

Neuronal correlates of decision-making in secondary somatosensory cortex

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Published online: 30 September 2002, doi:10.1038/nn950

The ability to discriminate between two sequential stimuli requires evaluation of current sensory information in reference to stored information. Where and how does this evaluation occur? We trained monkeys to compare two mechanical vibrations applied sequentially to the fingertips and to report which of the two had the higher frequency. We recorded single neurons in secondary somatosensory cortex (S2) while the monkeys performed the task. During the first stimulus period, the firing rate of S2 neurons encoded the stimulus frequency. During the second stimulus period, however, some S2 neurons did not merely encode the stimulus frequency. The responses of these neurons were a function of both the remembered (first) and current (second) stimulus. Moreover, a few hundred milliseconds after the presentation of the second stimulus, these responses were correlated with the monkey's decision. This suggests that some S2 neurons may combine past and present sensory information for decision-making.

When forming a decision based on sensory information, where and how in the brain do the neuronal responses that encode the sensory stimuli translate into responses that encode the decision? We investigated this question using a vibrotactile sequential discrimination task (Fig. 1). In this two-alternative, forced-choice task, subjects must decide which of two mechanical vibrations applied sequentially to their fingertips has the higher frequency of vibration. Subjects must then press one of two pushbuttons to report their categorical decision^{1,2}. The task thus requires perceiving the first stimulus (*f*₁), storing a trace of it in memory, perceiving the second stimulus (*f*₂), comparing *f*₂ to the trace of *f*₁, and choosing a motor act based on this comparison (*f*₂ – *f*₁). In contrast to previous studies of decision-making in the visual system^{3–7}, the decision in this task does not involve comparing a currently applied sensory stimulus to a referent stored in long-term memory. Instead, the subjects must compare a current stimulus (*f*₂) to a referent that varies on a trial-by-trial basis (*f*₁). This opens the possibility of observing components of the response that covary with the referent.

Briefly, our current knowledge is that during this task, neurons of the primary somatosensory cortex (S1) participate only in stimulus representation: they do not intervene in the working memory component of the task, nor do they participate in comparing the difference between the two stimulus frequencies^{8,9}. Instead, they faithfully encode stimulus features, and this encoding correlates closely with the subjects' discrimination performance^{8,9} in a causal manner^{10,11}. Ascending the cortical sensory hierarchy, neurons of S2 respond by encoding *f*₁ in their firing rates, and this encoding correlates closely with the subjects' discrimination performance⁸. Some neurons of S2 con-

tinue to encode *f*₁ for a few hundred milliseconds into the delay period between the first and second stimuli⁸. In the inferior convexity of the prefrontal cortex (PFC), unlike in S2 where there is a rapidly decaying trace of *f*₁, there are neurons that encode *f*₁ throughout the entirety of the delay period (which may last several seconds)¹². These neurons of the PFC thus form a candidate neural substrate for the short-term memory trace of *f*₁ required in the task. In an area linked to the eventual motor output, we have also found that neurons in the medial premotor cortex (MPC) encode *f*₁ twice: during *f*₁ presentation and then again near the end of the delay period, in apparent anticipation of the second stimulus¹³.

Where and how does the comparison between *f*₂ and *f*₁, and the decision based on this comparison, take place? Neural responses in S2 are of particular interest. S2 is connected to many cortical areas^{14–23} and is thus appropriately placed to integrate both bottom-up (sensory) and top-down (memory) information. Neurons in S2 show complex somatosensory responses^{24–27} and are known to be modulated by attention²⁷. Based largely on S2's pattern of connections with other cortical areas, it was suggested decades ago that in drawing a rough analogy between the visual and the somatosensory systems, S2 could be thought of as homologous to visual area IT (inferotemporal cortex)^{28,29}. Neurons in IT can respond in a manner that depends on combining short-term memory with incoming sensory information ('match suppression' in a visual delayed match-to-sample task³⁰). This is similar to the combination of information required to compare *f*₁ to *f*₂ in our somatosensory task. Such information-integrating responses are ultimately correlated with the decision that subjects make,

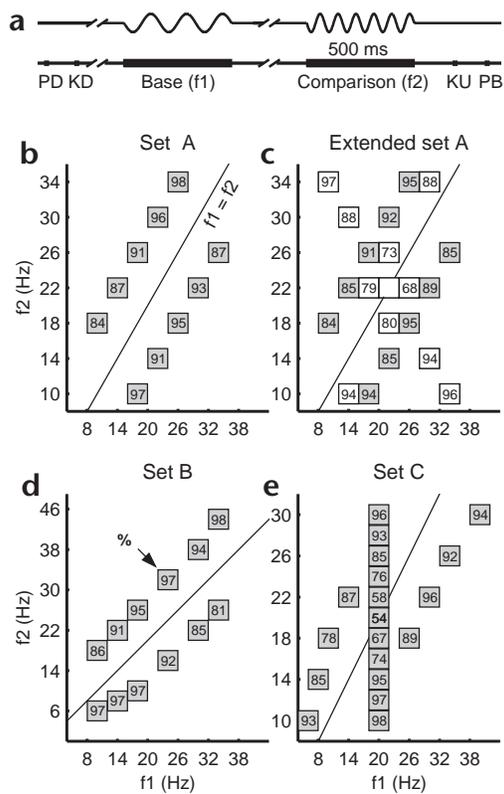


Fig. 1. Discrimination task. **(a)** Sequence of events during each trial. The mechanical probe is lowered, indenting the glabrous skin of one digit of a restrained hand (probe down, PD); the monkey places its free hand on an immovable key (key down, KD); the probe oscillates vertically at frequency f_1 ; after a delay (typically 3 s), a second mechanical vibration is delivered at the comparison frequency (f_2); the monkey releases the key (key up, KU) and presses one of two push buttons (PB) to indicate which stimulus, f_1 or f_2 , was the higher frequency. **(b–e)** Stimulus sets during recordings. Each box indicates an (f_1, f_2) stimulus pair used; the number inside the box indicates overall percent correct trials for that pair. **(b)** Gray boxes are set A, the most commonly used stimulus set; **(c)** gray boxes plus open boxes are extended set A. **(d, e)** Additional control sets, which were used to explore working memory **(d)** and psychometric thresholds **(e)**. For trials with $f_1 = f_2$ (when the correct button to press is undefined), monkeys pressed the $f_2 > f_1$ button 54% of the time.

finned to the hand on which vibratory stimuli were applied. A number of different stimulus sets were used, although set A was the one most commonly used (Fig. 1). The difference between f_2 and f_1 in set A was kept well above threshold, thus minimizing variations in attentional demands between trials. Results using all stimulus sets were similar.

