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Do Sensory Cortices Process More than One Sensory Modality during Perceptual Judgments?

Luis Lemus,[1] Adrián Hernández,[1] Rogelio Luna,[1] Antonio Zainos,[1] and Ranulfo Romo[1],*
[1] Instituto de Fisiología Celular—Neurociencias, Universidad Nacional Autónoma de México, 04510 México, D.F., Mexico
*Correspondence: rromo@ifc.unam.mx
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SUMMARY

Recent studies have reported that sensory cortices process more than one sensory modality, challenging the long-lasting concept that they process only one. However, both the identity of these multimodal responses and whether they contribute to perceptual judgments is unclear. We recorded from single neurons in somatosensory cortices and primary auditory cortex while trained monkeys discriminated, on interleaved trials, either between two tactile flutter stimuli or between two acoustic flutter stimuli, and during discrimination sets that combined these two sensory modalities. We found neurons in these sensory cortices that responded to stimuli that are not of their principal sensory modality during these tasks. However, the identity of the stimulus could only be decoded from responses to their principal sensory modality during the stimulation periods and not during the processing steps that link sensation and decision making. These results suggest that multimodal encoding and perceptual judgments in these tasks occur outside the sensory cortices studied here.

INTRODUCTION

Recent studies have reported that primary sensory cortices can respond to stimuli that are not of their principal sensory modality (Bizley et al., 2007; Brosch et al., 2005; Fu et al., 2003, 2004; Kayser and Logothetis, 2007; Kayser et al., 2008; Lakatos et al., 2007, 2009; Schroeder and Foxe, 2002, 2005; Schroeder et al., 2001; Werner-Reiss et al., 2003; and see Driver and Noesselt, 2008; Ghazanfar and Schroeder, 2006; Kayser et al., 2009; for reviews). It has been reported, for example, that primary somatosensory cortex (S1: areas 3a, 3b, 1 and 2) in addition to responding to somatosensory inputs, is also activated by visual and auditory stimuli (Zhou and Fuster, 2000, 2004). The idea is that, in cross-modal association tasks, S1 neurons reflect in their evoked activities visual and auditory cues associated with the touch of an object, not only during the sample stimulus period, but also during the delay and decision report periods (Zhou and Fuster, 2000, 2004). Similarly, in the auditory cortex, apart from responding to auditory cues during an auditory categorization task, neurons also respond to visual and somatosensory cues associated with the decision process of the categorization task (Brosch et al., 2005). However, both the identity of these multimodal responses and whether they contribute to perceptual judgments during these behavioral tests is unclear. On the other hand, cross-modal interactions in auditory fields have been often reported either in anesthetized or awake animals and the common finding is that weak responses are evoked by somatosensory and visual stimuli alone, whereas the auditory evoked-responses are influenced when delivered simultaneously with somatosensory or visual stimuli (Bizley et al., 2007; Brosch et al., 2005; Fu et al., 2003, 2004; Ghazanfar et al., 2005; Kayser and Logothetis, 2007; Kayser et al., 2008, 2009; Lakatos et al., 2007; Schroeder and Foxe, 2002, 2005; Schroeder et al., 2001; Werner-Reiss et al., 2003). Again, although these responses suggest that multimodal integration occurs in early sensory cortices, its functional meaning in perceptual judgments is unclear, because in many of these studies the subjects were not evaluating the stimuli and reacting accordingly, but rather perceived them passively.

We addressed these problems by recording from single neurons in S1 (areas 3b, 1 and 2), secondary somatosensory cortex (S2) and primary auditory cortex (A1) while trained monkeys discriminated the difference in rate of two flutter stimuli. On randomly interleaved trials, the subjects discriminated either two tactile flutter stimuli (range of 4–40 Hz; Hernández et al., 1997; Lemus et al., 2007; Luna et al., 2005; Romo et al., 2004) or two acoustic flutter stimuli (range of 4–40 Hz; Lemus et al., 2009a). In both tactile and acoustic flutter discrimination tasks, monkeys report whether the second stimulus rate (f2) is higher or lower than the first stimulus rate (f1). This cognitive operation requires that subjects compare information of f2 with a stored trace of f1 to form a decision, i.e., whether f2 > f1 or f2 < f1, and to report their perceptual sensory evaluation after a short, fixed delay period.

The first objective of this experiment was to determine whether S1 and S2 neurons encode not only tactile flutter, as shown before (de Lafuente and Romo, 2005, 2006; Hernández et al., 2000; Luna et al., 2005; Salinas et al., 2000), but also acoustic flutter. By encoding we mean that a neuron's response (either its firing rate or periodicity) varies significantly as a function of flutter rate (Hernández et al., 2000; Luna et al., 2005; Salinas et al., 2000). Similarly, we sought to determine whether A1 neurons encode not only acoustic flutter (Lemus et al., 2009a), but tactile flutter as well. We investigated this during the stimulus presentation periods and during the delay or working memory period of the tasks. In these tasks, we also sought to determine whether the neuronal activities that encoded the principal or another sensory modality, predicted the animal's motor choice. Our second objective, in a cross-modal variant of these tasks, was to test whether S1, S2 and A1 neurons showed cross-modal processing. In interleaved trials, animals discriminated pairs of flutter stimuli in which f1 was acoustic and f2 was tactile, and vice versa. Our third objective, in another variant of the flutter tasks, was to explore whether the processing of the principal sensory modality was influenced or modulated by an additional sensory modality. In this task condition, animals discriminated between f1 and f2 tactile flutter and acoustic flutter delivered synchronously.

We found neurons in S1, S2 and A1 that can respond to stimuli that are not of their principal sensory modality during these tasks. However, the identity of the stimuli could only be decoded from responses to their principal sensory modality during the stimulus periods. We also found, except for a few S2 neurons, that none of the neurons in S1 and A1 encoded information about either tactile or acoustic stimuli during the working memory component of these tasks. Few S2 neurons predicted in their activities the motor choice during either tactile flutter discrimination or acoustic flutter discrimination. Finally, we did not find cross-modal interactions or enhanced/suppressed responses by a second, congruent stimulus, neither during the stimulation periods nor during the cognitive components of the tasks used here. We think that these results are important for understanding the functional organization of sensory cortices in multimodal processing and perceptual judgments.

RESULTS

Two monkeys (*Macaca mulatta*) were first trained to discriminate, on randomly interleaved trials, either two tactile flutter stimuli or two acoustic flutter stimuli (Figures 1A–1C) until their discrimination thresholds were stable (Figure 1D). They were then trained to discriminate pairs of flutter stimuli, on interleaved trials, in which f1 was tactile and f2 acoustic, and vice versa (Figures 1E–1H). Animals also discriminated the frequencies of simultaneously delivered synchronous tactile and acoustic stimuli (Figures 1I–1K). In all these sets, trials can be divided into two types: those in which f2 > f1 and those in which f2 < f1. All neurons were recorded using stimulus sets B, C, F, G and J of Figure 1. Because of the task designs, the neuronal responses across trials can be analyzed as functions of f1, f2, f2 – f1, or as functions of the monkeys' two possible motor choices.

Responses of Area 3b Neurons during Tactile Flutter Discrimination and Acoustic Flutter Discrimination

We recorded from 74 single neurons in area 3b while monkeys discriminated, on interleaved trials, either two tactile flutter stimuli or two acoustic flutter stimuli (Figure 1A; Table 1). All these neurons had cutaneous receptive fields confined to the distal segment of one fingertip. We considered a neuron's response as task-related if during any of the relevant periods (f1, delay between f1 and f2, f2, and delay between the end of f2 and pu) its mean firing rate was significantly different from a control period preceding the beginning of probe indentation of each trial ($p < 0.05$, Wilcoxon rank-sum test [Siegel and Castellan, 1988]). We then measured the mean firing rate and periodicity for each task-related neuron's response during any of the relevant periods (Hernández et al., 2000; Salinas et al., 2000; Lemus et al., 2009a; Luna et al., 2005; see Experimental Procedures). Typical responses of an example area 3b neuron during either the tactile or the acoustic flutter discrimination are illustrated in Figures 2A and 2B. The neuron shows a brief response to the initial probe indentation (pd) at the beginning of each trial, during the tactile flutter stimuli (Figure 1A) and at the removal of the probe from the skin (pu), a typical rapidly adapting response. The mean firing rate of this neuron increased monotonically as a function of the tactile flutter frequency (first and third panels of Figure 2C) but not as a function of the acoustic flutter frequency (first and third panels of Figure 2D). In addition, the firing rate was not modulated during the working memory or postponed-decision periods for either the tactile flutter discrimination task (second and fourth panels of Figure 2C) or the acoustic flutter discrimination task (second and fourth panels of Figure 2D). We also measured whether this neuron represented the periodicity of the tactile or the acoustic flutter stimuli, and found that periodicity changes systematically only as a function of the tactile flutter stimulus and only during the presentation of f1 (first panel of Figure 2C).

