show the neuronal correlates of a decision during somatosensory perception. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

We focus on the neuronal mechanisms associated with somatosensory perception. To understand this cognitive function, three major questions need to be answered. In the first, we want to know how the mechanical stimuli are encoded from the primary afferents that are linked to mechanoreceptors up to the neuronal ensembles of the cerebral cortex. This section has a rich long tradition probing the peripheral neural code that matches the psychophysical performance [17,62,64,65,68]. In the second, we want to understand whether the cortical neural representations of the stimulus features are meaningful for somatosensory perception [50]. In the third, we want to understand how somatosensory processing is linked to the motor representations during the formation of a decision [50]. This operation requires understanding not only the sensory to motor transformations at each level of the system, but also proving that the correlations between neuronal representations and sensory stimuli are not simple coincidences.

These questions can only be addressed in combined psychophysical/neurophysiological experiments. But,

beyond this, the objective is not only to understand the functioning of the somatosensory system, but to use it as a model for exploring the higher functions of the brain. In this respect, we identify some elements of the organization of the somatosensory system that may facilitate the study of the construction of a sensation and the formation of a decision. For example, consider the simplicity of the anatomic organization of the somatosensory system from the periphery to the neocortex, compared with the visual system [10]. We know with some precision the mechanoreceptor organs and the primary afferents that link them with the central nervous system [7]. The pathways from the periphery to the brain are well known, as well as the connectivity between central somatosensory areas with the motor regions of the brain [50]. In addition, the peripheral encoding of simple and complex mechanical stimuli are known and their association with perception as well [17,62,64,65,67,68]. These elements, we believe, may allow investigators to address the question of how the somatosensory stimulus features are dynamically represented in the brain, how these representations are used for sensation and perception and, ultimately, how decisions are expressed through the motor apparatus. Therefore, the study of the somatosensory system is an important enterprise not only for understanding soma-

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tosensation, but also for understanding the cognitive functions of the brain.

2. Overview of the somatosensory system

The somatosensory system, together with the visual system, has served as a model to investigate stimulus information processing, and some general principles of the functional organization of the brain. There are some elements of the organization of the somatosensory system that are relevant to investigate neural coding of sensory stimuli both at the periphery and in the brain. For sake of simplicity, we restrict this review on the cutaneous information-processing channel.

2.1. Cutaneous primary afferents

The human hand contains four types of cutaneous afferent fibers that transmit information of the mechanical stimulus features to the central nervous system [7,64,65]. Two of these afferent fibers are rapidly-adapting: one is anatomically linked to the Meissner receptor organ (QA) and, the other, to the Pacinian receptor organ (PC). The other two afferent fibers are slowly-adapting and are linked to Merkel (SA-I) and Ruffini organs (SA-II), respectively. The monkey hand possesses these afferent fibers, except the SA-II. Although all these afferent fibers respond to a cutaneous stimulus, they become specialized to encoding spatio-temporal features of the stimuli [38,62]. This has been demonstrated in well-designed experiments aimed at exploring their capacities. The degree of sensitivity of these afferent fibers is evidenced by the fact that a psychophysical observer can detect even a single spike evoked in one single primary afferent [64,65].

2.2. Neocortical somatosensory areas

After a relay in the dorsal column nuclei and in the basal complex nuclei of the thalamus, somatosensory information reaches the primary somatosensory (S1) cortex. Primate S1 cortex is subdivided in four areas (area 3a, 3b, 1 and 2), each containing a somatotopic representation of the body [18,34]. Tactile information is processed mainly by areas 3b, 1 and 2, which are interconnected [58]. To a certain extent, neurons in S1 cortex replicate the functional properties of QA, SA-I and PC afferent fibers [32,41,62] and are referred as QA, SA and PC neurons. These subtypes are clustered in columns [28,41,61].

Information flows from S1 cortex to the posterior parietal cortex and to the lateral somatosensory areas. As for the visual system, it appears there is also a dorsal stream and a ventral stream in the cortical organization of the somatosensory system [27,33]. According to this organization, the dorsal stream flows through areas 5, and 7b [6,37,58] and the ventral stream flows through the lateral somatosensory areas [3,19,39,40]. The dorsal stream is more likely associated with processing somatosensory information that reaches premotor (PM) cortex [6,12,23,63]. The operations through this dorsal stream could be important for self-initiated or stimulus-triggered, voluntary movements involving sensory processing. The ventral stream is more likely associated with fine discrimination and recognition of stimulus patterns. This processing reaches also the PM [6,12,23] and the prefrontal cortex [5,42], and might be associated with fine discrimination of stimulus objects. Interestingly, both streams reach the M1 cortex [23,63], and both should drive the motor representations during sensory tasks that require indication of decision-making. The functional meaning of these streams, however, need to be investigated further and what aspects of somatosensory perception they contribute.

3. Formation of a sensation via a neural code

Mountcastle and colleagues pioneered this enterprise almost four decades ago [62,68]. The key conceptual advance was to combine psychophysics and neurophysiology, two experimental disciplines that had been divorced before in sensory research. Mountcastle and colleagues used mechanical stimuli applied to the fingertips of humans that changed in one dimension and measured the subjective estimates quantitatively [62,66]. Second, they recorded in anesthetized monkeys the responses of cutaneous afferent fibers using the same stimuli in the psychophysical experiments [62,68]. Their goal was to determine the relationship between the subjective sensation and the evoked peripheral activity produced by the stimuli. Indeed, they found a close relationship between the psychophysical performance and the evoked neural activity by the stimuli [62,68]. These pioneering experiments have been adapted since then as a tool for exploring the neural codes that underlie a sensation in the different sensory modalities.

