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Analysing neuronal correlates of the comparison of two sequentially presented sensory stimuli

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In a typical sequential sensory discrimination task, subjects are required to make a decision based on comparing a sensory stimulus against the memory trace left by a previous stimulus. What is the neuronal substrate for such comparisons and the resulting decisions? This question was studied by recording neuronal responses in a variety of cortical areas of awake monkeys (*Macaca mulatta*), trained to carry out a vibrotactile sequential discrimination task. We describe methods to analyse responses obtained during the comparison and decision phases of the task, and describe the resulting findings from recordings in secondary somatosensory cortical area (S2). A subset of neurons in S2 become highly correlated with the monkey's decision in the task.

Keywords: decisions; somatosensory cortex; sequential discrimination

1. INTRODUCTION

Consider the behavioural task illustrated in figure 1 and described in the corresponding caption. This task involves a variety of operations. The subject must sense f1; store a trace of f1 in memory; sense f2; compare the percept of f2 against the memory trace of f1; decide which of the two stimuli had the higher frequency of vibration; and, finally, carry out a motor act to report the result of the decision. With so many components, the task provides a rich substrate for neurophysiological investigation. The task is also convenient in that it is quantitatively parametrized. For example, the difficulty of carrying out the task depends on the magnitude of the difference between f1 and f2, and this difference can be varied continuously. This allows quantitative psychometrics to be straightforwardly carried out.

The neurophysiological and behavioural work of Romo and colleagues using this task has been recently reviewed in this journal. In order to allow the current paper to be read on its own, we will encapsulate some of the key results here, but point readers towards previous publications (Romo & Salinas 1999, 2001; Romo *et al.* 2002) for more comprehensive reviews. Those previous reviews focused on neuronal and behavioural responses during f1 and during the delay period between f1 and f2; our focus here will be on neuronal responses during f2, when the subjects are comparing the two stimuli and forming their behavioural decision. Responses during this period must be analysed as a function of both f1 and f2, and we will describe methods to carry out this analysis. We will focus on responses in S2. We find that S2, despite being often thought of as a sensory cortex, displays neuronal correlates of the subject's behavioural decision. All the neurons that will be described here were recorded extracellularly from highly trained awake macaque monkeys (*Macaca mulatta*), while the monkeys carried out the vibrotactile discrimination task. All vibration frequencies used were within the range known as 'flutter', *ca.* 5–50 Hz. Frequencies above the top of this range lead to a different qualitative percept ('vibration' rather than flutter) and activate skin mechanoreceptors that are different to those activated by flutter (Talbot *et al.* 1968).

2. A BRIEF REVIEW OF RESPONSES DURING F1 AND DELAY PERIOD

As the task is based on somatosensory stimuli, neuronal responses in both S1 and S2 are of interest (Mountcastle *et al.* 1990; Johnson & Hsiao 1992; Hsiao *et al.* 1993; Sinclair & Burton 1993; Jiang *et al.* 1997; Salinas *et al.* 2000; Pruett *et al.* 2001).

(a) *Area S1*

Figure 2 illustrates the typical results found in area S1 (Hernández *et al.* 2000) In columns of RA neurons, the cells respond phasically to each mechanical stimulation pulse.

As can be clearly seen from the spike rasters, the fine temporal structure of the spike trains carries information about the applied stimulus frequency. The firing rate, averaged over the entire f1 stimulus period, also carries information: figure 2*b* shows how the firing rate varies monotonically with the applied stimulus frequency. The higher the stimulation frequency, the higher the firing rate of the response. We call this type of firing rate response *positive monotonic*. After the end of stimulus f1, the neuron

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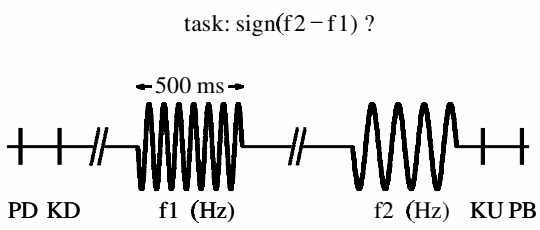