Responses of S2 neurons during the comparison period

Many neurons in S2 did not respond in a purely sensory manner: their response to stimulus f_2 was not simply a function of f_2 frequency. Two particularly clear example neurons are shown in Figs. 2 and 3. The trial blocks highlighted by thick black arrows in Figs. 2a and 3a, which share the same value of f_2 but differ in the value of f_1 , show that the neurons’ responses to the second stimulus were strongly modulated by f_1 . This is true even though f_1 had been applied 3 s earlier, and information about f_1 is not maintained throughout the delay period in the firing rates of either S1 or S2 neurons^{2,8} (Fig. 2c). In S2 neurons, f_1 -dependence in the delay period was only found at the beginning of the delay period, or, much more rarely, at the very end of the delay period (see Figs. S1, S2 and S3 in Supplementary Notes online).

Note that in the stimulus set A (Fig. 1b), all trials can be divided into two types: those in which $f_2 = f_1 + 8$ Hz (black in Figs. 2 and 3) and those in which $f_2 = f_1 - 8$ Hz (gray). During the first part of f_2 presentation, the curves for the two trial types (black and gray) overlap closely (Figs. 2d and 3b), indicating that the neurons’ responses did not depend on f_2 , but only on f_1 . That is, for any given f_1 , the responses were statistically the same regardless of whether f_2 was 8 Hz higher or lower than f_1 (t -tests, both $P > 0.1$). In contrast, during the final 200 ms of f_2 , the firing rates were modulated by both f_1 and f_2 (Fig. 2e). The main determinant of the firing rate was not, however, the particular values that f_1 or f_2 took on any given trial. Instead, it was simply whether the trial belonged to the $f_2 > f_1$ group or the $f_2 < f_1$ group. This corresponds to the monkey’s two possible action choices. Not only did f_1 modulate the response to f_2 in these neurons, but even more notably, this happened such that by the end of f_2 , the responses became mostly correlated with the monkey’s choice. The same was true for the neuron of Fig. 3c, although the correlation with the monkey’s choice occurred slightly later in the trial.

The qualitative analysis we have made so far depends in part on particular characteristics of stimulus set A (Fig. 1b). For a more general analysis, we took into account the possibility that responses during f_2 could be any arbitrary function of both f_1 and f_2 . For simplicity, we began by using a first-order approximation to an arbitrary function of f_1 and f_2 . That is, we

based on the results of combining memory and sensation. The analogy with IT would therefore suggest that decision-related responses might be found in area S2.

Here we focused on responses in S2 during and after the second stimulus, when the comparison and decision are taking place. We found that the responses of the neurons were a function of both the remembered (f_1) and current (f_2) stimulus, and were observed to change, after a few hundred milliseconds, into responses that were correlated with the monkey’s decision. Other brain areas may of course also be involved in the decision. We report elsewhere on responses in other cortical areas such as MPC¹³ and PFC (unpub. observ.) during this time period.

RESULTS

Four monkeys (*Macaca mulatta*) were trained to perform the task up to their psychophysical thresholds (on the order of a 2–4 Hz difference between f_1 and f_2 for the range of stimulus frequencies used here)^{1,2}. After training, single neurons of S2 were recorded extracellularly while the monkeys performed the task⁸. We recorded from 517 neurons that had average firing rates during the second stimulus period that were significantly different from their rates during a pre-trial control period (500 ms immediately before event probe down; PD in Fig. 1a; $P < 0.01$, Wilcoxon rank-sum test)³¹. Many of these neurons ($n = 309/517$, 60%) enhanced or reduced their firing rates during f_2 , but their firing rate did not depend significantly on the applied stimulus frequencies ($P > 0.01$; Methods). Here we focus exclusively on the 40% of neurons ($n = 208$) that were significantly stimulus-dependent. The data analysis we describe (except for Fig. 7) was carried out using responses to correct behavioral trials only. All of the studied S2 neurons had large cutaneous receptive fields con-