3.1. Peripheral coding of vibrotactile stimuli

A sensory neural code is that activity produced by a natural stimulus, which correlates with the psychophysical performance. Defining the peripheral coding of a somatosensory stimulus makes implicit that this approach might facilitate exploring the central neural mechanisms of somatosensory perception. Mountcastle and colleagues pioneered this research area using the sensory modality of the sense of flutter-vibration [62]. They showed that depending on the range of frequency of the mechanical vibrations applied to the skin of the hand, two sensations can be elicited: the sensation of

flutter at low frequencies (range of 5–50 Hz), and the sensation of vibration at high frequency (range of 60–300 Hz). Mountcastle and colleagues first quantified amplitude detection thresholds in humans, and then showed that the sensitivities of QA and PC afferents account for performance in the low and high frequency regimes, respectively [62]. This correspondence between perceptual and anatomic submodalities was later confirmed and extended by recording and microstimulating afferents in attending human subjects [24,36,64,65].

There were two major observations on the nature of the peripheral neural code underlying flutter-vibration perception [62]. First, the QA and PC afferents respond periodically to the periodic structure of the stimulus frequency. Second, the QA afferents change little the firing rate between the frequency range of 10–50 Hz, while the PC afferents increase their firing rate as a function of the increasing stimulus frequency (60–250 Hz). Thus, it was concluded that high frequencies could be encoded by the total number of PC spikes produced - a rate code [57,60]- but low frequencies could not, because the number of QA spikes seemed to be constant in the flutter range; it had to be encoded in the regular, periodic spikes produced by the flutter stimuli in the QA afferents—a temporal code. However, direct microstimulation of QA afferents produced flutter sensations of frequencies that were perceived to increase with evoked firing rate [36]. If the frequency of microstimulation current increases between the range of 5 and 100 Hz—presumably, producing a proportional increase in QA firing rate—humans subjects report gradual increases in perceived flutter frequency at a constant intensity [36].

The results reviewed above defined the roles that the different cutaneous afferents play in coding temporal stimuli. Clearly, the QA and PC systems encode the temporal features. Interestingly, it has been shown that the SA-I afferent system transmits information regarding the spatial properties of the stimulus features [17]. The neural coding of the physical properties of the stimuli seems to define and limit the capacity of the psychophysical observer to make detection, recognition and discrimination of the stimuli. These important observations have paved the way for investigating further the cortical processing of somatosensory inputs during perceptual tasks.

4. Cortical coding of vibrotactile stimuli and the link to perception

Compared with our knowledge of tactile coding in afferent fibers, the central mechanisms are less understood. This has been in part to the difficulties in adapting somatosensory tasks in behaving monkeys. Tracing a neural code from the periphery to the cerebral cortex has remained as the leading idea for under-

standing somatosensation. Key to approaching this question is the use of well-designed psychophysical tasks in behaving monkeys. In this section, we review developments on this research area.

4.1. Psychophysics

Mountcastle and colleagues [30] adapted to behaving monkeys the vibrotactile task used initially in human subjects. They trained monkeys to make amplitude detection and discrimination of stimulus frequencies in the range of flutter [21,30]. With intense training, monkeys showed amplitude detection thresholds of the stimulus frequency almost indistinguishable from those quantified in humans subjects in identical conditions [30]. Second, discrimination of two consecutive stimulus frequencies was almost similar to those measured in humans in identical conditions [21,31]. These results indicate that monkeys could be an appropriate model for exploring the central neural mechanisms associated to the flutter task. The discrimination flutter task is particularly rich in that comparison of the second stimulus frequency is made against the memory trace left by the first stimulus frequency. To solve this task the psychophysical observer requires a number of cognitive processes such as detection, working memory, comparison, and decision-making [13,31,46]. Some other tasks require that monkeys categorize moving tactile stimuli [45], detection of roughness [16,59] and/or discrimination of tactual stimulus orientation and form [4,15]. All these tasks require attention focused on the stimulus and indication of performance through voluntary movements; that is, from sensation to action. Investigators using these somatosensory tasks want to unravel the central mechanisms associated with the different components of these psychophysical tasks.

4.2. Coding of vibrotactile stimuli in S1 cortex

If QA afferents encode reliably the periodic structure of the flutter stimulus frequency, the question is whether QA neurons of S1 cortex do similarly, or whether there is another way of coding the stimuli. Shortly after their work on cutaneous afferent fibers, Mountcastle and colleagues [32] studied the responses of S1 neurons. Two decades later, S1 neurons were recorded again, this time in behaving monkeys trained to detect and discriminate the frequencies of flutter stimuli [21,31]. The results support previous findings. First, it was found that QA neurons of S1, 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 inferred performance based on the discriminability of the periodic inter-spike intervals [31]. 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 [31,32,62].

In support of this proposal, using flutter stimuli, Merzenich and colleagues compared psychophysical data from monkeys to S1 recordings in separate experiments from the same animals [43]. 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 anesthetized). Merzenich and colleagues made another important observation, that spike timing associated with the sine wave was much precise in trained animals compared with untrained monkeys [43]. 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 awake animals during the flutter discrimination task. Romo and colleagues trained monkeys to discriminate between flutter stimulus frequencies [14] and recorded many neurons with QA properties in areas 3b and 1 of S1 [52]. Each recorded neuron with QA properties was studied during the discrimination task. There were three major results. First, the majority of neurons from S1 were phase-locked to the input stimulus frequency; however, almost a third of QA neurons modulated their firing rates as a function of the stimulus frequency [52]. 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 [52]. Third, only those neurons that varied their firing rates as a function of the stimulus frequency were affected in error trials [52].

These findings question a unique role of periodic, spike timing in discrimination of flutter stimuli, and suggest that a firing rate code cannot be discarded [52]. But, apart of this, what do these findings suggest? They suggest the presence of two sub-populations of QA neurons in S1 cortex which behave differently in response to a periodic mechanical stimulus [52]. 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 might integrate the responses of the periodic neurons and transform them into a rate code [52]. 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 or not this is so.