Figure 1. The sequence of events during a single trial of an experiment using a vibrotactile discrimination task. PD: a mechanical stimulation probe comes into contact with the glabrous (hairless) skin of the subject's finger. The stimulation point remains the same, and the stimulated hand is kept still and steady, throughout all trials of the experiment. KD: the subject places their unstimulated, free hand on a touch-sensitive key, to indicate readiness for the task. f1: After a variable delay, a 500 ms long vibration stimulus is applied, at frequency f1. f2: After another delay (typically 3 s), a second 500 ms-long vibration stimulus is applied, at frequency f2. KU: The subject's free hand leaves the touch-sensitive key. PB: The subject uses their free hand to press one of two pushbuttons placed in front of them, thus indicating which of f1 and f2 was the higher; that is, the subjects respond according to their judgement of the sign of f2 − f1.

almost immediately ceases its response dependency on f1, and during the delay period after f1, no stimulus-dependent responses are seen. In all of these respects the neuron of figure 2 displays characteristics typical of neurons in area S1.

The briefest summary of responses in area S1 is that responses to f1:

(i) carry information about f1 in the temporal structure of their spike trains;
(ii) carry information about f1 in their average firing rate, with a positive monotonic relationship between the stimulus and firing rate; and
(iii) the responses stop reflecting information about f1 immediately after the end of the f1 stimulus.

(b) *Area S2*

Figure 3 illustrates typical results from cortical area S2 (Salinas *et al.* 2000). Most notable, in comparison to figure 2, is the absence of fine temporal structure in the spike trains. The neuron still carries information about f1 in its average firing rate, as displayed by figure 3*b*, but spike train temporal structure conveying information about f1 is conspicuously absent here. The responses have become much more irregular and Poisson-like. This is typical of most stimulus-dependent neurons in S2. (A few S2 neurons show some temporal modulation of their firing rate at the vibratory stimulus frequency for the very lowest f1 frequencies applied—10 and 14 Hz—but these neurons are rare, and even these lose the temporal modulation when middle or higher frequencies are applied.) A second aspect of the responses that contrasts with S1 is that the average firing rate of the neuron of figure 3 is the lowest for the highest f1; conversely, the neuron's highest firing rate corresponds to the lowest f1. We call this a *negative* monotonic response. While negative monotonic responses are almost entirely absent in area S1, they account for roughly half of the stimulus-dependent responses in S2. The other half are positive monotonic. Finally, a third aspect that contrasts with area S1 is that the neuron of figure 3 has f1-dependent responses that continue for a few hundreds of milliseconds after the end of f1, into the delay period. After some 500 ms, the stimulus dependency is gone. All of these aspects are illustrative of responses that are commonly found in area S2.

In summary, responses to f1 in area S2:

(i) do not carry information about f1 in the temporal structure of their spike trains;
(ii) carry information about f1 in their average firing rate, with some neurons having a positive and others a negative monotonic relationship between stimulus and firing rate; and
(iii) the responses can reflect information about f1 for a few hundreds of milliseconds after the end of the f1 stimulus.

(c) *PFC*

Although responses in S2 carry information about f1 into the delay period between f1 and f2, they do so for only a few hundreds of milliseconds. The delay periods we used in this task typically lasted several seconds. Thus, the early delay period responses in S2 cannot fully represent the subject's memory of f1. This memory must persist throughout the delay period, until f2, in order for the subjects to carry out the task. Figure 4 illustrates the responses of a commonly found stimulus-dependent neuron recorded in PFC (Romo *et al.* 1999). The neuron's firing rate has a positive monotonic relationship with the f1 stimulus throughout the entire delay period. Neurons such as this are thus candidates for the neural substrate of the subject's short-term memory of f1 during the task. Negative monotonic and positive monotonic neurons were found in similar numbers in the PFC.