We also quantified the different possible encoding schemes in area 3b, by modeling the firing rate and periodicity values during the tactile and acoustic tasks as arbitrary linear functions of both f1 and f2, such that for each neuron: firing rate $(t) = a1(t)f1 + a2(t)f2 + a3(t)$ (Draper and Smith, 1966; Hernández et al., 2002; Lemus et al., 2007, 2009a, 2009b; Romo et al., 2002, 2004). In this formulation, t represents time, and the coefficients a1 and a2 serve as direct measurements of the dependence on f1 and f2, respectively. These measures were calculated in sliding windows of 200 ms moving in steps of 50 ms. To illustrate this analysis, the resulting coefficients a1 and a2 for the neuron of Figure 2 are plotted in panels E and F as functions of time. The magnitude and sign of the coefficients reveal the tuning properties of the neuron — i.e., their selectivity — in terms of the firing rate (upper panels of Figures 2E and 2F) or the periodicity (lower panels of Figures 2E and 2F) of the evoked spike trains. This applies to the full trial duration. The neuron illustrated in Figure 2 thus turns out to encode preferentially the tactile flutter stimuli in its firing rate during the stimulation periods (upper panel of Figure 2E), and not during the acoustic flutter task (upper panel of Figure 2F). This analysis was extended to the entire neuronal population of area 3b for either the tactile discrimination task (Figure 2G) or the acoustic discrimination task (Figure 2H). The analysis showed that area 3b neurons encoded information about the tactile flutter stimuli periods only (Figure 2G). However, we also found that a few area 3b neurons responded during the stimulation periods in the acoustic discrimination task (Table 1). Their responses were weak and could occur during the stimulus periods, but were not modulated by the acoustic stimuli (Figure 2H). Also, their response latencies (mean: 223.92 ms, standard deviation [SD]: 43.6) were significantly longer (one-tailed t test, $p < 0.01$) in comparison to those evoked by the tactile flutter stimuli (mean: 27.78 ms, SD: 10.35).

We also explored the possibility that area 3b neurons predicted in their activities the animal's choice (Experimental

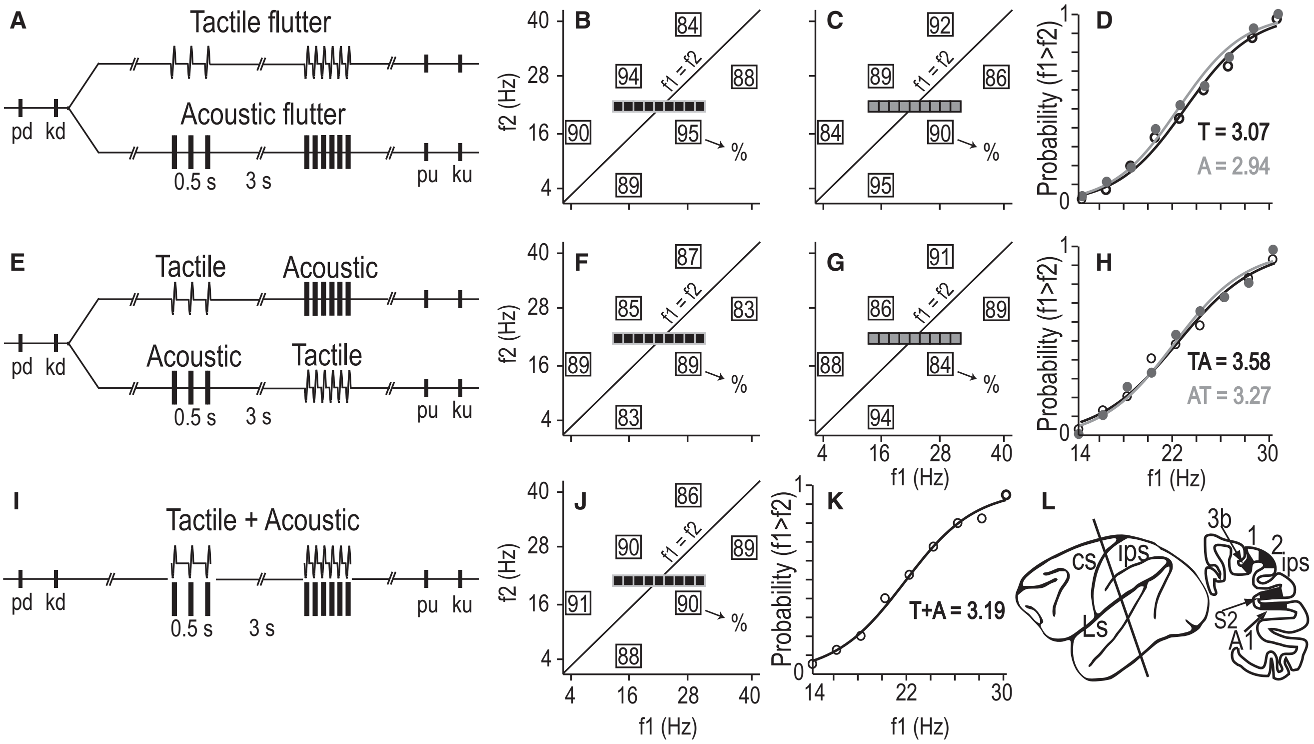

Figure 1. Discrimination Tasks, Stimulus Sets, and Psychophysical Performance

(A) Sequence of events during discrimination, on interleaving trials, between two tactile flutter stimuli or two acoustic flutter stimuli. (B) Tactile flutter stimulus set. (C). Acoustic flutter stimulus set. (D) Psychophysical performance resulting from discrimination of stimulus pairs in panels B (T = tactile discrimination threshold in Hz) and C (A = auditory discrimination threshold in Hz). (E) Temporal cross-modal discrimination task. (F) Stimulus set when the first stimulus was tactile and the second stimulus was acoustic (f2). (G) Stimulus set when the first stimulus was acoustic and the second stimulus was tactile. (H) Psychophysical performance resulting from discrimination of stimulus pairs in panels F (when the first stimulus was tactile and the second stimulus was acoustic; TA = discrimination threshold in Hz) and G (when the first stimulus was acoustic and the second stimulus was tactile; AT = discrimination threshold in Hz). (I) Discrimination task when both tactile flutter stimuli and acoustic flutter were delivered synchronously. (J) Stimulus set used in I. (K) Psychophysical performance resulting from discrimination of stimulus pairs of panel J (T+A = discrimination threshold in Hz). Sequence of events during discrimination trials in A, E and I. The mechanical probe is lowered, indenting the glabrous skin of one digit of the restrained hand; the monkey places its free hand on an immovable key (kd); after a variable delay 1-3 s, the first flutter stimulus is delivered; after a delay of 3 s, a second flutter stimulus is delivered at the comparison frequency; after another delay of 3 s between the end of the second stimulus and probe up (pu, the cue that triggers the beginning of the decision report), the monkey releases the key (ku) and presses either a lateral or a medial push-button (pb) to indicate whether the second stimulus was higher or lower than the first stimulus. (B, C, F, G and J) Stimulus sets used during recordings. Each box indicates an (f1, f2) stimulus pair. The number inside each box indicates overall percentage of correct trials for each (f1, f2) pair. (L) Recording sites in primary somatosensory cortex (S1: areas 3b, 1 and 2), second somatosensory cortex (S2) and primary auditory cortex (A1). cs, central sulcus; ips, intraparietal sulcus; ls, lateral sulcus.

Procedures). For this, we sorted the responses into hits and errors and calculated a choice probability index (Britten et al., 1996; Green and Swets, 1966; Hernández et al., 2002; Lemus et al., 2007; Romo et al., 2002, 2004). This quantified for each (f1, f2) pair whether responses during error trials were different from responses during correct trials. Choice probability indices were computed separately for neurons that encoded information about the flutter tactile stimuli and for those neurons that simply responded during either task. The result is shown in Figure 7, which plots the choice probability index as a function of time for both tasks. None of the area 3b neurons predicted in their activities the animal's choice, neither through firing rate nor through modulation periodicity. The results show that the responses of area 3b neurons encode tactile flutter stimuli only during the stimulation periods, and not during the working memory and decision-making components of this task.

Responses of Area 1 Neurons during Tactile Flutter Discrimination and Acoustic Flutter Discrimination

The results described above prompted us to investigate whether the same encoding scheme observed in area 3b occurred also in area 1, or whether bimodal responses could be recorded in this somatosensory area. We recorded from 132 single neurons in area 1, again while monkeys discriminated either tactile or acoustic pairs of flutter stimuli (Figure 1A; Table 1). All these neurons had larger cutaneous receptive fields compared to those of area 3b neurons and were often confined to two fingertips. We applied the same analysis described for area 3b neurons. In general, the neuronal population of area 1 responded similarly to the neuronal population of area 3b. Most neurons responded to the tactile flutter stimuli (Figure 3A) and not to the acoustic flutter stimuli (Figure 3B). The example area 1 neuron of Figure 3 illustrates this fact. Clearly, it increased its firing

Table 1. Database of S1 (Areas 3b, 1, and 2), S2, and A1

		Tactile Flutter				Auditory Flutter			
		f1	Delay f1-f2	f2	Delay f2-pu	f1	Delay f1-f2	f2	Delay f2-pu
Area 3b	Responsive	74(100%)	5(7%)	74(100%)	–	13(18%)	–	1(1%)	–
n = 74	Periodicity	50(68%)	–	39(53%)	–	–	–	–	–
	Firing rate	48(65%)	–	45(61%)	–	–	–	–	–
Area 1	Responsive	132(100%)	16(12%)	132(100%)	25(19%)	17(13%)	4(3%)	37(28%)	20(15%)
n = 132	Periodicity	42(32%)	–	36(27%)	–	–	–	–	–
	Firing rate	47(36%)	2(1%)	44(33%)	2(1%)	–	–	–	–
Area 2	Responsive	122(69%)	34(19%)	87(49%)	26(15%)	24(14%)	13(7%)	18(10%)	12(7%)
n = 176	Periodicity	29(16%)	–	31(18%)	–	–	–	–	–
	Firing rate	49(28%)	4(2%)	70(40%)	3(2%)	–	–	2(1%)	1(1%)
S2	Responsive	88(68%)	18(14%)	80(62%)	36(28%)	14(11%)	9(7%)	35(27%)	27(21%)
n = 129	Periodicity	10(8%)	–	8(6%)	–	–	–	–	–
	Firing rate	45(35%)	14(11%)	64(50%)	40(31%)	1(1%)	3(2%)	14(11%)	25(19%)
A1	Responsive	8(11%)	–	1(1%)	–	49(69%)	15(21%)	48(68%)	13(18%)
n = 71	Periodicity	–	–	–	–	7(10%)	–	6(8%)	–
	Firing rate	–	–	–	–	31(44%)	–	39(55%)	–

rate as a function of the increasing tactile flutter rate (first and third panels Figure 3C), but was insensitive to the acoustic flutter rate (first and third panels of Figure 3D). The coefficients values a1 (f1) and a2 (f2) reflect this as well, both in terms of the cell's firing rate (upper panels of Figures 3E and 3F) and periodicity (lower panels of Figures 3E and 3F). These observations were true at the population level too in terms of firing rate (upper panel of Figure 3G) and periodicity (lower panel of Figure 3G). Thus area 1 did not encode information about the acoustic flutter, neither through the firing rate (upper panel of Figure 3H) nor through periodicity (lower panel of Figure 3H) in any of the relevant periods of these tasks.