4.3. Neuronal correlates of vibrotactile discrimination in S1 cortex

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

The vibrotactile discrimination task requires the comparison of the second stimulus frequency against the first [13]. 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, and a second that, although not periodically entrained, has average firing rates during the stimulus
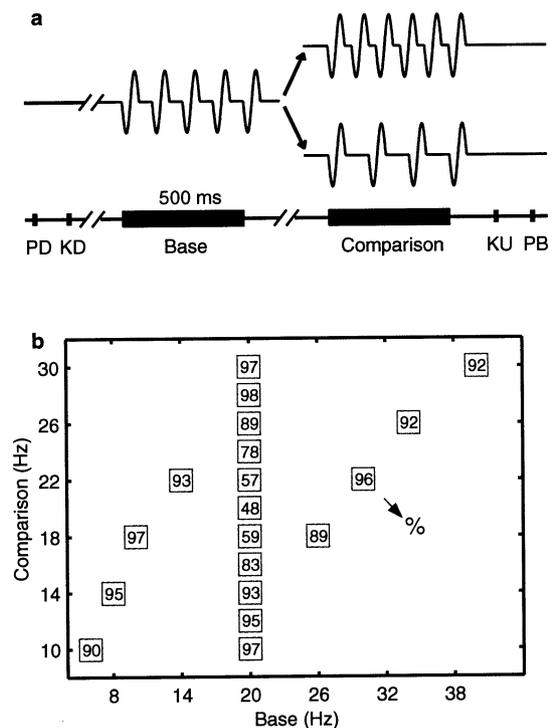

Fig. 1. Discrimination task. (a) Sequence of events during discrimination trials. The mechanical probe is lowered, indenting the glabrous skin of one digit of the hand (PD); the monkey places his free hand on an immovable key (KD); the probe oscillates vertically, at the base frequency; after a delay, a second mechanical vibration is delivered at the comparison frequency; the monkey releases the key (KU) and presses one of two push-buttons (PB) to indicate whether the comparison frequency was higher or lower than the base. (b) Stimulus set used during recording. Each box indicates a base frequency/comparison frequency stimulus pair used; the number inside the box indicates overall percent correct trials for that base/comparison pair. Adapted from Hernández et al. [14].

period that are modulated as a function of the stimulus frequency [14,52]. To investigate which of these two representations is associated with the psychophysical performance, Romo and colleagues determined the probability that an observer (a cortical region central to S1 cortex) could distinguish the difference between the two stimuli [14]. This could be based on a comparison of the neuronal response distributions of the second stimulus frequency ($f2$) made against the neuronal response distributions of the first stimulus frequency ($f1$). According to this, the observer could use a simple rule: if the number of spikes during the second stimulus is higher than during the first stimulus, then $f2$ is higher than $f1$. The same rule can be used when considering the periodicity values: if the periodicity (estimated as the frequency with greatest power in a Fourier transform of the spiking responses) during the second stimulus period ($f2$) is higher than during the first stimulus ($f1$), then $f2$ is higher than $f1$. The effect of this type of rule is equivalent to determining the area under the curve ROC (receiver operating characteristic) generated by the neuronal response distributions for each pair of stimulus frequencies, using both periodicity and firing rate values [14]. 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 of $f2$ are much higher than the neuronal distributions of $f1$, ROC values are close to 1; if the neuronal response distributions of $f2$ are much lower than the neuronal response distributions of $f1$, ROC values are close to 0; for overlapping distributions, intermediate ROC values 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, we are now in the position to address the question of which of the two representations is meaningful for frequency discrimination.

Neurometric functions based on periodicity or firing rate of single S1 neurons were directly compared with the psychometric thresholds [14]. The results of this analysis show that neurometric threshold values based on periodicity are far lower than psychometric thresholds (Fig. 2). This is not the case when neurometric thresholds based on firing rate are compared with the psychometric thresholds (Fig. 3). 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
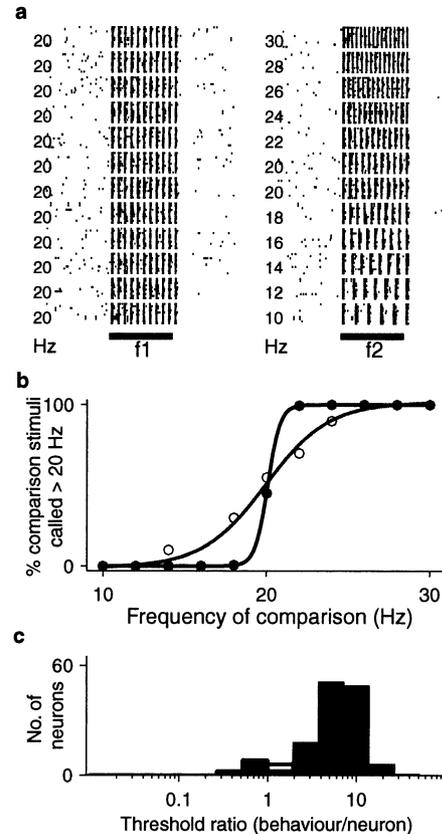

Fig. 2. Periodic responses of a QA neuron of area 1 during the discrimination task. (a) Raster plots. Each row of ticks represents a trial, and each tick represents an action potential. Trials were randomly delivered. Grey horizontal lines indicate the first ($f1$) and the second ($f2$) stimulus. (b) Relationship between psychometric and neurometric discrimination functions. This is plotted as the probability that the second stimulus is judged higher than the first; data and sigmoidal fits (χ^2-test, $P < 0.001$) for 11 pairs of stimulus frequencies in which the base frequency was 20 Hz. Grey and black lines represent psychometric and neurometric functions, respectively. (c) Thresholds ratios (psychometric/neurometric thresholds) calculated from neurons with periodic responses (grey bars). Open bars represent the threshold ratios between psychometric and neurometric thresholds calculated from a small number of neurons with modulations in their firing rate. Adapted from Hernández et al. [14].