Neurons with a variety of different response properties were observed in the PFC. Although some neurons, such as the one of figure 4, did not respond during the f1 stimulus period itself, others, such as the one of figure 5, did. Furthermore, not all neurons with f1-dependent responses during the delay period were f1 dependent throughout the entirety of the delay period. Roughly one-third of the neurons had f1-dependent responses only during the early part of the delay period (similarly to the neuron of figure 3). Roughly one-quarter of the neurons had responses that were f1 dependent throughout the entire delay period, as in figure 4. And roughly one-third of the neurons had f1-dependent responses that appeared only at the end of the delay period, as is shown in figure 5. The remaining neurons could not be classified into one of these three types.

In summary, responses to f1 in PFC:

(i) carry information about f1 in their average firing rate; some neurons have a positive and others a negative monotonic relationship between stimulus and firing rate; and
(ii) the neuronal responses carry information about f1 into the delay period, with some neurons carrying it only during the early part of the delay period, others only during the late part of the delay period, and still

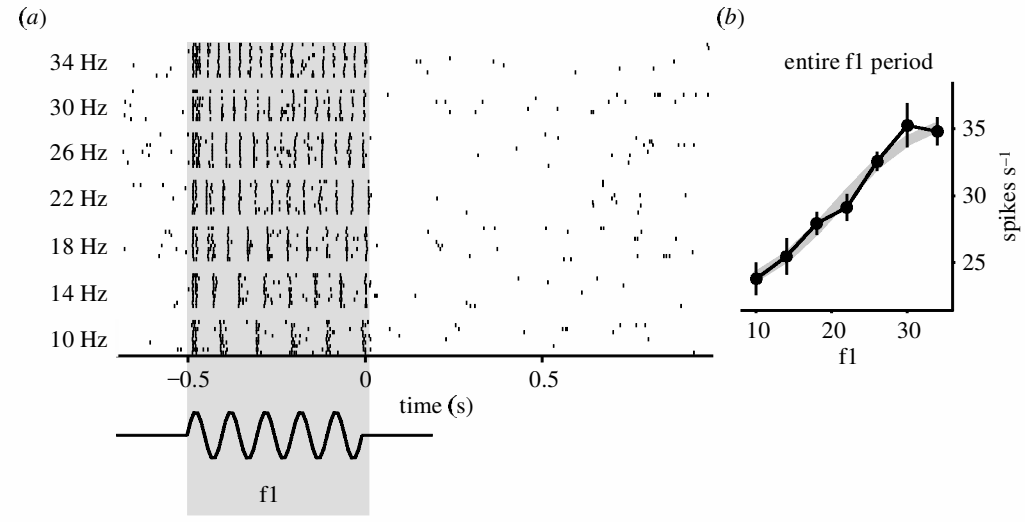

Figure 2. The extracellularly recorded responses of a typical RA neuron in cortical area S1, during stimulus f1 and the subsequent delay period. (*a*) Stimuli were delivered in random order, but have been sorted out here into groups of equal f1. (*b*) The average firing rate of this cell over the entire f1 period, mean ± s.e.m.

others persistently throughout the entire delay period.

(**d**) *MPC*

Briefly, neurons in MPC respond during f1 and the subsequent delay period, similarly to 'late' neurons of PFC (figure 5; Hernández *et al.* 2002). That is, some MPC neurons respond during f1 itself, with either positive or negative monotonic tuning; and many respond also in an f1-dependent manner during the late part of the delay period.

3. RESPONSES IN AREA S2 DURING F2

Upon presentation of f2 each trial of the task is no longer defined by one variable (f1), but by two (both f1 and f2). The potential repertoire of responses thus increases greatly, and analysis of the data must take this into account.