In addition to these results, we found some neurons in area 1 that not only responded briskly during the stimulation periods in the tactile task, but also responded weakly during the delay periods (Table 1). However, none of these neurons encoded the tactile flutter frequency during the delay periods, during which information must be maintained in working memory. Concerning the acoustic flutter discrimination task, we did observe a variety of weak responses (Table 1), either during the stimulation periods or during the delay periods (Figure S1 available online), but none of them encoded the rate of the acoustic stimuli, neither according to their firing rates nor according to their periodicity. Furthermore, as in the case of area 3b, the response latencies of these cells were significantly longer (one tailed t test, $p < 0.01$) for the acoustic stimuli (mean: 201.01 ms, SD: 38.49) than for the tactile stimuli (mean: 36.97 ms, SD: 18.5). The responses to the tactile and acoustic stimuli of Figure S1 are quite revealing. While this example neuron did modulate its firing rate as a function of the tactile flutter frequency (Figure S1A, C and E), in response to the acoustic stimuli simply increased its firing rate just before the f2 presentation, but did so regardless of the acoustic frequency (Figure S1B, D and F). Thus, this neuron encoded flutter rate but only for the tactile flutter stimuli, not for the acoustic flutter stimuli.

As for the area 3b neurons, we also explored the possibility that area 1 predicted the animal's choice (Experimental Procedures). The results are shown in Figure 7, which plots the choice probability indices as function of time for both tasks. None of the area 1 neurons predicted in their activities the animal's choice.

Responses of Area 2 Neurons during Tactile Flutter Discrimination and Acoustic Flutter Discrimination

It has been reported that area 2 neurons respond not only to somatosensory inputs but also to auditory and visual inputs (Zhou and Fuster, 2000, 2004). We recorded from 176 single neurons in area 2 while monkeys performed either the tactile or the acoustic discrimination tasks (Figure 1A; Table 1). All of these neurons had larger cutaneous receptive fields than those from area 1 neurons; they covered three or four fingertips. As for areas 3b and 1, we found that most of the single neurons of area 2 responded during the tactile flutter task, but there were also some neurons that responded during the acoustic flutter task too (Table 1). The example neuron of Figure 4 shows that the strongest response occurred during the tactile flutter stimuli (Figure 4A), but it also shows some weak responses during the acoustic f1 period (Figure 4B). However, when we quantified the firing rate and periodicity across the relevant task periods of the flutter discrimination tasks, we found that this neuron modulated its firing rate as a function of the tactile flutter stimuli only (first and third panels of Figure 4C and upper panel of Figure 4E) and not as functions of the acoustic flutter stimulus rate (first and third panels of Figure 4D and upper panel of Figure 4F). This neuron showed also some modulation in its periodicity as a function of the tactile flutter stimulus rate (lower panel of Figure 4E), but again not to the acoustic flutter stimuli (lower panel of Figure 4F). As for the neurons of areas 3b and 1, this neuron encodes neither the stimuli during the delay periods between f1 and f2 nor during the delay period between the end of f2 and the cue that triggers the motor response. The analysis

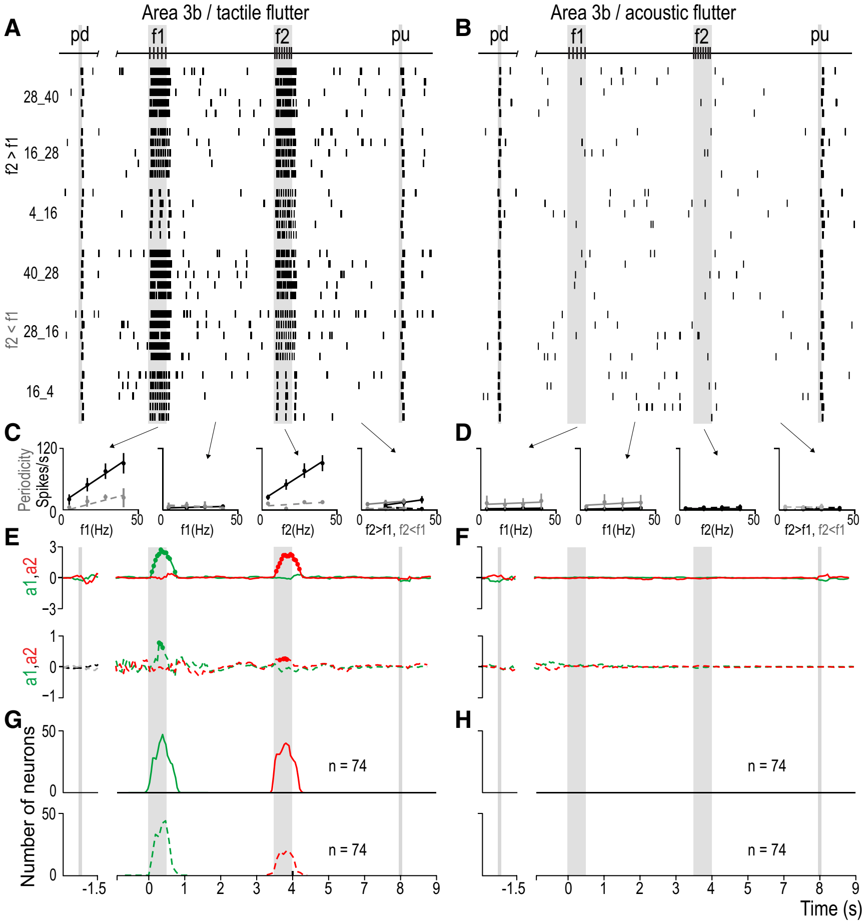

Figure 2. Responses of Area 3b Neurons during Discrimination of Either Tactile Flutter Stimuli or Acoustic Flutter Stimuli

(A) Raster plots during discrimination of two tactile flutter stimuli. (B) Raster plots during discrimination of two acoustic flutter stimuli. Each row of ticks is a trial, and each tick represents an action potential. Trials were delivered during discrimination, on interleaved trials, of either tactile flutter stimuli or acoustic flutter stimuli (10 trials per stimulus pair; only 5 trials are shown). Only stimulus pairs with large (12 Hz) differences between the first stimulus (f1) and the second stimulus (f2) are shown. Gray vertical boxes indicate f1 and second f2 stimulation periods, with rate values on the left. (C and D) Periodicity and firing rate (mean ± SD) as a function of stimulus rate. (E and F) Coefficient values for f1 (a1, green) and f2 (a2, red) for the neuron's responses in panels A and B as a function of time. Upper panels in E and F are coefficients values based on firing rates as a function of time. Lower panels in E and F are coefficients values based on periodicity as a function of time. Circles indicate significant values. Upper panels in G and H are the number of neurons that, in their firing rates, provided information about coefficients a1 (f1) and a2 (f2) during either the tactile flutter task or during the acoustic flutter task. Lower panels in G and H are the number of neurons that, in their periodicity, provided information about f1 and f2 during either the tactile flutter task or the acoustic flutter task. Trials were ordered as function of f2 > f1 or f2 < f1 in both tasks. n, number of neurons tested in either tactile or acoustic flutter tasks.

of the neuronal population showed that area 2 contains more neurons that encoded information about the tactile flutter stimuli through its firing rate during the stimulation periods (upper panel of Figure 4G) than through its periodicity (lower panel of Figure 4G). As for areas 3b and 1, no one single neuron of area 2 encoded the acoustic stimuli through its firing rate (upper panel of Figure 4H) or through its periodicity (lower panel of Figure 4H). As for area 1, some of the neurons responded during the delay periods between f1 and f2 or during the delay period between the end of f2 and the cue that triggers the motor report during either the flutter tactile task or acoustic flutter task (Table 1), but again none encoded the stimuli and the decision motor report. Figure S2 shows an example of such responses. This neuron modulated its firing rate as a function of the tactile flutter rate (Figures S2A, S2C, and S2E) but not as a function of the acoustic flutter rate (Figures S2B, S2D, and and S2F). This neuron also shows some activation before the acoustic f2 presentation but not during the tactile flutter task (Figure S2B). For those area 2 neurons that responded to one of the two acoustic stimuli, the response latencies were significantly (one-tailed t test, $p < 0.01$) longer (mean: 170.15 ms, SD: 59.8) than to the tactile stimuli (mean, 35.9 ms; SD, 13.65).