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 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, Hernández and colleagues [14] found QA neurons in S1 whose firing rates are modulated by the stimulus frequencies, and their neurometric thresholds based on firing rates are closely similar to the monkey's psychophysical thresh-
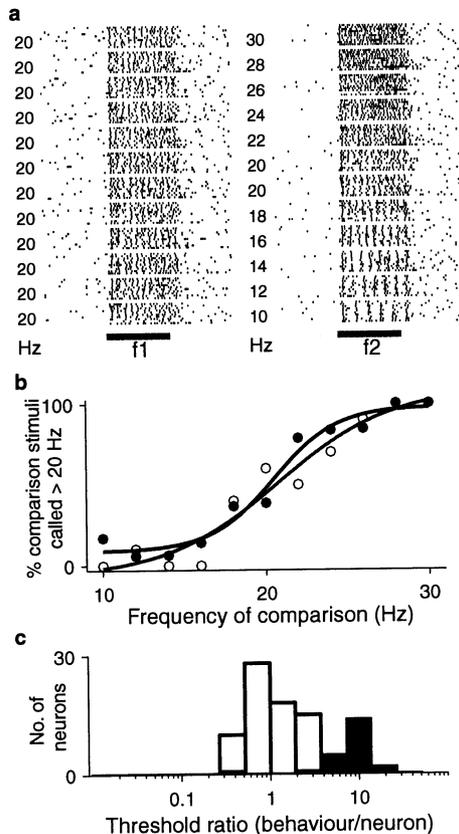
Fig. 3. Firing rate modulation of a QA neuron of area 3b during the discrimination task. Same format as Fig. 2. (a) Raster plots. (b) Relationship between psychometric and neurometric discrimination functions. (c) Threshold ratios calculated between psychometric and neurometric thresholds for each neuron, which varied the firing rate as a function of the stimulus frequency (open bars). Grey bars represent the threshold ratios between psychometric and neurometric thresholds calculated from a small number of neurons that show periodicity. Adapted from Hernández et al. [14].

Fig. 4. Firing rate modulation of a QA neuron of area 1 during the discrimination of aperiodic stimuli. Same format as Fig. 2, but both base (f1) and comparison (f2) frequencies (mean frequencies) lack periodicity. (a) Raster plots. (b) Relationship between psychometric and neurometric discrimination functions. (c) Threshold ratios calculated between psychometric and neurometric thresholds for each neuron during the discrimination of periodic stimulus frequencies (open bars). Black bars represent threshold ratios between psychometric and neurometric thresholds during the discrimination of aperiodic frequencies. Adapted from Hernández et al. [14].

olds (Fig. 3). However, these measurements do not prove they are sufficient for discrimination [45,46].

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 strength the proposal that discrimination of flutter stimuli depends on the periodic structure of the spike trains evoked in S1. 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 [46].

Hernández and colleagues [46] then studied QA neurons in each of two conditions: while monkeys discriminated between periodic stimuli, and while monkeys discriminated aperiodic stimuli. Due to the aperiodic stimulus design, even highly stimulus-entrained neurons do not carry information about stimulus
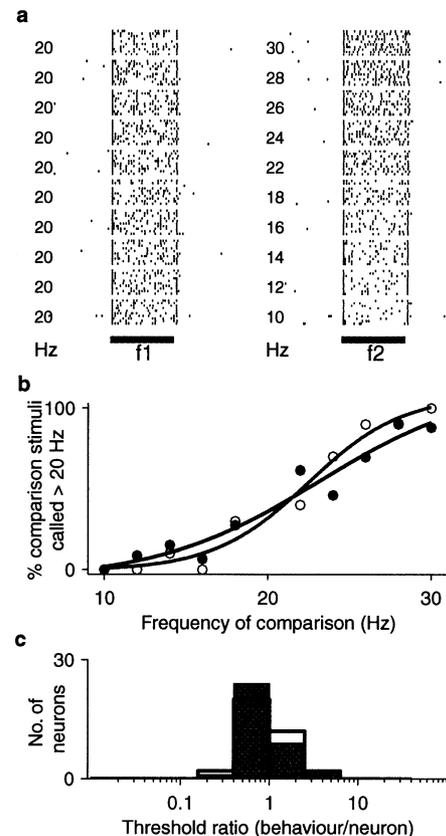
frequency in their periodicity. Clearly, neurometric thresholds based on the firing rate were again closely associated with the psychometric thresholds (Fig. 4). As in the periodic condition, a psychophysical observer could exploit firing rate for frequency discrimination of aperiodic stimuli. These 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.

5. Probing the flutter coding by microstimulation of S1 cortex

Unequivocal proof that the activity of a localized cortical neuronal population provides sufficient basis for a specific cognitive function has rarely been obtained. Neurophysiological studies often reveal close associations between neuronal activity and sensory

events, but does such activity have an impact on perception and subsequent behavior? We typically assume so, but this is hard to verify. Intracortical microstimulation has provided the most compelling evidence to date of a causal link between the activity of localized populations of neurons and specific cognitive functions [2,45,46,55]. Electrical microstimulation directly activates small cluster of neurons, and has been shown to bias a monkey's choice during the decision stage of an ongoing perceptual task [56]. A convenient model to approach this question is the flutter sensation, for which humans and monkeys have similar discrimination thresholds [13,31]. During the vibrotactile discrimination task, subjects pay attention to the frequency of the first (base) stimulus, store a trace of it during the delay period between the two stimuli and compare the stored trace to the frequency of the second (comparison) stimulus. This task, therefore, contains a number of cognitive processes, such as stimulus detection, working memory, discrimination between the two stimuli, and decision-making. These cognitive processes should be initiated by the evoked neuronal activity in S1 cortex [50]. As reviewed above, the QA circuit of S1 distributes the representation of the flutter stimuli to more central structures anatomically linked to it to solve this task. Romo and colleagues [46] used intracortical microstimulation in S1 to manipulate the neural code for flutter discrimination.

A first approach was to manipulate the comparison stimulus frequency during the discrimination task [46]. In each trail of the task, the monkeys discriminated between the frequency of two successively presented sinusoidal vibrations delivered to the fingertips, termed the base stimulus and the comparison stimulus. After the animals mastered the discrimination of the mechanical stimuli, microstimulation of S1 was substituted for the comparison stimulus in half of the trials (Fig. 5a). Artificial stimuli consisted of periodic current bursts delivered at the same comparison frequencies as the mechanical comparison stimulus. Microstimulation sites in S1 were selected to have QA neurons with receptive fields on the fingertip at the location of the mechanical stimulating probe. Remarkably, the monkeys could discriminate between the mechanical (base) and electrical (comparison) signals with performance profiles indistinguishable from those obtained with natural stimuli only (Fig. 5a). Therefore, the artificially induced sensation probably resembled natural flutter closely [46].