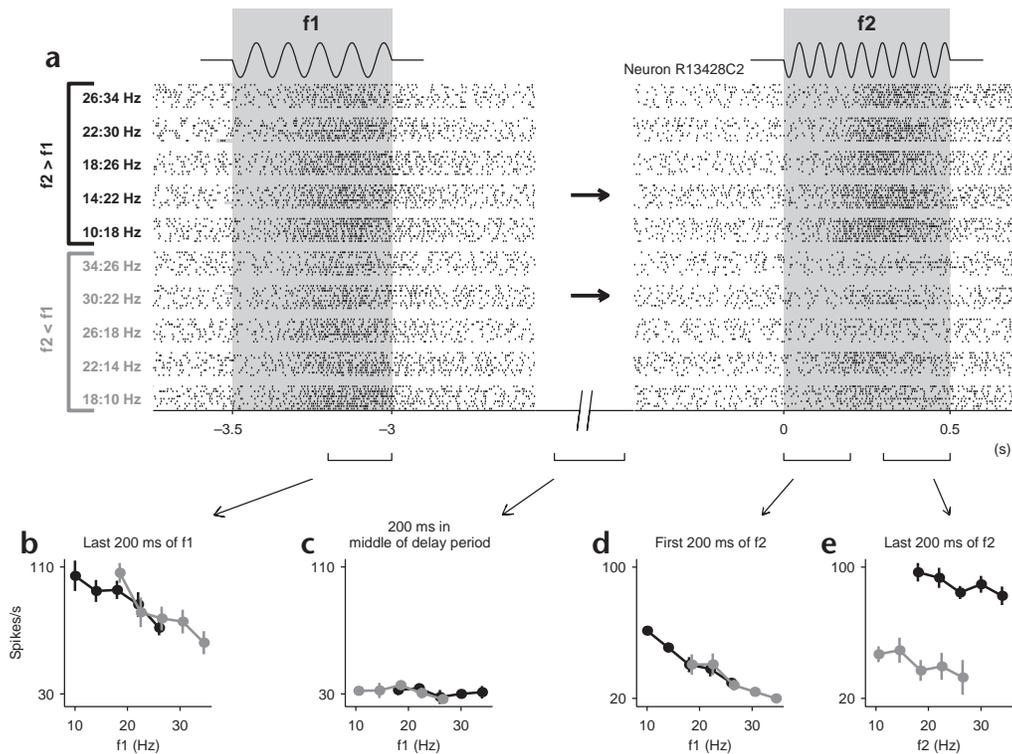


Fig. 2. A representative S2 neuron with a response to the second stimulus (f_2) that shifted to reflect the $(f_2 - f_1)$ comparison. **(a)** Raster plots of responses to stimuli f_1 and f_2 . (For completeness, we include the responses to stimulus f_1 here, but our focus was on the responses to f_2 .) Each row of ticks is a trial, and each tick is an action potential. Trials were delivered in random order. Labels at left indicate $(f_1:f_2)$ stimulus frequencies. Thick black arrows highlight trials mentioned in Results ($f_1:f_2 = 14:22$ and $30:22$ Hz). Stimulus set used was set A (**Fig. 1**). **(b)** Average firing rate during the last 200 ms of stimulus f_1 . Black indicates $f_2 > f_1$ ($f_2 = f_1 + 8$ Hz for this stimulus set); gray indicates $f_2 < f_1$ ($f_2 = f_1 - 8$ Hz). Since f_2 has not yet been applied, the response does not depend on f_2 , and the two curves overlap. **(c)** At 1.5 s into the delay period, information about f_1 is no longer present in the firing rate. **(d)** First 200 ms of f_2 , plotted as a function of f_1 . **(e)** Last 200 ms of f_2 , plotted as a function of f_2 . (Note that with stimulus set A, the choice of plotting as a function of f_1 or f_2 differs only in a horizontal shift of the black and gray lines.) Both the black and gray lines are very close to horizontal, and there is a large vertical separation between the two lines, indicating that the main determinant of firing rate was whether $f_2 > f_1$ or $f_2 < f_1$.

approximated firing rates as linear functions of f_1 and f_2 : firing rate = $a_1 * f_1 + a_2 * f_2 + \text{constant}$ (see **Supplementary Notes** for further information and tests of quality of linear fits)^{32,33}. In this formulation, the coefficient a_1 serves as a direct measurement of the firing rate's dependence on f_1 . The firing rate of each neuron, averaged over the second stimulus period, was fit in this way, and the resulting coefficients a_1 and a_2 for each neuron are plotted in **Fig. 4a**. Three lines are of particular importance in this panel: points that fall on the $a_1 = 0$ axis represent responses that depend on f_2 only (as would be expected for a purely sensory response to the second stimulus), points that fall on the $a_2 = 0$ axis represent responses that depend on f_1 only (here, these would be responses dependent on the memory of f_1), and points that fall on the $a_2 = -a_1$ line represent responses that are a function of $f_2 - f_1$ only. With stimulus set A, in which $|f_2 - f_1| = 8$ Hz for all trials, we cannot determine for points on the $a_2 = -a_1$ diagonal the specifics of the function of $(f_2 - f_1)$. For example, responses that were either a linear or sigmoidal function of $(f_2 - f_1)$ would both produce similar points on the $a_2 = -a_1$ diagonal. But what we can do is conclude that the stimulus frequencies are relevant only in the combination $(f_2 - f_1)$. Responses that are a function of $(f_2 - f_1)$ only are of particular importance for our ordinal comparison task, since correct behavior depends only on the sign of $(f_2 - f_1)$: the

neural computation and representation of $(f_2 - f_1)$ are thus of direct relevance to the monkey's task.

About half of the neurons (110/208, 53%) had a_1 coefficients that were significantly different from zero (more than 2.5 standard deviations (s.d.) from 0, corresponding to $P < 0.01$ in our null hypothesis permutation tests; **Methods**), indicating a significant f_1 -dependence of responses during the second stimulus.

We also used several controls. In none of the stimulus sets was f_1 independent of f_2 (**Fig. 1**). Perhaps the particular choice of stimuli, for example the 'diagonal' arrangement of stimuli in set A, could bias the coefficient results away from the horizontal or vertical axes. To test for this, we applied the linear fit method to situations where we knew *a priori* that the data points should lie along the horizontal axis: before f_2 has been applied, neuronal responses should depend only on f_1 . For data from both cortical areas S1 and S2, the linear fit method with the same stimulus sets, led to the conclusion that responses during f_1 depended only on f_1 (**Fig. 4b** and **d**). Thus the choice of stimulus sets did not bias the results away from the cardinal axes and cannot account for the results of **Fig. 4a**.