As for the area 3b and 1 neurons, we also explored the possibility that area 2 neurons that encoded the tactile flutter stimuli and those that simply responded during any of the task components of this task predicted the animal choice (Experimental Procedures). The same analysis was done also for those few area 2 neurons that responded in the acoustic flutter task. The results are shown in Figure 7, which plots the choice probability indices as a function of time for both tasks. In both tasks, none of the area 2 neurons predicted in their activities the animal's choice. The results show that area 2 neurons encode only the tactile flutter stimuli during the stimulus periods and that they do not encode the cognitive components of both tasks.

Responses of S2 Neurons during Tactile Flutter Discrimination and during Acoustic Flutter Discrimination

Previous studies have found that S2 neurons encode tactile information not only during the stimulus presentation (Burton and Sinclair, 1991; Chapman and Meftah, 1995; de Lafuente and Romo, 2006; Hsiao et al., 1993; Romo et al., 2002, 2003; Salinas et al., 2000) but also during the working memory and decision-report periods of the tactile discrimination task (Romo et al., 2002; Salinas et al., 2000). But whether S2 encodes another sensory modality is unclear (Menzel and Barth, 2005). So, we analyzed the task-related responses of S2 neurons

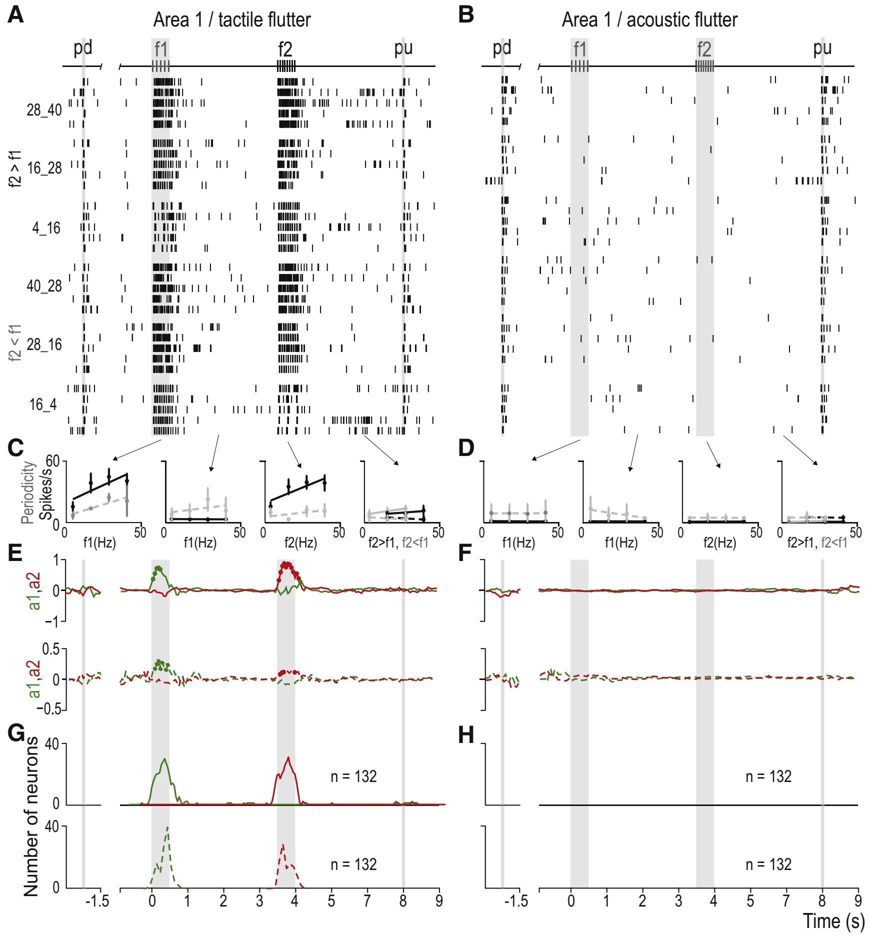

Figure 3. Responses of Area 1 Neurons during Discrimination of Either Tactile Flutter Stimuli or Acoustic Flutter Stimuli

Same labels as in Figure 2.

during the tactile and acoustic discrimination tasks, just as we did for S1. We recorded from 129 single neurons in S2 that had larger cutaneous receptive fields than the cells in area 2. These receptive fields covered the whole hand and very often included the two hands (60 of 129 neurons). Consistent with previous reports, we found that most S2 neurons increased their firing rate as a function of increasing tactile flutter stimulus rate, and the periodicity of their spike trains was very low (Salinas et al., 2000). We illustrate this type of response in Figures 5A and 5C. This neuron did not respond to the acoustic flutter stimulus rate in any way (Figures 5B, 5D and upper panel in 5F). By analyzing the a1 and a2 coefficients as functions of time, we confirmed that the majority of S2 responses were sensitive to tactile flutter rate (Figure 5G) but not to acoustic flutter rate (Figure 5H). However, S2 neurons were more complex in two different ways. First, some of them (Table 1) responded during the working memory period between f1 and f2, and an even larger fraction (Table 1) did so during the delay period between the end of f2 and the onset of the cue (pu) that triggered the motor response, and contrary to the activity observed in areas 3b, 1, and 2 some of these neurons did encode tactile flutter rate in their firing rate during the working memory period (Table 1 and upper panel of Figure 5G). Second, during the postponed decision period some of these neurons encoded information about f1 and f2 in both tasks (Table 1 and Figure S3 and upper panels of Figures 5G and 5H). We found also some neurons in S2 that encoded the tactile flutter stimulus but that also responded to the acoustic stimuli during the acoustic flutter task. However, none of these neurons encoded the acoustic flutter rate and their response latencies were significantly (one tailed t test, $p < 0.01$) longer (mean: 175.18 ms, SD: 74.71) than those evoked by tactile stimuli (mean, 64.18 ms; SD, 20.65).

We also explored the possibility that S2 neurons that encoded the tactile flutter stimuli and those that simply responded during any of the task components of this task predicted the animal choice (Experimental Procedures). The same analysis was done also for those few area S2 neurons that responded in the acoustic flutter task. The results are shown in Figure 7, which plots the choice probability indices as function of time for both tasks. Few S2 neurons predicted in their activities the animal's choice. From these results, we conclude that S2 is basically associated with encoding information about tactile flutter, not only during stimulus presentation but also to a certain degree during the delay and decision-making periods of the tactile task. However, its activity is more varied and more complex that that observed in areas 3b, 1, and 2. Furthermore, a small number of the S2 neurons did respond in the acoustic version of the task, and their choice probabilities revealed a significant correlation with the animal's choice, so it appears that an incipient multimodal integration process takes place in this area.

Responses of A1 Neurons during Acoustic Flutter Discrimination and Tactile Flutter Discrimination

The results described above using the tactile and acoustic discrimination tasks suggest that, except for a minority of S2 neurons that seem to encode the cognitive processes during the two tasks, S1 and S2 primarily encode the tactile flutter stimuli, and that very few neurons are modulated by the acoustic flutter stimuli. We wondered if the same was true in A1; that is, whether this area processes not only auditory inputs but also somatosensory inputs, as reported before (Brosch et al., 2005; Lakatos et al., 2007). We recorded from 71 single A1 neurons while monkeys performed the two tasks, as

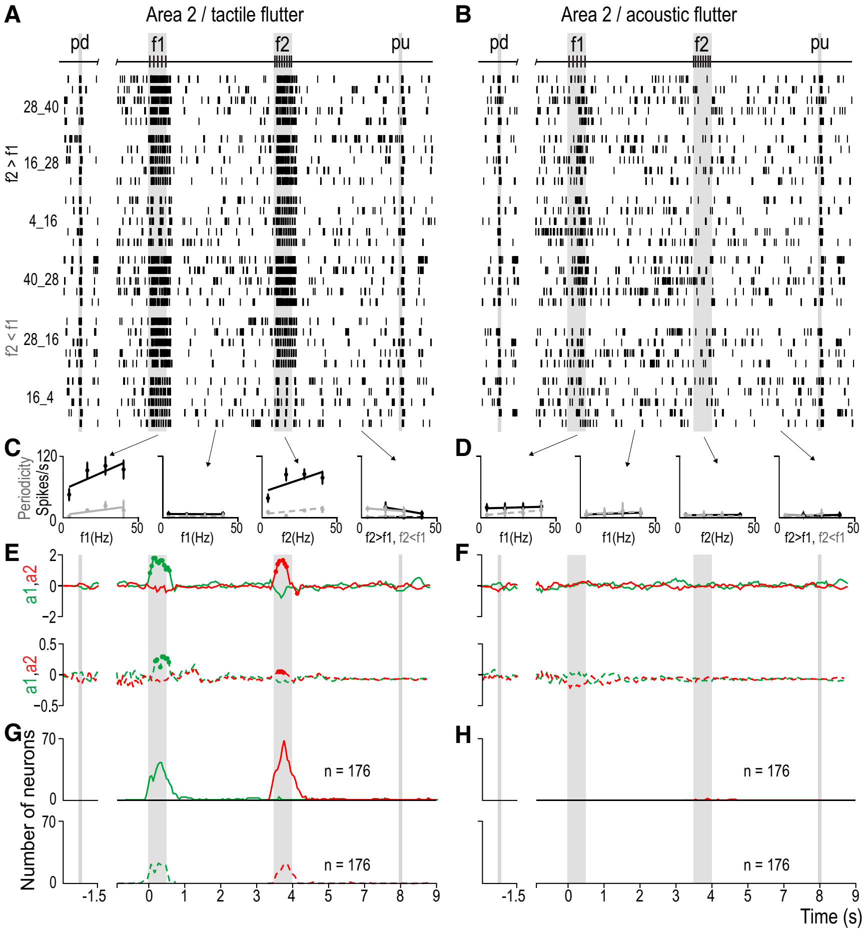

Figure 4. Responses of Area 2 Neurons during Discrimination of Either Tactile Flutter Stimuli or Acoustic Flutter Stimuli