To investigate the role of spike periodicity in flutter discrimination, aperiodic microstimulation patterns were also applied in QA neurons of S1 cortex [46]. The same mean frequencies were also used in this condition −20 Hz still corresponded to 10 current bursts delivered in 500 ms- but the current bursts were separated by random time intervals. The monkeys had to compare the base and comparison frequencies just as
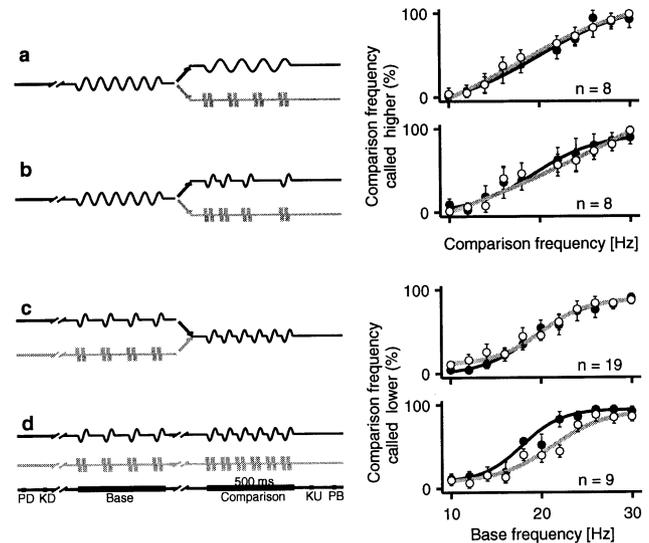

Fig. 5. Psychophysical performance in frequency discrimination with natural, mechanical stimuli and with artificial stimuli injected into clusters of QA neurons of area 3b. Monkeys were trained to compare two vibratory stimuli presented sequentially to the fingertips. To receive a reward, they had to indicate correctly whether the frequency of the comparison stimulus was higher or lower than the first. Both frequencies changed from trial to trial. The diagrams on the left show two types of trials that were interleaved during the experiments. In half of the trials, the monkeys compared two mechanical vibrations delivered on the skin. In the other half, one or both stimuli could be replaced by electrical frequencies microinjected into clusters of QA neurons of area 3b. The curves on the right show the animals' performance in the different situations, illustrated on the left. Filled and open circles indicate mechanical and electrical stimuli, respectively. (a) Psychophysical performance using periodic stimuli; the comparison stimulus could be either mechanical or electrical frequencies. (b) Psychophysical performance when the comparison stimulus could be either aperiodic, mechanical or artificial stimulus frequencies. (c) Psychophysical performance when the base stimulus could be either periodic, mechanical or artificial stimulus frequencies. (d) Psychophysical performance when both periodic, mechanical stimuli could be replaced by periodic, artificial stimulus frequencies. In (a) vibrotactile stimuli were mechanical sinusoids. In (b–d), vibrotactile stimuli were trains of short mechanical pulses; each of these pulses consisted of a single-cycle sinusoid lasting 20 ms. In (a) and (b), the y-axis corresponds to the percentage of times the monkeys called the second stimulus frequency (x-axis) higher than the first (20 Hz). In (c) and (d), the y-axis corresponds to the percentage of times the monkeys called the comparison stimulus (20 Hz) lower than base stimuli at the frequency specified in the x-axis. PD, indentation of the glabrous skin by the mechanical probe; KD, detection of indentation; KU, detection of the end of the comparison stimulus; PB, the monkeys presses one of two push buttons to indicate whether the second stimulus frequency was higher or lower than the first Adapted from Romo et al. [45,46].

before, and microstimulation and mechanical stimulation trials were again interleaved. From the very beginning, the animals were able to discriminate between the aperiodic signals with practically the same performance level reached with natural, periodic vibrations (Fig. 5b). Periodic and aperiodic stimuli are, of course, different in the time course of the stimulating pulses, but the neural codes for flutter frequency

underlying the discriminations performed by the monkeys might be the same for both. If so, the result might imply that spike periodicity does not pay a functional role in our monkey's performance of the frequency discrimination task.

Because of the design of this task, comparison of the second stimulus frequency is made against the memory trace of the first stimulus. Romo and colleagues [45] wondered whether, in addition to using artificial stimuli during the decision stage of the task, monkeys could store and use a quantitative trace of an electrical stimulus delivered to QA neurons in S1 cortex in place of the first mechanical stimulus. They also wondered whether monkeys could perform the entire task on the basis of purely artificial stimuli. This would demonstrate that activation of QA neurons was sufficient to initiate the entire cognitive process involved in the task.

Again, the mixed mechanical/microstimulation protocol was used, in which microstimulation trials were randomly intermixed with standard, purely mechanical trails [45]. The frequency pairs and event sequence were the same in both mechanical and microstimulation trials, except that in microstimulation trials the first or both mechanical stimuli were substituted by trains of current pulses injected in S1 and delivered at the frequency of the mechanical stimulus they were replacing. Design of the stimulus set assured to explore the working memory component of the task and determine discrimination thresholds.

Psychophysical performance with electrical microstimulation patterns in S1 cortex at the mechanical base stimulus frequencies they were replacing was almost similar to that measured with the mechanical stimulus (Fig. 5c). These results show that monkeys were able to memorize the base artificial stimulus frequency and make quantitative comparisons of the second stimulus frequency against the trace left by the artificial stimulus. As for substituting the comparison stimulus with electrical patterns, monkeys could not reach the usual level of performance when clusters of SA neurons were microstimulated. Nor could they discriminate when microstimulation patterns were made at the border between QA and SA clusters (45). These control experiments tell us about the specificity of the QA circuit of SI cortex in flutter discrimination. Finally, in most sessions in which the two mechanical stimuli were replaced by microstimulated patterns, monkeys were able to reach discrimination levels close to those measured with mechanical stimuli delivered to the fingertips (Fig. 5d). This indicates that microstimulation elicits quantitative memorizable and discriminable percepts, and shows that activation of the QA circuit of S1 cortex is sufficient to initiate the entire subsequent neural process associated with flutter discrimination [45].