Dependence on f_1 during the second stimulus period could, in theory, be simply due to passive adaptation to the first stimulus, potentially as early in the somatosensory pathways as the skin mechanoreceptors. We analyzed data recorded during f_2

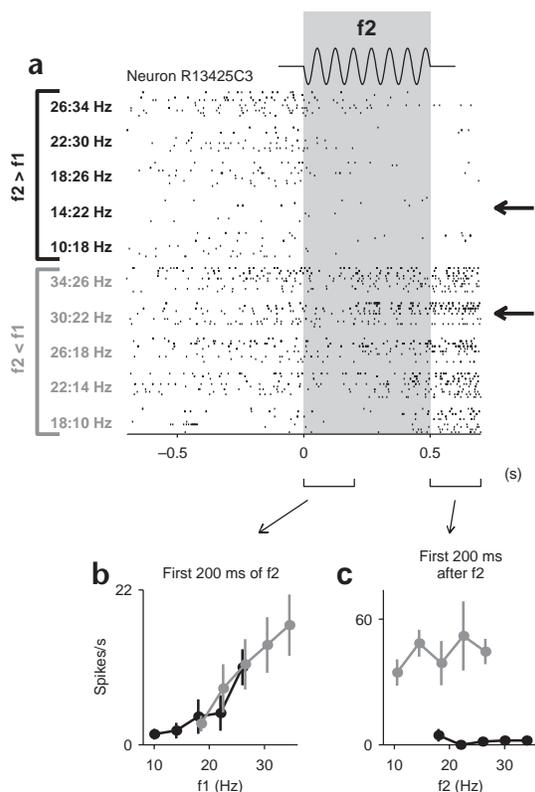


Fig. 3. A representative S2 neuron with an $(f_2 - f_1)$ -dependence opposite to that of the neuron in **Fig. 2**. Format is the same as that of **Fig. 2**, except that responses to stimulus f_1 are omitted in **(a)**.

arm and hand. Activity before the end of f_2 was negligible, and the choice of button to be pressed did not significantly modulate any of the three EMGs before the end of f_2 (see **Fig. S6** in **Supplementary Notes**). This rules out any potential somatosensory contribution from the free hand to f_1 -dependent modulation in area S2 during the second stimulus.

Dynamics of the comparison process in S2

The response properties of S2 neurons can vary markedly over the course of f_2 (**Figs. 2** and **3**). We therefore carried out linear fits as a function of time. Neuronal firing rates were first smoothed in time with a Gaussian window with a narrow s.d. (45 ms); fits of the linear equation were then done every 25 ms. The coefficients $a_1(t)$ and $a_2(t)$ that resulted from this procedure for the neuron in **Fig. 2** confirm that initially, the neuron's response depends on f_1 only, but that approximately 200 ms after the start of f_2 , the neuron shifts response properties and becomes largely a function of the $(f_2 - f_1)$ comparison (**Fig. 5a**, data points close to the $a_2 = -a_1$ line). It thus becomes correlated with the monkey's choice. The final-fit coefficients, lying on the diagonal, correspond to the near-horizontal fits of **Fig. 2e**. Similarly, the results shown in **Fig. 5b** corroborate our prior conclusions (**Fig. 3b** and **c**). Notably, the example neuron of **Figs. 2** and **5a** showed a latency of responses, during the first 200 ms of f_2 , that was systematically stimulus-dependent (**rasters in Fig. 2a**).

Because of the temporal smoothing carried out on the firing rates to reduce noise, our analysis has temporal resolution of ~ 100 ms. Thus, this analysis alone cannot distinguish between stimulus-dependence due to a latency effect within this window, and stimulus-dependence due to modulation of firing rates, separate from latency. We devised an analysis that is fully independent of response latency, based on the peak firing rate reached in response to each stimulus pair: peak firing rate was measured independently of when it occurred (**Fig. S7** in **Supplementary Notes**). The results of this analysis confirm that most of the effects reported here—particularly the correlation of firing rates with the monkey's behavioral choice, as seen toward the end of f_2 (neuron in **Figs. 2** and **5a**)—can be accounted for by modulations in firing rate itself, entirely independent of response latency. Furthermore, for the neuron of **Figs. 2** and **5a**, the mean onset latency was 186 ms after the start of f_2 (see **Supplementary Notes** for details and population results of latency analysis). Yet firing rates measured within 100 ms from the start of f_2 already showed significant f_1 -dependence (see **Fig. S8** in **Supplementary Notes**). We thus conclude that the main effects reported here are largely dependent on firing rate, and not on response latency.

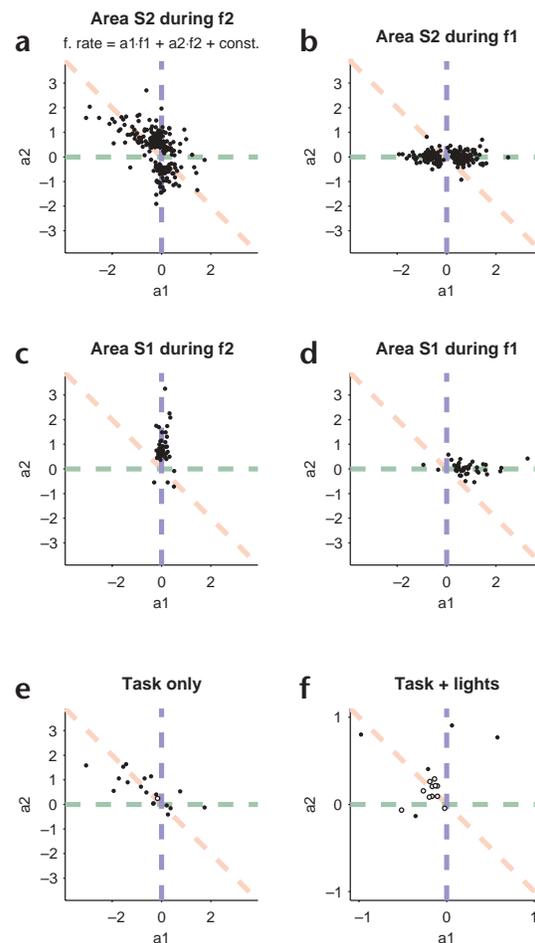
We show a time-dependent analysis for four further example neurons (**Figs. 5c–f**). Many neurons had simple sensory responses, similar to **Fig. 5c**, in that their response during f_2 depended only on f_2 . Others, as in **Fig. 5d**, responded in a purely $(f_2 - f_1)$ -dependent manner, which was typical in that these types of neurons tended to have long response latencies. Still other neurons began with a response that was f_2 -dependent, only to later shift to $(f_2 - f_1)$ -dependence (**Fig. 5e**). We classified the initial response type of each neuron on the basis of the first three significantly stimulus-dependent (a_1, a_2) data points (**Methods**). Twenty-four neurons had an initial response that was classified as unambiguously f_1 -dependent (24/208, 12%, **Fig. 5a** and **b**), 99 neurons