Same labels as in Figure 2.

described above (Figure 1A; Table 1). We found that the majority of A1 responses encoded acoustic flutter rate through modulations in their firing rate, as reported before (Lemus et al., 2009a). In addition, we found that these cells did not respond in the tactile version of the task, as illustrated in Figures 6A, 6C, and 6E. The firing rate of the example neuron of Figure 6 increased monotonically as a function of the acoustic flutter stimuli (Figure 6B and first and third panels of Figure 6D, and upper panel of Figure 6F), and the responses of this cell also reflected the periodicity of the presented stimuli, particularly during f1 (Figure 6D and lower panel of Figure 6F). As indicated above, none of the A1 neurons encoded the tactile flutter stimulus (Figure 6G), and the large majority encoded the acoustic flutter stimulus in their firing rate (upper panel of Figure 6H). As in the case of areas 3b and 1, although we found few A1 neurons that responded to the secondary sensory modality (Table 1), again none of these responses encoded tactile flutter stimulus. Also, the response latencies to the tactile stimuli were significantly (one tailed, t test, $p < 0.01$) longer (mean, 138.6 ms; SD, 105.35) than those obtained with acoustic stimuli (mean, 53.0 ms; SD, 21.0). Finally, none of the A1 neurons responded during the delay periods in either tasks, nor did they reflect the animal's choices, as quantified by the choice probability indices (Figure 7). Therefore, as far as we can tell with these tasks, A1 neurons are primarily devoted to encoding the acoustic flutter task, as are those in S1 for the tactile flutter task.

Cross-Modal Discrimination Processing of S1, S2, and A1 Neurons

We sought to determine the neuronal response properties of S1, S2, and A1 while monkeys performed in cross-modal discrimination stimulus sets (Figure 1E). It has been shown, particularly in S1 that some neurons respond to visual and auditory cues when these cues are associated with the touch of an object (Zhou and Fuster, 2000, 2004). But, again, the identity of these responses during cross-modal discrimination tasks is unclear. We focused on this problem in animals that discriminated pairs of either two flutter stimuli or pairs of stimuli in which f1 was acoustic and f2 tactile, and vice-versa (Figure 1E). We found that the discrimination thresholds were similar when animals performed in the condition f1 acoustic flutter and f2 tactile flutter (Figure 1H; discrimination threshold: 3.27 Hz) and when animals performed in the condition f1 tactile flutter and f2 acoustic flutter (Figure 1H; discrimination threshold: 3.58 Hz). These discrimination thresholds were not different from those obtained during the tactile flutter discrimination task and during the acoustic flutter discrimination task (Figure 1D). We then recorded single neurons in S1 (areas 3b, 1, 2), S2, and A1 while animals performed in these discrimination tests (Figures 1E–1G). The results are plotted in panels A and B of Figure 8 for each cortical neuronal population tested with these stimulus sets. Clearly, neurons from the somatosensory cortices encoded the tactile flutter stimuli and not to the acoustic stimuli (Figures 8A and 8B). Conversely, A1 neurons encoded the acoustic flutter stimuli and not the tactile flutter stimuli (Figures 8A and 8B). The responses for their principal modality were exclusively confined to the stimulation periods and not to the working memory and decision report periods during the discrimination sets. Few of the S1 (10/123) and S2 (7/51) neurons responded to the acoustic flutter stimuli in the cross-modal association task. We found, however, that none encoded information about the acoustic stimuli. Finally, in the same test conditions, some few A1 neurons responded to the tactile flutter stimuli (2/34), but again none encoded information about the tactile flutter. These results

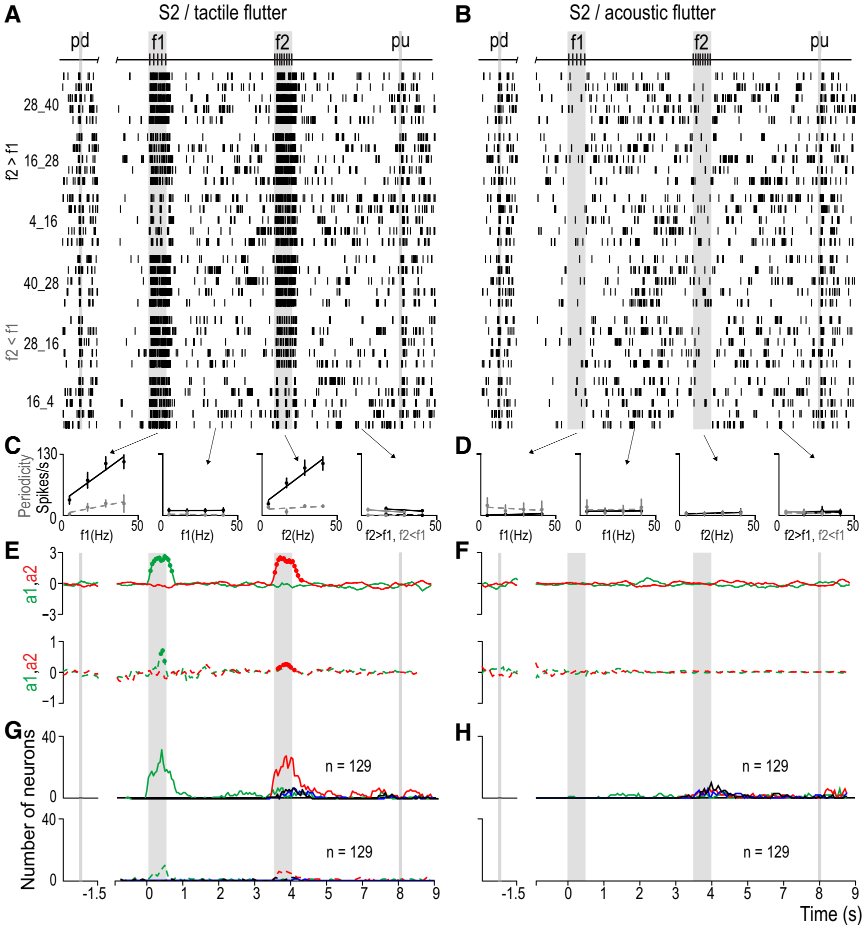

Figure 5. Responses of S2 Neurons during Discrimination of Either Tactile Flutter Stimuli or Acoustic Flutter Stimuli

Same labels as in Figure 2, but in addition, blue traces indicate number of neurons with coefficients a1 (f1) and a2 (f2) that were significant and of different magnitudes and had opposite signs; these are partial differential responses. Black traces indicate number of neurons with coefficient a1 and a2 that were significant and of similar magnitude and opposite signs; these are fully differential or categorical responses.

show that S1 and A1 do not show cross-modal associations across the relevant periods of these tests. However, some S2 neurons (9/51) gave information about the difference between the flutter stimuli and between the acoustic stimuli, indicating that these cortical areas contain neurons that code the decision report in these tasks.

Acoustic Influences on Tactile Processing of S1 and S2 Neurons

Previous studies have found that the neuronal responses of early sensory cortices to their principal sensory modalities can be influenced by another sensory modality (Bizley et al., 2007; Brosch et al., 2005; Fu et al., 2003, 2004; Ghazanfar et al., 2005; Kayser and Logothetis, 2007; Kayser et al., 2008, 2009, 2010; Lakatos et al., 2007, 2009; Schroeder and Foxe, 2002, 2005; Schroeder et al., 2001; Werner-Reiss et al., 2003). We explored whether the tactile flutter processing of S1 (areas 3b, 1, and 2) and S2 neurons was influenced by the acoustic flutter stimuli. We recorded S1 and S2 neurons while animals discriminated between f1 and f2 flutter tactile stimuli and acoustic flutter stimuli delivered synchronously (Figures 1I and 1J). We found that the discrimination threshold in this test condition was similar (Figure 1K) to those shown in panels D and H of Figure 1. Concerning the neuronal responses, we found that they again encoded their principal sensory modality during the stimulation periods, and not during the working memory and decision components of these tasks (Figure 8C). We then measured the acoustic influences on the S1 and S2 neuronal responses elicited by the tactile stimuli (Figure 8D). For each neuron, we plotted the slope values based on the firing rate modulation when the animal discriminated, on interleaved trials, either between two tactile flutter stimuli or between two synchronously tactile and acoustic stimuli. The results indicate that these influences, if they are, are not statically significant (Figure 8D; $p > 0.05$, Wilcoxon rank-sum test; Siegel and Castellan, 1988). Thus, under these test conditions, it seems that the acoustic flutter stimuli do not influence the S1 and S2 neuronal responses elicited by the tactile flutter stimuli.