Figure 6 illustrates the responses of one neuron in cortical somatosensory area S2 during and around stimulus f2. The set of (f1,f2) stimuli used to explore the responses of this neuron is illustrated in figure 6*b*. In this stimulus set f2 was always either 8 Hz higher or 8 Hz lower than f1. Thus, we can divide all trials into these two groups; trials with f2 = f1 + 8 Hz are shown with black symbols and with black data points, while trials with f2 = f1 − 8 Hz are shown with grey symbols. Figure 6*c* shows that the firing rate of this neuron during the first 200 ms of the second stimulus clearly depended on f1. By contrast, the response at that time did not depend on f2: the overlap between the black and grey curves indicates that for a given value of f1, the response was the same regardless of whether f2 was 8 Hz higher or lower than f1. In fact, although not shown directly in the figure, this is also true immediately before stimulus f2. This neuron is thus similar to some 'late' neurons of MPC and PFC, in that towards the end of the delay period the neuron's firing rate is a monotonic function of f1.

By the end of f2, however, the response has become strongly modulated by both f1 and f2 (figure 6*d*). During the first 200 ms of the reaction time (after the end of f2 and before the KU event (see figure 3)), the response depends only on whether f2 = f1 + 8 Hz or f2 = f1 − 8 Hz. As can be seen in figure 6*d*, the particular values of f1 and f2 do not make a significant difference to the firing rate of the neuron. The response of the neuron has therefore become highly correlated with the animal's decision, which also depends only on whether f2 = f1 + 8 Hz or f2 = f1 − 8 Hz.

The neuron of figure 6 was chosen for illustration because its responses are particularly clear, and lend themselves straightforwardly to interpretation in terms of the vibrotactile task and its parameters. However, functional response dependencies on f1 and f2 may be more complex for other neurons. In the absence of any *a priori* knowledge, neuronal responses could in principle be any arbitrary function of these two variables. How can we quantify this? For simplicity, we began by using a first-order approximation to an arbitrary function of f1 and f2. That is, we simply approximated neuronal firing rates as linear functions of both f1 and f2

$$\text{firing rate } a_1 \cdot \text{f1} + a_2 \cdot \text{f2} + \text{const.} \tag{3.1}$$

We found that for the majority of neurons and stimulus sets used, equation (3.1) fit the data reasonably well. Furthermore, if the neuron's firing rate is actually given by the more complex function

$$\text{firing rate} = g(b_1 \cdot \text{f1} + b_2 \cdot \text{f2} + \text{const}_1) + \text{const}_2, \tag{3.2}$$

where $g()$ is an unknown static nonlinearity, then it can be shown that the vector (a_1,a_2) found by fitting equation (3.1) will be parallel to the vector (b_1,b_2). The ratio $|a_1/a_2|$ will therefore be equal to the ratio $|b_1/b_2|$. Thus, even for some complex nonlinear response dependencies, fitting equation (3.1) can provide an accurate report of the relative strength of response modulation by the stimulus parameters f1 and f2.