from 45 neurons located in area S1, from one of the same monkeys, using the same stimulus sets, during the same task (**Fig. 4c**). Coefficients cluster closely around the $a_1 = 0$ axis, showing no f_1 -dependence. Thus, f_1 -dependence during the second stimulus period arose at the level of area S2 or higher. Alternatively, f_1 -dependent responses could be due to adaptation in S2, such that after firing strongly to f_1 , neurons subsequently respond less strongly to f_2 . We calculated the correlation between responses to f_1 and f_2 for individual stimulus pairs (f_1, f_2). Instead of finding a negative correlation that would be consistent with adaptation, we found a weak positive correlation (Pearson's r , 0.21 ± 0.01 , mean \pm s.e.m., across stimulus pairs and neurons³²). A positive correlation would tend to move data points in **Fig. 4a** (also **Figs. 5** and **6**) into the upper right and lower left quadrants, opposite to the observed accumulation in the upper left and lower right quadrants. Thus, adaptation in S2 does not explain the results.

As the monkeys reported their decision by a motor act, we asked to what extent responses in S2 were reflecting a purely motor signal. In addition to the standard task, 17 neurons from S2 were studied during a variant of the task in which the same somatosensory stimuli were applied and the monkey made the same button-press motions, but they could choose which button to press based on visual, not somatosensory information (**Methods**). Under this condition, most S2 neurons reduced their firing rate (overall average firing rate during f_2 went from 29 ± 4 to 15 ± 4 spikes/s), and most f_1 and even f_2 dependence was lost (**Fig. 4e** and **f**). Thus, if there was a motor signal influencing responses in S2, it was strongly gated by the presence or absence of the somatosensory task itself.

In separate experiments, electromyograms (EMGs) were recorded from three sets of muscles leading to the monkey's free

Fig. 4. Area S2 responses to the second stimulus depend on the previously applied first stimulus during the discrimination task. Each panel shows the result of fitting the equation firing rate = $a_1 * f_1 + a_2 * f_2 + \text{constant}$, averaged over either the entire f_1 or the entire f_2 stimulus period, for neurons in areas S1 and S2. Each data point represents one neuron. Points that fall on the $a_1 = 0$ axis (blue dashes) represent responses that depend on f_2 only; points that fall on the $a_2 = 0$ axis (green dashes) represent responses that depend on f_1 only; points that fall on the $a_2 = -a_1$ line (red dashes) represent responses that are a function of $(f_2 - f_1)$ only. (a) Data from S2 during the second stimulus period. Many neurons produced a_1 coefficients different from zero. (b) Data from S2 during the first stimulus period. Coefficients cluster closely around the $a_2 = 0$ line. (c) Data from S1 during the second stimulus period. Coefficients cluster around $a_1 = 0$, showing that there is no history-dependence in area S1. (d) Data from S1 during the first stimulus. Coefficients are clustered closely around the $a_2 = 0$. (e) Data recorded from a subset of neurons in area S2, those also studied under the conditions of (f). Black points are significantly different from (0,0) and open points are not ($P < 0.01$; Methods). (f) The same neurons as in (e) recorded during a variant of the somatosensory task in which visual cues eliminated the requirement to pay attention to the somatosensory stimuli. Most points are not significantly different from (0,0), indicating no dependence on either f_1 or f_2 . This panel zooms in close to the origin: notice the sharply reduced range of the axis scale in (f) compared with (a–e). For clarity, only points significantly different from (0,0) are shown in (a–d); all points are shown in (e–f).



began their response as f_2 -dependent (99/208, 48%, Fig. 5c and e) and 36 neurons began their response as $(f_2 - f_1)$ -dependent (36/208, 17%, Fig. 5d). The initial response of the rest of the neurons (49/208, 23%) could not be unambiguously classified. A rough visual inspection of 208 panels such as those shown in Fig. 5 (one panel per neuron) suggested that about half of the neurons had trajectories that could allow a straightforward interpretation, with one or two clear response-dependency periods, as in Fig. 5a–e. But variability was great, and many neurons (exemplified by the neuron in Fig. 5f) had trajectories complex enough or noisy enough to defy any such simple interpretation.

We found a clear overall trend, however, when the population of neurons was analyzed as a whole. We carried out planar fits for the neuronal population as in Fig. 4a, but using sliding 200-ms time windows. We then quantified the overall response dependency by fitting ellipses to the population data (Fig. 6). Immediately after the start of f_2 , the long axis of the ellipse was closely aligned with the vertical $a_1 = 0$ axis, indicating an overall dependence on f_2 (Fig. 6a). But as time moved on, the data points clustered progressively closer to the $a_2 = -a_1$ line (Fig. 6b). From 300 ms after the start of f_2 onward, the ellipse orientation became aligned to within 5° of the $a_2 = -a_1$ diagonal (Fig. 6c; $P < 0.001$ under the null hypothesis described in Methods, $n = 1,000$ shuffles per neuron). Thus, during the interval lasting from 300 ms after the start of f_2 until the beginning of the monkey's motor act (Fig. 6c and d), the firing rates of the population of S2 neurons became, on average, a function of $(f_2 - f_1)$, in the sense that if a single axis of the f_1, f_2 plane were to be used to describe the population response during this period, it should be the $(f_2 - f_1)$ diagonal rather than any other. Nevertheless, because most neurons had a mixed response dependency, the breadth of the ellipse was not negligible, and a complete description of the responses requires two axes of the f_1, f_2 plane, not merely one: the average population response was composed of a variety of individual neuron responses (Fig. 5). We used the time period starting 300 ms after the onset of f_2 until the onset of the monkey's motor movement (Fig. 6c and d) to divide our set of

208 significantly stimulus-dependent neurons into three groups (red, orange and black in Figs. 6 and 7). The first group (red) was composed of neurons with average firing rates during this period that could be unambiguously described as $(f_2 - f_1)$ -dependent ($n = 41/208$, 20%). A second group (orange) was composed of neurons with responses that could be unambiguously described as f_2 -dependent during the same time period ($n = 28/208$, 13%). All other neurons (black) were placed in a third, intermediate/ambiguous group ($n = 139/208$, 67%).