Tactile Influences on Acoustic Processing of A1 Neurons

We explored whether the acoustic flutter processing of A1 neurons was influenced by the tactile flutter stimuli. We recorded A1 neurons while animals discriminated between f1 and f2 flutter tactile stimuli and acoustic stimuli delivered synchronously (Figures 1I and 1J). Concerning the A1 responses in these test conditions, we found that again they encoded their principal modality during the stimulation periods and not during the working memory and decision components of these tasks (Figure 8C). We then measured the tactile influences on the A1 neuronal responses elicited by the acoustic stimuli (Figure 8D). For each neuron, we plotted the slopes values based on the firing rate modulation when the animal discriminated, on interleaved trials, either between two acoustic flutter stimuli or between two synchronously tactile and acoustic stimuli. The results indicate that these influences, if they are, are not statically significant (Figure 8D; $p > 0.05$, Wilcoxon rank-sum test; Siegel and Castellan, 1988). These results suggest that the tactile flutter stimuli do not influence the A1 neuronal responses elicited by

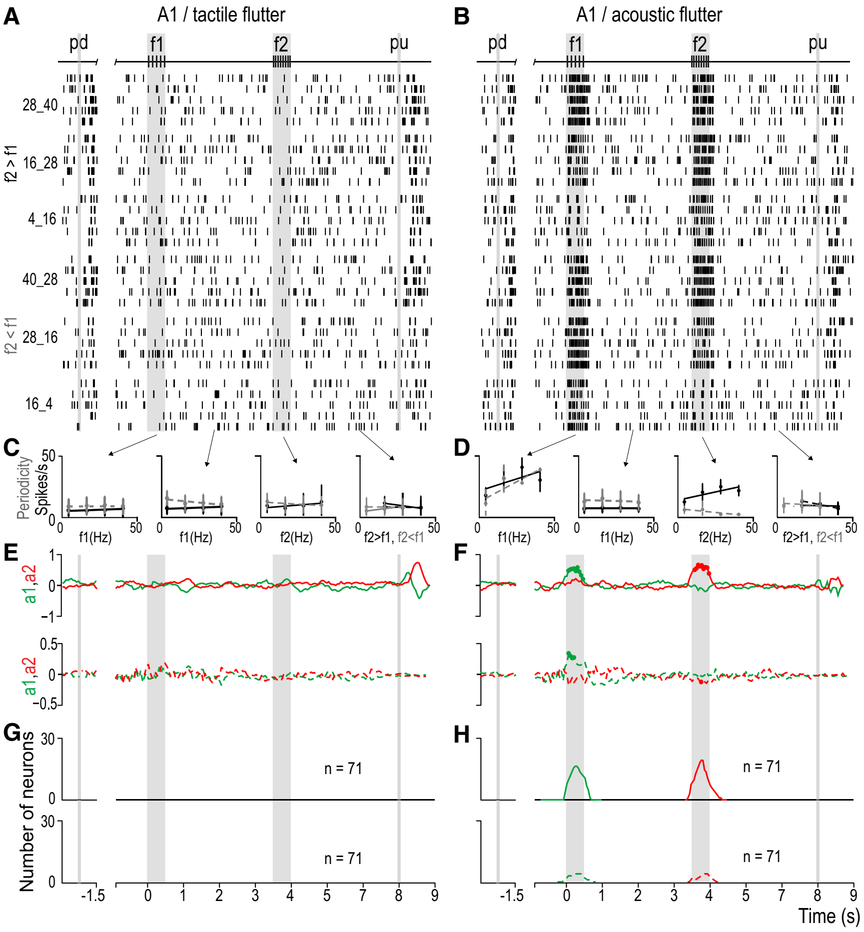

Figure 6. Responses of A1 Neurons during Discrimination of Either Tactile Flutter Stimuli or Acoustic Flutter Stimuli

Same labels as in Figure 2.

the acoustic stimuli. However, it might be possible that we missed such influences in A1 since a low number of neurons were tested in this condition.

DISCUSSION

These experimental results show that the S1 neurons that encoded the tactile flutter stimulus rate during the stimulation periods did not encode the acoustic flutter stimulus rate. Similarly, the A1 neurons that encoded the acoustic flutter stimulus rate did not encode the tactile flutter stimulus rate. While some S1 neurons showed some responses to the acoustic flutter stimuli and the A1 neurons to the tactile flutter stimuli, however, they did not encode information about the stimuli. The results also show that S1 and A1 do not encode information about their principal sensory modality or another sensory modality during the working memory periods and do not show any activity correlated with the decision report. This was not the case for some few S2 neurons, since they not only encoded the tactile flutter stimulus but also encoded information about the acoustic flutter stimulus during the sensory, working memory, and decision components of these tasks. These results suggest that S1 and A1 are primarily devoted to encoding information about the identity of the stimulus of their principal sensory modality and that multimodal encoding and multimodal perceptual judgments might start in cortical areas (S2) central to these primary sensory cortices during the tasks used here.

Some of our results agree with previous observations in that some few S1 and S2 neurons can respond to acoustic stimuli (Zhou and Fuster, 2000, 2004) and that some A1 neurons can respond to tactile stimuli (Brosch et al., 2005; Kayser et al., 2009). Although not related with audio-tactile cross-modal interactions, Bizley and King (2008) have reported that A1 neurons of anesthetized ferrets show visual spatial location coding, suggesting that these responses could serve to improve auditory location. Furthermore, consistent with this observation is the fact that A1 neurons improve the coding of acoustic stimuli when they are paired with visual stimuli (Kayser et al., 2010). These authors have also reported that many A1 neurons show this property, but that the visual inputs alone evoke insignificant responses. This result agrees with our observations obtained in A1 since none of the recorded neurons encoded tactile flutter. These results also suggest that the tactile flutter stimuli do not influence the A1 neuronal responses elicited by the acoustic stimuli. However, it might be possible that we missed such influences in A1 since a low number of neurons were tested in this condition.

Our results show that neurons of S1 and A1 do not show temporal cross-modal associations during the stimulation periods, working memory, and decision periods of the tasks used here. We found, however, that some few neurons from S1 and A1 responded to another sensory modality during the tasks components. But the fact that these responses did not convey information about the stimuli leads us to suggest that responses associated with concurrent nonsensory inputs could be interpreted as the neural correlates of cross-modal association (Brosch et al., 2005; Zhou and Fuster, 2000, 2004). A strong argument against cross-modal association in S1 is that no one single neuron encoded the acoustic stimulus, when the f1 was acoustic and had to be discriminated against the f2 when it was tactile, and vice versa. Similarly, no one single A1 neuron encoded the flutter stimulus, when f1 was tactile and had to be discriminated against an f2 acoustic stimulus, and vice versa. These results suggest that cross-modal interactions must occur outside these cortical areas (Andersen et al., 1997; Barraclough

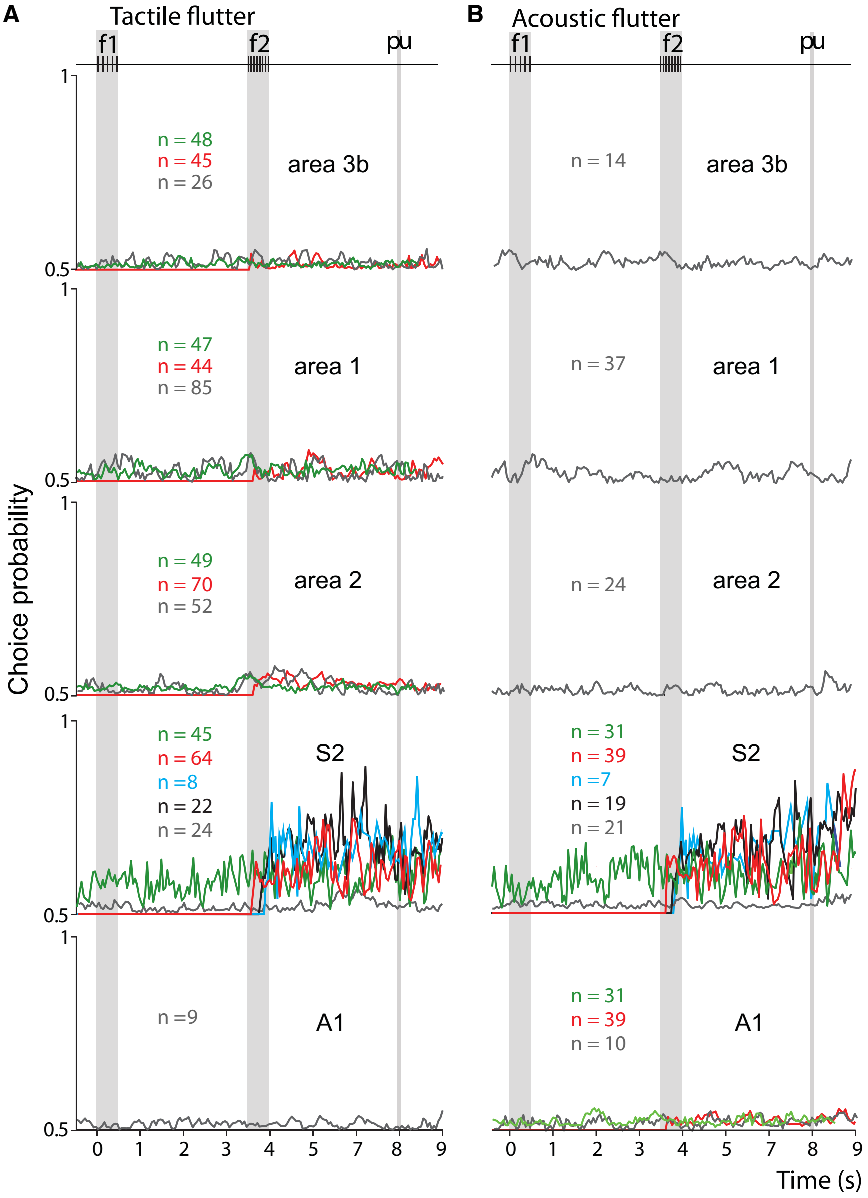

Figure 7. Correlation between Neuronal and Behavioral Responses

Choice probability indices as a function of time. (A and B) Green traces, neurons that encoded information about f1; red traces, neurons that encoded information about f2; gray traces, neurons that responded but did not encode information about f1 or f2 during the task components; blue traces, partially differential response neurons that carried information about f1 and f2 (d); black traces, fully differential response neurons that carried information about f2 – f1 only (c). n, number of neurons that responded according to the above description during discrimination of either the tactile flutter task or the acoustic flutter task.

et al., 2005; Bruce et al., 1981; Fuster et al., 2000; Graziano et al., 1997, 1999; Hikosaka, 1993; Jones and Powell, 1970; Schroeder and Foxe, 2002; Stein and Arigbede, 1972). However, other studies have reported cross-modal interactions particularly in A1 when an acoustic stimulus is paired with a visual stimulus (Kayser et al., 2008). As indicated above, in our task conditions we did not find cross-modal interactions in S1 and A1; however, some few S2 neurons showed some cross-modal encoding, suggesting that an incipient multimodal processing starts in this cortical area.