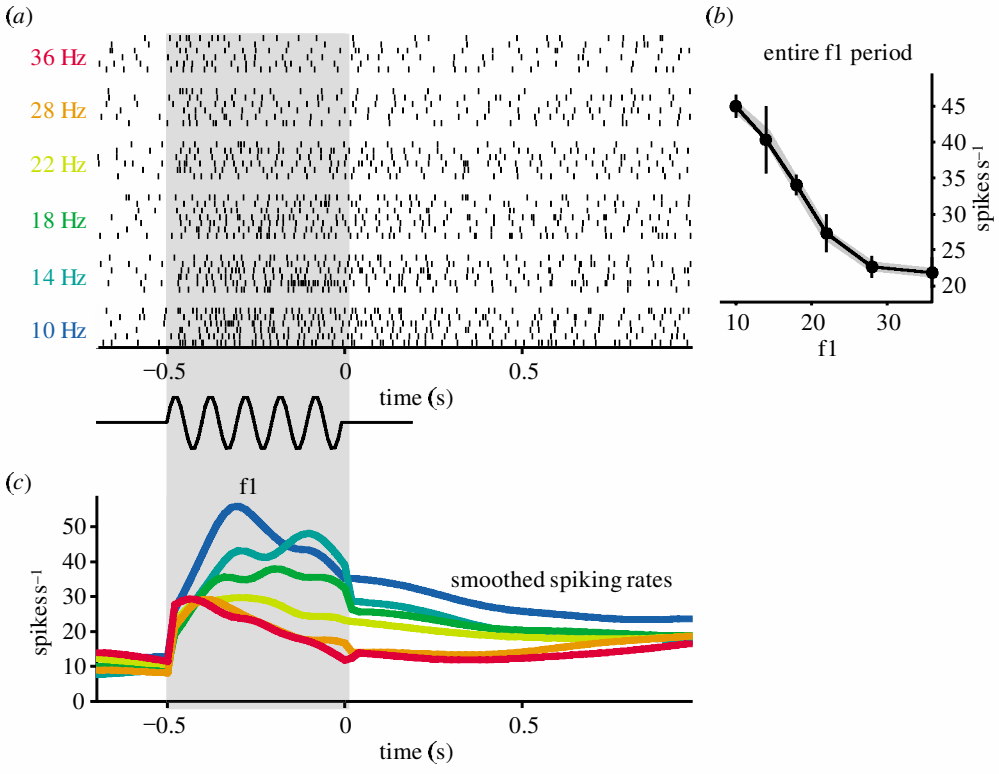

Figure 3. (*a*,*b*) The extracellularly recorded responses of a typical stimulus-dependent neuron in cortical area S2, during stimulus f1 and the subsequent delay period. The format is similar to figure 1 with (*c*) showing for each f1 stimulus the post-stimulus time histograms after smoothing with a Gaussian kernel.