S2 responses correlate with decision-reporting motor act

Responses during correct trials alone did not allow us to determine to what extent $(f_2 - f_1)$ -dependent responses were correlated with the sensory stimuli, or with the monkey's action choice itself, which may be only partly based on the sensory stimuli. We analyzed error trials and asked, for each (f_1, f_2) pair, whether responses during error trials were different from responses during correct trials. If purely dependent on sensory stimuli, responses should show little or no difference between error and correct trials. In contrast, if closely linked to the monkey's choice, responses to fixed stimuli should vary strongly according to which button the monkey chose to press. We quantified the difference in responses by computing the 'choice probability' for each (f_1, f_2) pair^{34,35}. This represents the probability with which an observer of a neuron's response to a given (f_1, f_2) pair would accurately predict the monkey's choice. We found that the closer a neuron's



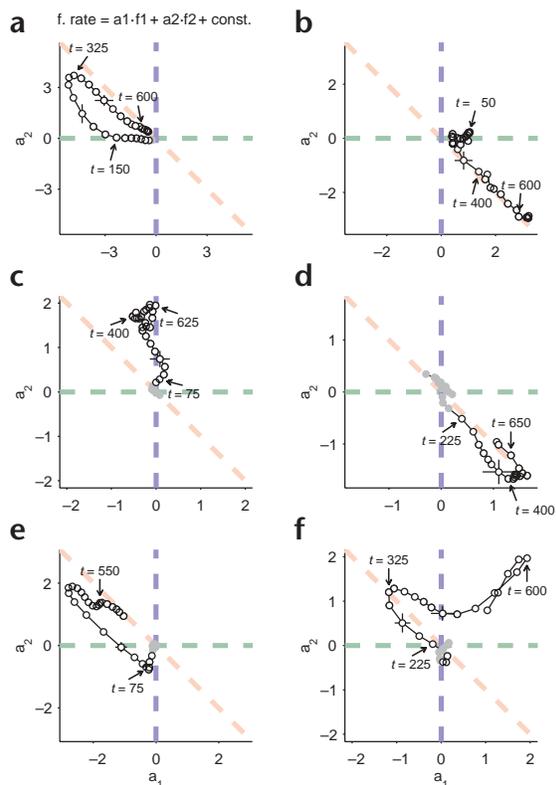


Fig. 5. Response dynamics of six example neurons from area S2. In all panels, time-zero corresponds to the start of the second stimulus. Each symbol in each panel corresponds to a planar fit, separated from its neighbors in steps of 25 ms. (Note that temporal smoothing blurs temporal features faster than 100 ms.) Representative error bars have been placed at some points. Neurons of (c and d) were studied using extended set A (Fig. 1c); all others were studied using set A (Fig. 1b). (a) The neuron of Fig. 2. (b) The neuron of Fig. 3. (c) A neuron that shows no $f1$ -dependence. (d) A neuron that responds as a function of $(f2 - f1)$ throughout the second stimulus. (e) A neuron that initially responds purely as a function of $f2$, but then switches to a response that depends largely on $(f2 - f1)$. (f) A neuron with a complex, not easily interpretable trajectory.

but less markedly for the intermediate group, and least of all for the $f2$ -dependent group. These results cannot be accounted for by differences in average firing rates between the three groups (Fig. 7b). Neither can these results be accounted for by sensory adaptation, as sensory adaptation alone does not predict that the responses to a particular $(f1, f2)$ pair would be correlated with the monkey's behavior.

Could the observed correlation with the monkey's motor act be due to feedback to S2 from motor cortex? We recorded from 21 neurons in primary motor cortex (M1) that had differential responses for the two pushbutton movements. These recordings were from one of the same monkeys, using the same stimulus sets, during the same task (Supplementary Notes). We analyzed these neurons with the same methods (as in Fig. 5) and defined response latency as the time of the first planar fit that was significantly different from $(0,0)$. We compared the responses of the M1 neurons to the responses of those S2 neurons from the same monkey that had been previously classified as beginning their response in a $(f2 - f1)$ -dependent manner. The S2 neurons had a significantly shorter response latency than the M1 neurons (S2 latency, 236 ± 21 ms; M1 latency 295 ± 20 ms; $P < 0.03$, one-sided t -test). In addition, 30% of the S2 neurons had latencies shorter than the shortest M1 latency (Supplementary Notes). This suggests that $(f2 - f1)$ -dependent responses in S2 lead similar responses in M1 and are therefore not due to an efference copy signal arising in M1. However, we cannot rule out the possibility that there might be an effect due to an efference copy signal arising in some other motor-related cortex, such as the MPC¹³.

responses to correct trials were to pure $(f2 - f1)$ -dependence, the higher the separation between responses to correct and error trials, as quantified by a higher choice probability. We also found that choice probabilities increased during the course of $f2$ (Fig. 7). Neurons of each of the three groups (red, black and orange) were analyzed separately. The choice probabilities for all three groups increased over time, but they did so most markedly for the $(f2 - f1)$ -dependent group, which reached a high choice probability (mean 0.81, Fig. 7a) comparable to that found in prefrontal⁴ and premotor³ areas during the latter stages of a visuo-motor decision task. The choice probability increased significantly