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

6. Coding of vibrotactile stimuli in cortical areas central to S1

The results reviewed above are the basis for exploring the somatosensory network central to S1. This is an important enterprise, considering that S1 cortex is only one of many brain structures that participate in somatosensory perception. But, in the flutter task, what is the neuronal representation of flutter stimuli in structures central to S1? Assuming that it is periodicity, do S2 neurons represent flutter stimuli in the same format? What is the neural correlate for flutter discrimination in central structures to S1? An obvious candidate to explore these questions is the second somatosensory (S2) cortex. SI cortex is strongly connected with S2 [3,19]. This central somatosensory region belongs to the ventral stream [27,33].

6.1. Coding of flutter stimuli in S2 cortex

Unlike the majority of S1 neurons, very few S2 neurons are periodically entrained by the flutter stimuli [52]. There are basically three groups of neuronal responses during the stimulus periods: the first group increases the firing rate as a function of the stimulus frequency; the second decreases the firing rate as a function of the increasing stimulus frequency; and the third, which responds but is not modulated as a function of the stimulus frequency. According to this, there is a dramatic change in the flutter representation from S1 to S2. Clearly, the most interesting responses in S2 are those which modulate their firing rate as a function of the stimulus frequency. These responses are affected by the animal's state. These responses are more prominent

during the discrimination task than when the same stimuli are delivered in non-working conditions. These distinct populations are operating simultaneously in S2 and should produce a computation that is useful for frequency discrimination in an analogous manner to that reported in central visual areas like the middle temporal cortex [1]. Finally, an important result obtained in S2 neurons is that many of them retain information about the base stimulus during the early component of the delay period between the two stimulus frequencies. They do similarly as for the stimulation periods: that is, if the neuron increases its firing rate as a function of base stimulus frequency, the same representation is maintained during the early component of the delay. We consider this as a neural correlate of the working memory component of the task. This information must be translated to structures central to S2 that contain a network for working memory in this task.

6.2. Parametric encoding of flutter stimuli during working memory in the prefrontal cortex

As reviewed above, some neurons of S2 cortex retain the base stimulus frequency during the early component of the delay period [52]. They do so by retaining the base stimulus frequency monotonically during the early memorization component of the task [52]. Where, then, is this early representation projected and held during the whole delay period between the two flutter stimuli? Is this associated to the stimulus parameters? Romo and colleagues [44] recorded in the prefrontal cortex and sought to determine the neuronal correlate for the working memory component of this task. Although there is no clear direct input from S2 or S1 cortex to the prefrontal cortex, in a pilot experiment Romo and colleagues recorded above and below the principal sulcus in prefrontal cortex while a monkey performed the flutter discrimination task. Recordings in the first monkey suggested that the inferior convexity of the prefrontal cortex contained neurons whose activity varied, during the delay period between the two stimuli, as a monotonic function of the stimulus frequency [44]. This finding was then further investigated in three more animals performing the flutter discrimination task. Some of the delay responses responded most weakly after stimulation with the lowest base frequency, and increased their firing rates steadily for increasing frequencies (positive monotonic; see Fig. 6a, c, e). Others had discharge rate rates that varied in the opposite direction (negative monotonic; see Fig. 6b, d, f). These types of responses in prefrontal cortex are similar to those recorded in S2 during the early part of the delay period in the same task [52]; the most important difference between S2 and prefrontal cortex was that many neurons in prefrontal cortex prolonged their monotonic responses through to the end of the delay
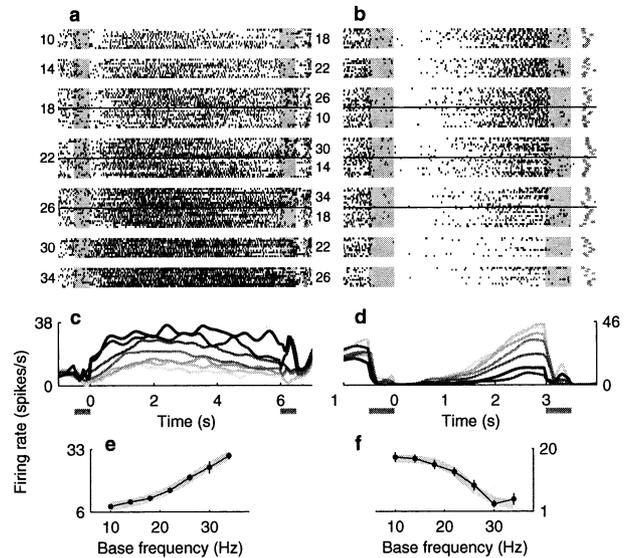

Fig. 6. Monotonic responses of two neurons of the prefrontal cortex during the delay period between the two vibrotactile stimuli. (a), (b) Raters. Each row of ticks represents a trial, and each tick represents an action potential. Trials were delivered in a random order, but have been sorted into blocks of equal base stimulus frequency, indicated on the left. Trials have been further sorted into groups of equal comparison frequency (indicated in the center), separated by a horizontal black line. Grey boxes (and short horizontal grey lines in c and d) indicate base and comparison stimulus periods; thick grey tics after the comparison stimulus indicates the beginning of the motor response (KU; see Fig. 1a). Time axes for (a) and (b) are shown in (c) and (d), respectively. (c), (d) Time-dependent spike densities for each base frequency stimulus condition. Grey level indicates the base frequency: the lightest grey line corresponds to 10 Hz and the darkest line corresponds to 34 Hz. (e, f) Mean firing rates, averaged across the entire delay period. Small vertical lines are ±S.E.M. Thick grey lines are soft sigmoid fits to the data Adapted from Romo et al. [44].

period. Thus, the base stimulus frequency, a scalar analogue value, appeared to be encoded directly in the neuron's firing rate (also a scalar analogue value), most often in a smoothly grade fashion. These results led Romo and colleagues [44] to conclude that smooth monotonic encoding found in prefrontal cortex is consistent with the existence of a parametric, rather than categorical, representation of the memorized stimulus during the working memory component of this task. In the same vein, these results could suggest that monotonic encoding might be the basic representation of sensory magnitude continua during working memory, in tasks that require ordinal comparisons between scalar analogue stimuli.