Our results also show that discrimination performance did not improve when the tactile and acoustic stimuli were synchronously presented. This result contrasts with the beneficial effect assigned by another sensory modality on perceptual judgments based on one sensory modality (reviewed by Driver and Noesselt, 2008; Ghazanfar and Schroeder, 2006; Kayser et al., 2009). This could be due to the task demands and to the stimulus-paired protocol used here. In this test and in the other tests, animals must work at high attention and motivation levels, operating with a high efficient sensory evaluation to maximize reward. In fact, animals showed very low thresholds in the cross-modal and in both tactile and acoustic flutter tests and, therefore, it would be difficult that they could improve these thresholds in the synchronous paired stimulus test.

The responses of S1, S2, and A1 neurons showed similar encoding to their principal sensory modality when they were delivered synchronously with another sensory modality. Thus, during the simultaneous presentation of the two stimuli, the somatosensory cortices encode the tactile flutter and A1 the acoustic flutter. Because we did not observe integration of the two sensory representations in S1 or in A1, the question is whether a central area uses the two modalities or only one to solve this task. We speculate that when the two stimuli were delivered synchronously, the representation of one sensory modality competes against the other and that it is very likely that the animal uses only one of the two sensory representations to solve the task. If this is the case, selection of one over the other must occur in areas central to S1 and A1. In the same vein, we did not observe cross-modal processing in S1 and A1 and very likely this central mechanism combines the two sensory representations to solve the task. This central mechanism must efficiently adapt to task demands. In this respect, it is worth mentioning that ventral premotor cortex neurons during tactile flutter discrimination (Hernández et al., 2010; Romo et al., 2004) and during auditory flutter discrimination (Lemus et al., 2009b) encode the stimuli during the stimulus periods, working memory, and correlate with the animal's decision reports. Also, neurons from this premotor cortex respond to visual stimuli during a visual discrimination task (Pardo-Vázquez et al., 2008). Thus, single neurons from this cortical circuit are good candidates to encode more than one sensory modality and therefore multimodal processing during perceptual judgments.

These results suggest that the role of S1 and S2 is to encode primarily their principal sensory modality (de Lafuente and Romo, 2005; Hernández et al., 2000; Lemus et al., 2009a; Salinas et al., 2000) and that these representations could be used by a central area(s) at the service of decision making during these tasks (Hernández et al., 2002, 2010; Lemus et al., 2009b; Romo et al., 2002, 2004). However, it is possible that under some other behavioral test conditions the beneficial effects of another modality over the principal sensory modality can be observed in a primary sensory cortex, where the inverse effectiveness principle of Stein and Meredith (1993) might profoundly impact sensory processing. This could be the case during detection or discrimination of sensory stimuli at threshold level (de Lafuente and Romo, 2005; Hernández et al., 1997). In this case the processing of the principal sensory modality in a sensory cortex could be enhanced (or suppressed) by another sensory modality (Kayser et al., 2008; Lakatos et al., 2007) and influence sensory performance.

In brief, our results show that S1 and A1 do not encode more than one sensory modality in our task conditions. Our results also suggest that events associated with memory and comparison between acoustic and tactile stimuli might occur outside S1 and A1. However, it might be possible that other types of encoding during cross-modal tests could be present, as reported recently in auditory cortices (Kayser et al., 2010; Lakatos et al., 2007, 2009). Furthermore, the most consistent result about multimodal processing in primary sensory cortices is that another sensory modality enhances or suppresses the neuronal responses evoked by the principal sensory modality. However, most of the multimodal studies have been made in nonbehaving animals, which makes it difficult to address the problem of the influences of another sensory modality over the principal sensory modality. Thus, further studies are needed to tease apart the contributions of another sensory modality over the principal sensory modality in early sensory cortices during perceptual judgments. This would require neuronal recordings in animals trained in more than one sensory task.

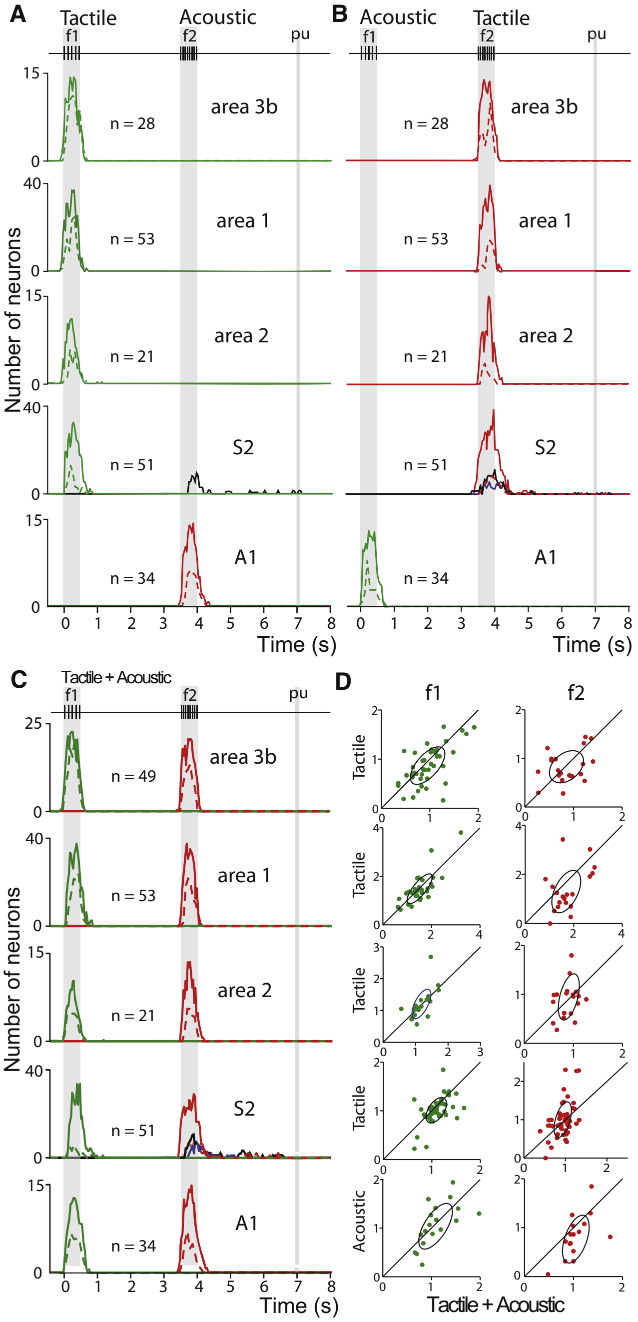

Figure 8. Cross-Modal Discrimination Processing and Influences of Acoustic and Tactile Stimuli on Somatosensory and Auditory Processing

Cross-modal discrimination processing in primary somatosensory cortex (areas 3b, 1 and 2), secondary somatosensory cortex (S2) and primary auditory cortex (A1), and the influences of acoustic and tactile stimuli on somatosensory and auditory processing. (A) Number of neurons that responded when f1 was tactile and f2 acoustic. (B) Number of neurons that responded when f1 was acoustic and f2 tactile. (C) Number of neurons that responded in S1, S2 and A1 when the tactile and auditory stimuli were delivered synchronously. (D) Acoustic influences on tactile processing in S1 and S2 and tactile influences on acoustic processing in A1. For each neuron of panel C we calculated the slope of the best linear fit of the firing rate as a function of the stimulus rates during discrimination of either two tactile flutter stimuli or two acoustic flutter stimuli delivered synchronously (f1, tactile + acoustic; f2, tactile + acoustic). We required a good fit (χ^2, $Q > 0.05$) and the slope of the linear fit to be significantly different from zero ($p < 0.01$, $n = 1000$, permutation test [Siegel and Castellan, 1988]). Each data point corresponds to the intersection of the slopes in the case of the response during the tactile flutter task and acoustic flutter task (y axes) versus the responses during discrimination when in f1 and in f2 the tactile and acoustic stimuli were delivered simultaneously. Ellipses are 2σ-contour for a two-dimensional Gaussian fit to the data point distributions. Continuous lines in C correspond to neurons that modulated their firing rates as a function of the stimulus rate; broken lines correspond to neurons that modulated their periodicity as functions of the stimulus rate. Green lines and dots correspond to f1; red lines and dots correspond to f2.