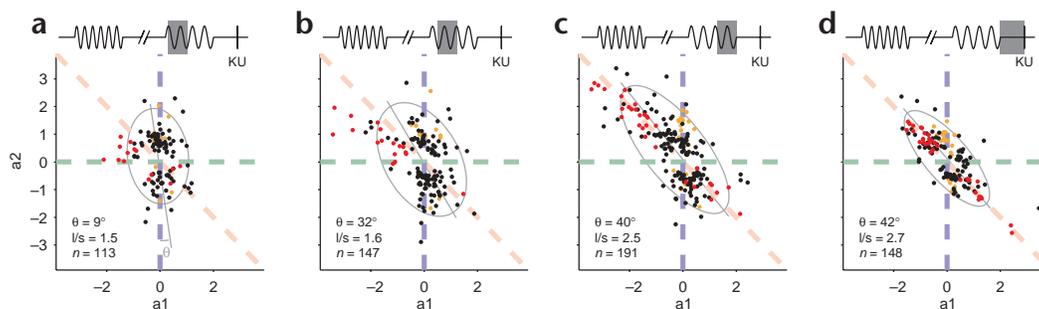
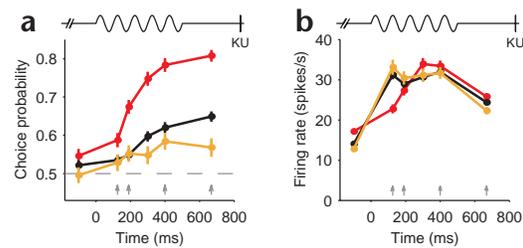


Fig. 6. Population responses gradually become aligned to the $a2 = -a1$ axis. The analysis here is as in Fig. 4a, but was carried out for short time windows; the gray box in the task schematic above each panel indicates the time window for that panel: 25–225 (a), 90–290 (b) or 300–500 (c) ms after onset of $f2$; (d) window from 500 ms after $f2$ -onset to start of motor response (mean = 336 ms after end of $f2$). Each dot represents a neuron; only data points significantly different from $(0,0)$ are shown. Ellipses are the 2σ -contour for a two-dimensional Gaussian fit to the data point distribution. θ , angle of ellipse's long axis w.r.t. vertical. l/s , ellipse's long axis length/short axis length. n , number of data points in panel. Colors refer to data sets analyzed in Fig. 7.

Fig. 7. Error trials analysis: neurons that are ($f_2 - f_1$)-dependent in response to correct trials are highly correlated with the monkey's choice of button to press. **(a)** Choice probabilities, averaged over (f_1, f_2) pairs and neurons, for three different groups of neurons. Red, ($f_2 - f_1$)-dependent neurons; black, intermediate/ambiguous neurons; orange, f_2 -dependent neurons (Fig. 4). The sensory stimulus (f_2) runs from time-zero to 500 ms. The data points were calculated from responses within the following time windows: -200 ms to time-zero, $20-220$ ms, $90-290$ ms, $200-400$ ms, $300-500$ ms, 500 ms to KU. Error bars are standard errors. Dashed line indicates 0.5, chance level, and arrows indicate the four time windows used in Fig. 6. **(b)** Overall average firing rates for same time windows and neuronal groups as in (a).



DISCUSSION

Neurons in S2 often have broad, multi-digit or bimanual receptive fields. They can be modulated by task context and attention, and often display complex responses to somatosensory stimuli²⁴⁻²⁷. A previous study reports history-dependent responses in S2 during a perceptual decision task involving the comparison of two stimuli (see, for example, Fig. 2 in ref. 26). But such responses have generally not allowed a simple interpretation. Here we used a somatosensory task that involved comparing a second stimulus (f_2) to a previously applied first stimulus (f_1) and then making a decision about this comparison ($f_2 - f_1$). We found that for this specific task, the apparently complex neuronal responses of S2 allowed a particularly straightforward interpretation. The characteristic population response gradually became dominated by responses that were a function of ($f_2 - f_1$). This indicates history-dependent responses that correlate with the monkey's choice of action. History-dependence in S2 (represented by a tilt of the ellipses in Fig. 6 off the vertical) is not in itself necessarily surprising. But there are two more remarkable aspects of this history-dependence: (i) out of all possible tilts, the ellipse became almost perfectly aligned to 45° away from the vertical; it is at this particular tilt that the population response is most highly correlated with the monkey's choice and (ii) the history-dependence grew with time (progressively larger tilts in Fig. 6). Both of these are consistent with responses related to a gradual formation of the monkey's decision. Analysis of errors (Fig. 7) supported the conjecture that the behavior of neurons classified as ($f_2 - f_1$)-dependent during correct trials would be most closely linked to the monkey's decision, as quantified by their high choice probabilities.

It is tempting to interpret responses that gradually become highly correlated with the monkey's choice, and that occur well before that choice is reported, as being themselves involved in the formation of the choice. However, recent recordings in MPC during the same task¹³ have shown that choice-correlated responses can arise there by 160 ms after onset of f_2 , which is sooner than in S2. Choice-related responses can arise in PFC even earlier (unpub. observ.). It is therefore possible that choice-correlated responses in S2 may merely reflect the result of a choice that has already been formed elsewhere. Whether or not S2 neurons directly participate in forming the choice itself, and what the precise functional role of such a strong decision/motor 'efference copy' might be if they do not, remain open questions. Somatosensory neurons can be modulated by upcoming motor acts, a phenomenon known as 'somatosensory gating', but this usually takes the form of a reduction in excitability, and is observed in subcortical areas as well as in primary somatosensory cortex³⁶⁻³⁸. The modulation reported here, however, was not a reduction in excitability, nor was it observed in S1 (Fig. 4c).

The history-dependence that leads to a correlation with the monkey's choice depends on information about stimulus f_1 being available (either directly or indirectly) to S2 neurons during the second stimulus period. Indeed, some neurons (such as those of Figs. 2 and 3) show a direct f_1 -dependence at the beginning of f_2 stimulation. Where is this information stored, and how is it able to affect S2 neurons? Previous results show that information about f_1 is not maintained throughout the delay period in the firing rates of neurons in primary^{2,8} or secondary⁸ somatosensory cortex. Such information may be stored in intracellular variables inaccessible to our extracellular recordings, or in temporal firing patterns of S1 or S2 neurons (although preliminary analysis has provided no evidence so far for the latter). Although the precise anatomical pathways remain unclear, we speculate that information about f_1 may have been fed back to S2 neurons from higher areas, such as the PFC, in a manner analogous to that in which the PFC can feed information back to IT cortex³⁹. In contrast to S1 and S2, PFC firing rates¹² reflect short-term memory information about f_1 throughout the delay period. Neurons of S2 might then receive information about f_1 at the beginning of f_2 , in much the same manner as 'late' neurons of the PFC¹² and the MPC¹³ receive information about f_1 near the end of the delay period.