Monotonic encoding of the stimulus frequency in the prefrontal cortex may be derived from inputs from cortical somatosensory areas. As described above, in recordings from S1 and S2 cortices during the same frequency discrimination task, neurons were found in S2 cortex that responded in a manner similar to 'early' neurons, encoding the base stimulus frequency monotonically during the delay period between the two

stimuli. Although many neurons of S1 cortex responded during the two stimulus periods, none did so during the delay period, in contrast to results obtained in a different tactile task involving working memory [70]. These results constitute a neurophysiological demonstration that neurons of the prefrontal cortex can retain working memory information induced by non-visual modalities.

7. From somatosensation to action

In the past decade, an important advance has been made in sensory physiology; that is, sensory physiologists not only seek the neuronal correlates of sensory perception, but also the neuronal mechanisms underlying decision-making: from sensation to action. Physiologists in the motor system would refer to this as the sensory-motor interface. However, the cornerstone to exploring decision-making is to investigate it in psychophysical tasks [35,49]. The investigator controls the stimulus input, to know the encoding of the stimulus in the early sensory areas, and to have a precise control of the motor outputs as functions of the stimulus parameters. Performance is measured with psychophysical techniques and the neuronal responses are quantified with neurometric techniques; that is, neuronal responses are evaluated as if it were measured by an ideal psychophysical observer.

7.1. Defining a somatosensory task for exploring decision-making mechanisms

Romo and colleagues [48,49] designed a somatosensory task in which monkeys categorized the speed of moving tactile stimulus. Monkeys had to decide whether the stimulus speed was high or low. Categorization was indicated through an arm-hand movement directed to one or two push buttons. Performance was measured with psychophysical techniques, and the motor responses were quantified by measuring the reaction and motor times. Under these conditions, it is possible to study in S1 cortex the responses of neurons to the tactile stimuli and the neuronal activity in motor areas of the frontal lobe. What do we want to explore in this task? We want to know how a somatosensory signal after being processed in S1 cortex is transported to the neuronal ensembles of frontal motor areas during the decision stage.

The direction of a moving tactile stimulus is represented in the evoked neuronal activity of S1 cortex and it can be quantified in the form of a population vector, whose magnitude is modulated by the speed of the stimulus [51]. This dynamic internal representation provides the initial substrate for higher order processing of moving tactile stimuli. If this is so, a salient question

is whether this representation of the moving tactile stimuli in S1 cortex can be correlated directly with the sensory performance of the animal. Delivering the moving tactile stimulus across the cutaneous receptive field of the recorded neuron while the monkey performed the categorization task gave two salient results [47]. First, S1 neurons increased their firing rates as a function of the stimulus speed. Second, these responses were almost identical when the same stimuli were delivered passively, in the non-working condition. This suggests that the neuronal signals associated with the perception of the tactile stimuli may be occurring in more central areas anatomically linked to S1 cortex. However, removing S1 cortex impaired categorization of the moving tactile stimuli, but not detection [69]. A similar result was observed in the flutter discrimination task and suggests that these representations are essential for somatosensory perception [22].

7.2. Decision signals in premotor cortex

Where to look for the neural decision mechanisms during somatosensation? This should be investigated in those somatosensory areas central to S1 cortex. However, little neurophysiological data is available, except for the motor areas of the frontal lobe [29,26,48,49,53,54]. Anatomic studies have shown that the supplementary motor cortex (SMA) receives direct inputs from the posterior parietal cortex and the lateral somatosensory areas (reviewed above). The output of the SMA is directed to MI and to the spinal cord [8,9]. In addition, the SMA maintains an important one way connection with the neostriatum and the brainstem (20, 25). Given this prominent connection with motor centers, neurophysiologists have looked at the role of SMA in motor behavior. However, it might be possible that the SMA is involved also in some aspects of the sensory perceptual process. Romo and colleagues [48,49] have investigated this possibility by recording single neurons in the SMA contralateral and ipsilateral to the stimulated hand during the execution of the categorization task.

Of particular interest for decision-making was the recording of neurons in the SMA ipsilateral and contralateral to the stimulated hand that responded differentially during the categorization task [48,49]. These neural responses occurred mainly during the stimulus period, during the stimulus and reaction time, and during the reaction-movement time periods. These neurons encoded in their activity whether the stimulus speed was low or high. A number of these neurons were then tested when the same set of stimuli was delivered passively. None of them responded in this condition. Another important test is that these differential responses occurred exclusively during the categorization task; these neurons did not respond differentially when

the same hand-arm movement was guided by visual cues in the absence of somatic stimuli. But, interestingly, the differential responses were considerably attenuated when a visual cue predicted whether the tactile stimulus was low or high. Some neurons even showed such modulatory effects during the waiting periods before stimulus delivery.

With these elements in hand, we should be able to inquire whether these differential neural responses are related to the animal's decision. Decoding information from these neural responses show that indeed they are decision signals clearly correlated with the sensory-motor performance [53]. But, is this a unique property of the SMA? Probably not, given the large interconnectivity between motor and somatosensory areas.

7.3. Decision signals in neostriatum

The neostriatum receives bilateral inputs from the SMA [20,25], so is this structure associated to decision-making during somatosensation? Single neuronal recordings were made in the neostriatum ipsilateral and contralateral to the stimulated hand during the categorization task [26]. Again, a large proportion of neurons in the bilateral neostriatum showed differential responses. That is, groups of neurons responded selectively when the animal indicated that the category of the stimulus was low and others responded when the animal indicated the category of the stimulus speed was high. As for the SMA, these responses occurred exclusively during the categorization task, these neural signals were not present when the same stimuli were delivered passively. Clearly, these differential responses were modality specific because these neurons failed to respond when the same differential movements were guided by visual cues in the absence of somatic stimuli. Although decoding analysis was not carried out as for the SMA neurons [53], it is very likely, according to the neural response profiles, that they are similarly linked to the psychophysical performance. This would indicate that decision neural signals are widely distributed in those motor areas of the brain that are anatomically linked to the somatosensory cortex.