EXPERIMENTAL PROCEDURES

Discrimination Tests

Two monkeys (*Macaca mulatta*) were initially trained to discriminate the difference between two tactile flutter stimuli, as described before (range, 4–40 Hz; Hernández et al., 1997; Lemus et al., 2007; Romo et al., 1998, 2004). Once the animals had stable discrimination thresholds, they were then trained to discriminate between two acoustic flutter stimuli, as described before (range, 4–40 Hz; Lemus et al., 2009a). Briefly, two 500 ms long acoustic pulse trains were delivered by a computer-controlled free-field speaker located 30 cm directly in front of the animal. Each pulse lasts 20 ms at 1 kHz and the interval between the pulse trains is determined by the frequency (Figure 1A). Stimulus amplitudes were adjusted to equal subjective intensities, for example 74 dB at 14 Hz rate and 70.7 dB at 30 Hz rate. The sinusoid signal was generated by a computer-controlled HP 8904 function generator (Agilent Technologies, Palo Alto). Again, once the animals showed stable discrimination thresholds in the acoustic and tactile flutter tasks, they were then introduced to discriminate, on interleaved trials, either between two tactile flutter stimuli or between two acoustic flutter stimuli (Figures 1A–1D). Once the animals were able to perform in this task condition, they were then trained to discriminate, on interleaved trails, between two flutter stimuli in which f1 was tactile and f2 was acoustic, and vice versa (Figures 1E–1H). At this point of the training period, animal could do all discrimination tests described above in one single run. The last discrimination test consisted in that animals discriminated between f1 and f2 flutter tactile stimuli and acoustic stimuli delivered synchronously (Figures 1I–1K). This last protocol was very easy for both animals and they could perform this test alone, on interleaved trials, with the other stimulus tests in one single run.

During task performance, the right hand, arm, and fingers were held comfortably, but firmly fixed throughout the experiments. Monkeys were trained to use the left hand to indicate, at the end of each trial, which of the two stimuli had the higher rate, by pressing one of two side-by-side pushbuttons placed in front of the monkey's left side (lateral pushbutton for f2 > f1, medial for f2 < f1). Trials began when a computer-controlled mechanical stimulator (2 mm round tip, BME Systems, MD) indented (500 μm) the skin of one fingertip (pd in Figures 1A, 1E, and 1I). The monkey reacted by placing its free hand in an immobile key (kd in Figures 1A, 1E, and 1I), and after a variable period (1–3 s), two flutter stimuli separated by a delay of 3 s were delivered through the mechanical stimulator (in the case of the tactile flutter) or by a free speaker (in the case of the acoustic flutter); after another delay period of 3 s between the end of the f2 and the mechanical probe up from the skin (pu in Figure 1A, E and I) the animal releases the key (ku in Figures 1A, 1E, and 1I) and presses either a lateral or medial push-button (pb) to indicate whether the comparison (f2) stimulus was higher or lower than the base (f1) . Monkeys were rewarded with a drop of liquid for correct discriminations. Performance was quantified through psychometric techniques (Hernández et al., 1997, 2000; Lemus et al., 2009a; Romo et al., 1998). Animals were handled according to the standards of the National Institutes of Health and the Society for Neuroscience.

Recordings Sessions and Sites

Neuronal recordings were obtained with an array of seven independent, moveable microelectrodes (2–3 $M\Omega$; Romo et al., 1999), inserted into S1 (areas 3b, 1, or 2), S2, or A1 of the left hemisphere and ipsilateral to the responding arm. We used well-established criteria to distinguish areas 3b, 1, and 2 of S1 and S2 (Hernández et al., 2000; Luna et al., 2005; Romo et al., 2002, 2003; Salinas et al., 2000). We also used well-established physiological anatomic criteria to distinguish A1 from the subdivisions of the auditory cortex (Bendor and Wang, 2007; Lemus et al., 2009a; Merzenich and Brugge, 1973; Rauschecker and Tian, 2000; Recanzone et al., 2000).

Data Analysis

For each neuron studied during the discrimination tasks, off-line analyses and statistical tests were done by using custom and MATLAB software (Mathworks, Natick, MA). We considered a neuron's response as task-related if during any of the relevant periods (f1, delay between f1 and f2, f2, delay between f2 and pu) its mean firing rate was significantly different from that in a control period (500 ms) of equal duration but preceding the initial probe indentation at the beginning of each trial (Wilcoxon test, $p < 0.01$; Siegel and Castellan, 1988). By definition, f1 and f2 correspond to the base and comparison periods, respectively. The first delay was divided into consecutive intervals of 500 ms beginning at the end of f1 and up to the beginning of f2. Similar intervals were used for the second delay between f2 and pu. The reaction time was the period from the end of pu to the beginning of the ku (Figures 1A, 1E and, 1I). The movement time was the period from the end of ku to the beginning of the push-button press (not shown in the Figures 1A, 1E, and 1I). We did not carry further analyses during the reaction and movements times since the S1, S2, and A1 neurons did not change their firing rates during these periods.

The dependence on f1 and f2 was quantified through multivariate regression analysis (Draper and Smith, 1966; Hernández et al., 2002; Lemus et al., 2007, 2009a, 2009b; Romo et al., 2002, 2004). After finding the best-fit coefficients a1 and a2, differences between fitted and measured responses to the individual (f1, f2) stimulus pairs were calculated, resulting in a full 2D covariance matrix of errors (Draper and Smith, 1966; Hernández et al., 2002; Lemus et al., 2007; Romo et al., 2002). Coefficients were considered significantly different from (0, 0) if they were more than two standard deviations away. Neuronal responses were defined unambiguously as dependent on either f1 or f2 if the coefficients of the planar fit were within two standard deviations of either the a2 = 0 or the a1 = 0 lines; responses were considered dependent on f2 − f1 if the coefficients were more than two standard deviations away from these two lines and within two standard deviations of the a2 = −a1 line. Responses not satisfying this criterion were classified as "mixed." The dynamics of these coefficients was analyzed using a sliding window of 200 ms duration moving in steps of 50 ms. We did not include neuronal responses with R^2 = < 0.5.

The beginning of the f1-tuned response (latency) was estimated for each neuron by identifying the first of three consecutive 20 ms bins after f1 onset in which a1 was significantly different from zero and a2 was not significantly different from zero. The beginning of the f2 tuned-response was similarly estimated for each neuron. For those neurons that had no tuned f1 and f2 responses as function of the flutter rates, the response latency was calculated using the first of three consecutive 20 ms after f1 or f2 in which these bins were significantly different from a control period of 500 ms preceding the beginning of the response during any of the two stimuli (Hernández et al., 2010).

The choice probability index was calculated using methods from signal detection theory (Britten et al., 1996; Green and Swets, 1966; Hernández et al., 2002, 2010; Lemus et al., 2007; Romo et al., 2002, 2004). This quantity measures the overlap between two response distributions, in this case between correct and error trials for each (f1, f2) pair. We restricted the analysis to those (f1, f2) pairs for which the animals had between 30% and 70% of errors. Notice that a value of 0.5 indicates full overlap and 1 indicates completely separate distributions. Thus, the choice probability index quantifies selectivity for one or the other outcome of the discrimination process. To compute it at different times, we used a sliding window of 200 ms duration moving in 50 ms steps, beginning 1000 ms before f1 and ending 1000 ms after the animal reported the comparison between f2 and f1. To establish the significance of the choice probability values, the neuronal responses in each time window were shuffled, such that correct and error trials were randomized, and new choice probability indices for the shuffled data were generated (permutation test, $n = 1000$, $p < 0.01$; Siegel and Castellan, 1988). By comparing the indices from the shuffled and unshuffled data and repeating the process 1000 times, we estimated the probability of obtaining choice probability values as large or larger than those observed initially (with the unshuffled data) just by chance.

The analysis showed that S1 and S2 neurons encoded in their firing rates the tactile flutter stimuli, and that A1 neurons encoded in their firing rates the acoustic flutter stimuli. However, we also sought to quantify the periodicity of these neurons, i.e., the degree to which their spikes are synchronized with the stimuli. For each trial, the power spectrum of the spike trains evoked during the stimulus period was computed (fast Fourier transform, $n = 2^{16}$; sampling frequency, 10 kHz; resolution, 0.15 Hz; range, 4–100 Hz; Draper and Smith, 1966; Press et al., 1992). As an estimate of the periodicity, we calculated the median frequency around the peak in power, weighted according to the power at each frequency. The frequencies used for this measure were limited to those within a factor of 1.8 of the peak (to avoid contamination by harmonics) and to frequencies with a power greater than 15% of the peak power (to avoid noise). The median frequencies calculated in this way could then be used directly to determine whether $f2 > f1$ or $f2 < f1$ in each trial (see below). In each trial, we also calculated the mean firing rate for the stimulus periods. Thus, for each stimulus frequency, we computed the mean ± SD of the periodicity and the firing rate over all trials with that stimulus frequency. For further analysis, we selected those neurons that had the best linear fit (χ^2, $Q > 0.05$) of the periodicity or firing rate values as functions of stimulus frequency (Draper and Smith, 1966). We also required the slope of this linear fit to be significantly different from zero ($p < 0.05$, $n = 1000$, Permutation test; Siegel and Castellan, 1988).

SUPPLEMENTAL INFORMATION

Supplemental Information includes three supplemental figures and can be found with this article online at doi:10.1016/j.neuron.2010.06.015.

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