Any evaluation of a current sensory stimulus must be carried out in conjunction with information stored in memory⁴⁰, whether this is long-term memory generated as a result of training, or a short-term sensory referent that is part of the current trial, as in the task used here. Varying the memory referent in a parametrically controlled, trial-by-trial manner allowed us to observe the dynamics of the comparison and (presumably ensuing) decision processes. This work opens the possibility of determining whether the comparison and decision processes are separate from one another and what the mechanisms of each might be, and will allow further elucidation of how memories and sensations interact in the decision-making process.

METHODS

Discrimination task. The two-alternative forced-choice discrimination task used here has already been described^{1,2}. Briefly, two 500 ms-long vibration stimuli, separated by a delay period of several (typically 3) seconds, were delivered to the skin of the distal segment of one digit of the right hand by a computer-controlled stimulator (2-mm round tip, BME Systems, Baltimore, Maryland); right arm, hand and fingers were held comfortably but firmly fixed throughout the experiments. Vibrotactile stimuli were mechanical sinusoids. Stimulation amplitudes were adjusted to produce equal subjective intensities^{1,2}. Monkeys were trained to use their free left hand to indicate at the end of each trial which of the two stimuli had the higher vibration frequency, by pressing one of two side-by-side pushbuttons placed in front of the monkey's left side (lateral pushbutton for $f_2 > f_1$, medial for $f_2 < f_1$). Monkeys were handled according to the institutional standards of the National Institutes of Health and Society for Neuroscience.

Visual instruction task. Trials in this control task proceeded as in Fig. 1a, but at the PD time, the correct target pushbutton was illuminated. Vibrotactile stimuli were delivered while the light was on, and at the end of the second stimulus, the probe was lifted from the skin and the light went off. The monkey was rewarded for pressing the previously illuminated pushbutton. Arm movements in this situation were identical to those in the somatosensory discrimination task but were cued by visual stimuli.

Recording sessions and sites. Neuronal recordings were obtained with an array of seven independent microelectrodes ($2\text{--}3\text{ M}\Omega$)^{1,8} inserted into the region of hand representation in S2. The locations of the penetrations were confirmed through standard histological techniques. All neurons recorded had large cutaneous receptive fields confined to the hand contralateral to the recording site. Typically, ten trials per (f1,f2) stimulus class were recorded (average 9.7 trials, ten classes, therefore 97 total trials per neuron). Recording sites changed from session to session.

Data analysis. Planar fits for the second stimulus period, firing rate = $a_1 \cdot f_1 + a_2 \cdot f_2 + \text{constant}$, were obtained through linear regression; the coefficients (a_1 and a_2) quantify the response dependence on f_1 and f_2 , respectively³². The variance in responses to individual (f1,f2) vibrotactile stimulus pairs in a stimulus set was used to derive a two-dimensional covariance matrix of errors in (a_1, a_2)³³, and this, in turn, was used to derive the variance along the straight line leading from (a_1, a_2) to (0,0). Neurons with (a_1, a_2) > 2.5 s.d. away from (0,0) along this straight line were considered to be significantly dependent on applied stimulus frequencies. We took the 208 significant neurons that we found, shuffled both their f_1 and f_2 labels, and reanalyzed for stimulus dependence; our criteria showed two significant neurons in the shuffled data, confirming a stringent net significance level of $P < 0.01$ (2/208). To test specifically for f_1 -dependence, we took trial types for which a single f_2 was preceded by more than one possible f_1 (for example, in set A of Fig. 1, $f_2 = 22\text{ Hz}$ may be preceded by $f_1 = 14$ or $f_1 = 30\text{ Hz}$) and randomly permuted f_1 labels within each of these f_2 groups. The results of such shuffling were treated as a source of null hypothesis data in which f_2 -dependence was maintained while f_1 -dependence was destroyed. The procedure was repeated 1,000 times for each neuron, producing a mean zero null-hypothesis distribution of a_1 coefficients; measured a_1 coefficients evaluated as $P < 0.01$ under this distribution were taken as significantly different from zero. Neuronal responses were defined as unambiguously f_1 -, f_2 - or ($f_2 - f_1$)-dependent if the coefficients of the planar fit were within 2 s.d. of one of the corresponding three lines ($a_2 = 0, a_1 = 0$ or $a_2 = -a_1$, respectively) and more than 2.5 s.d. from the other two lines. Any responses not satisfying this criterion were classified as 'ambiguous'. In the analysis of Fig. 2d, neurons whose first significantly stimulus-dependent coefficients were classified as the same stimulus-dependent type for three successive 25-ms time steps (bins) were defined as having a clear initial response dependence; the first of these bins was defined as the neuron's stimulus-dependent latency. Smoothing of spike trains for time-dependent fits was carried out as described previously¹². When calculating choice probabilities^{34,35} for each neuron, we took only those (f1,f2) trial types for which there had been at least one error. If there were only correct trials, the choice probability for that neuron was undefined.

Note: Supplementary information is available on the Nature Neuroscience website.

Acknowledgments

We thank W.T. Newsome for comments and discussions. R.R.'s research was partially supported by an International Research Scholars Award from the Howard Hughes Medical Institute and grants from Millennium Science Initiative-CONACT and DGAPA-UNAM. R.R. led the experiments and carried them out together with A.H., A.Z. and L.L.; C.B. and A.H. designed and carried out the data analysis; C.B. and R.R. co-wrote the paper.

Competing interests statement

The authors declare that they have no competing financial interests.

RECEIVED 25 JUNE; ACCEPTED 6 SEPTEMBER 2002

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