7.4. Decision signals in primary motor cortex

If premotor areas of the brain show decision neural signals, does MI cortex contains a neural apparatus associated with the categorization process? Given the prominent role of MI cortex in coding movement parameters [11], decision signals could simple drive populations of neurons in MI, for expressing the decision through a goal directed movement (in this case to the push buttons). If this were so, a differential neuron during the categorization task would respond similarly when the same hand-arm movement is per-

formed during visual guidance. If not, this would indicate that some MI neurons make the link between somatosensory processing that leads to decision and motor output during the categorization task. To probe this, Salinas and Romo [54] recorded in the arm area of MI while monkeys performed in the tactile categorization task.

Remarkably, about a fifth of the recorded neurons discharged differentially during the tactile categorization task (Fig. 7a). Salinas and Romo [54] reasoned these could be neural signals encoding arm direction, given the prominent role of neuronal populations of MI neurons in encoding this variable [11]. However, this is unlikely for two main reasons. First, assuming they are representing the direction of arm movements, direction coding has not been proven to occur when targets are close together (they were separated by an angle of 11°. The second and most important argument is that differential neurons tested while visually guiding the hand-arm movements towards the push buttons failed to respond differentially in this condition (Fig. 7b). Needless to say, none of these motor cortex neurons, as the reviewed above, responded when the same stimuli were delivered passively, in the non-working condition.
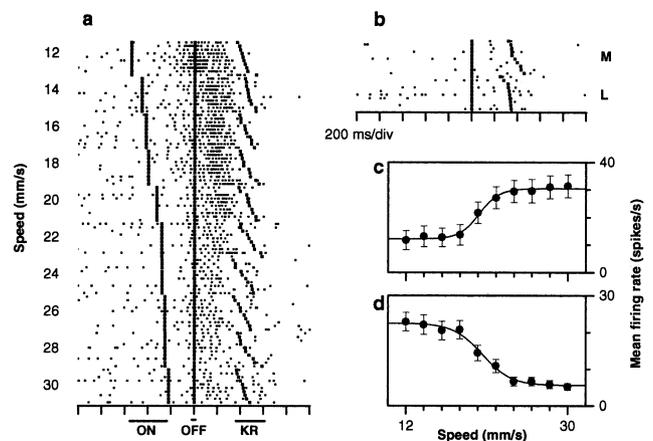

Fig. 7. Responses related to categorical decisions in primary motor cortex. Monkeys classified the speed of a probe moving across the glabrous skin of a fingertip as either low (< 20 mm/s) or high (> 20 mm/s). (a) Raster plot of a neuron that fired more intensely for low speeds. Each line corresponds to one trial, and each small tick represents and action potential. Squares represent behavioral events: onset of probe movement (ON); offset of probe movement (OFF); or key release (KR) which marked the initiation of the hand-arm movement to indicate the decision. Stimulus speeds are indicated on the left. (b) Responses of the same neuron when identical arm movements, to the medial (M) or lateral (L) button, were triggered by visual cues, in the absence of tactile stimuli. In each trial, the first square indicates the visual go signal, and the second square indicates KR. No differential activity was observed in this condition. (c) Mean firing rate as a function of the stimulus speed averaged over a population of 20 neurons that were selective for high speeds, Error bars indicate ±S.E.M. (d) As in (c) but for a population of 20 neurons selective for low speeds. Adapted from Salinas and Romo [54].

Analysis by decoding information from these neural responses together with the psychophysical performance provided two main types of information regarding the identity of these neural signals in the categorization task [53,54]. First, the neurometric profile clearly matched the psychophysical performance (Fig. 7c, d). Second, error trials revealed these neurons are neither sensory nor motor [53]. They are both. Therefore, it appears the MI cortex possesses a type of neuron, which had not been identified before, which makes the link between a sensory signal and a motor signal.

From a teleological perspective, sensory representations are meaningful only if they are relevant for the construction of sensations, forming memories and reaching decisions. The results reviewed above clearly suggest that the large territories of the brain receive a copy of a sensory decision, which is then expressed through a voluntary motor action. The fact that the outputs of premotor cortex and basal ganglia are directed to MI cortex suggests that the information from multiple processing nodes finally converges in MI cortex and suggests a strong link between sensory processing and motor activity. The remarkable spread of the decision-related representations in the brain may indicate something fundamental about how decision-making is implemented by neurons.

8. Concluding comments

Decision-making is present in all sensory tasks. This is elaborated in the sensory areas of the brain during processing afferent inputs. A decision is expressed through voluntary motor actions. However, as shown here, few examples exist exploring this function in the somatosensory system. Similarly, exploring the central neural mechanisms that lead to the construction of a sensory percept has also proceeded at a low pace. This has not been the case for revealing the neural representation of tactile stimuli in the afferent component of the somatosensory system. This has produced strong important concepts, as that afferent fibers represent in their activity the stimulus features and that they limit and account for the psychophysical performance. This idea is currently tested in the brain. In other words, how these sensory representations account for sensation and decision-making. Indeed, one of these representations has been proven to be sufficient for sensory discrimination [45,46]. A remarkably finding is that working memory in one-dimensional stimulus discrimination task has a parametric representation in the brain [44]. This should be similar in other sensory modalities involving processing of these types of stimuli. Finally, an effort has been made to test the neural signal that matches decision-making in the somatosensory system. This encoding is associated with early sensory represen-

tations [26,48,49,53,54]. However, more studies are needed to have a complete picture of how a sensory percept is built up in the somatosensory network.

To conclude, we believe that there are two divergent research lines when exploring the neuronal correlates of tactile perception. The first relies on stimulus encoding; that is, 'the representational problem'. The second relies on neuronal changes that occur when animals shift from one condition to another. While we believe that it is important to show that the neuronal responses in the somatosensory system are associated with behavioral changes, however, these studies may have greater impact if they are in line with the 'representational problem'; that is, how the attended stimulus that is discriminated and memorized is represented in the brain, and whether these representations are meaningful for somatosensory perception.

Acknowledgements

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