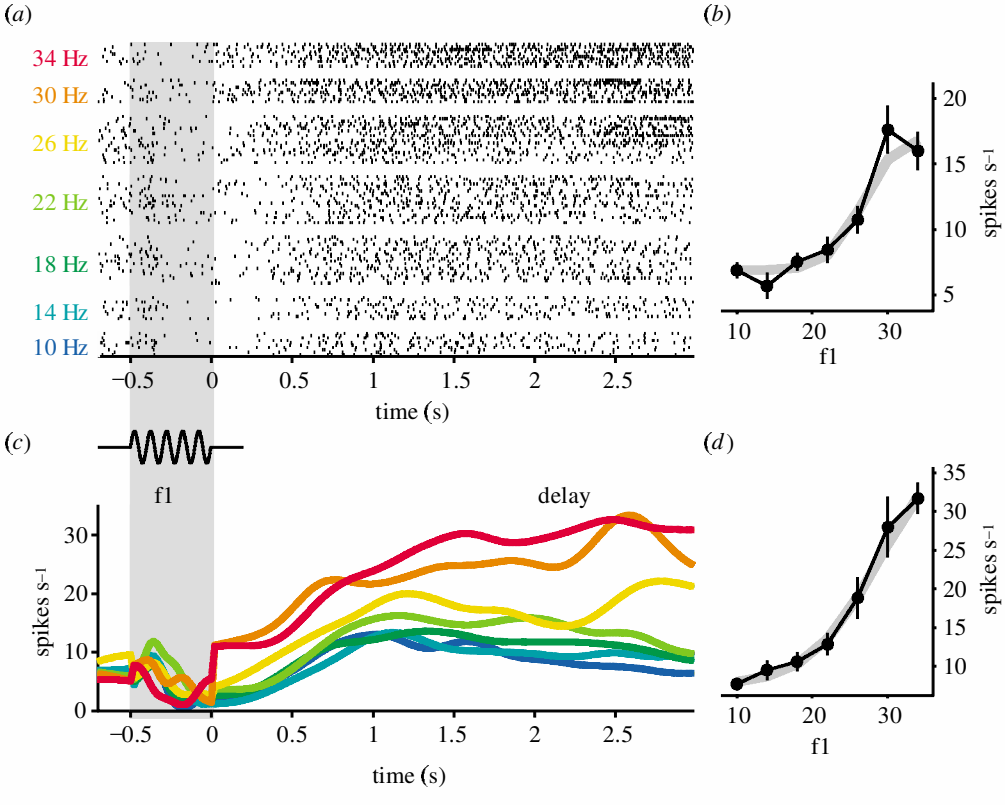

Figure 4. Extracellularly recorded responses of a typical stimulus-dependent neuron in PFC during stimulus f1 and the subsequent delay period. The rightmost edge of the raster graph represents the end of the delay period (start of f2). (*b*) The first second of the delay period, (*c*) the smoothed spiking rates and (*d*) the last second of the delay period.

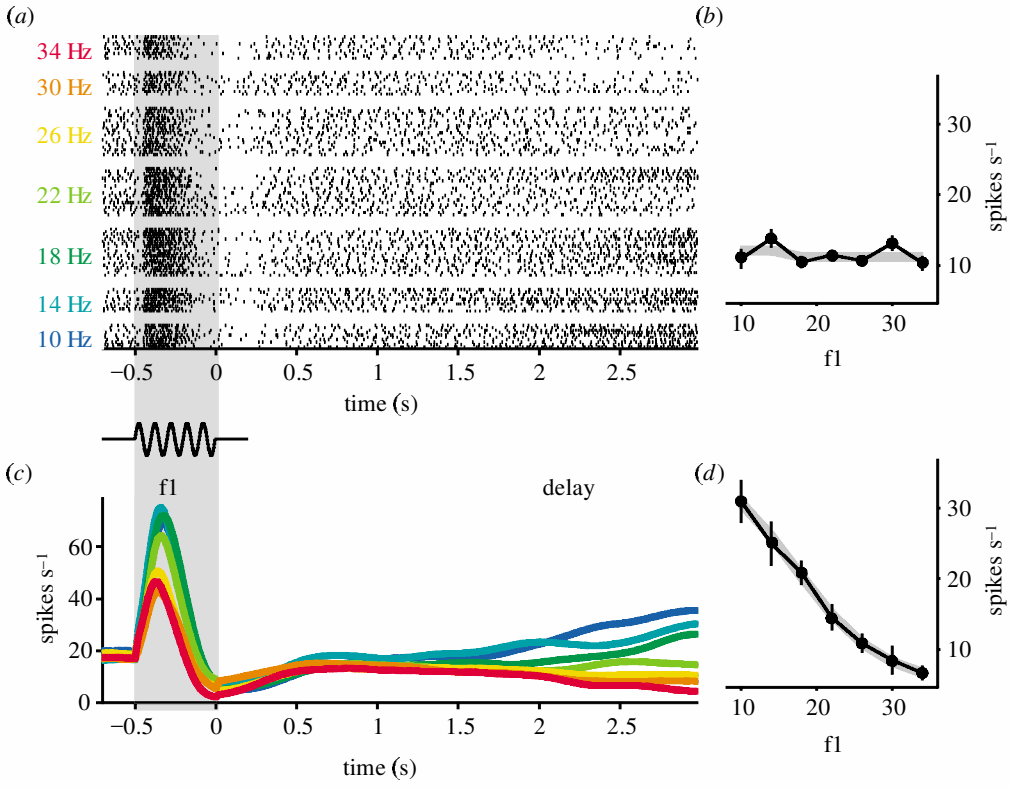

Figure 5. Another neuron from PFC; same format as figure 4. (*b*) The first second of the delay period, (*c*) the smoothed spiking rates and (*d*) the last second of the delay period.

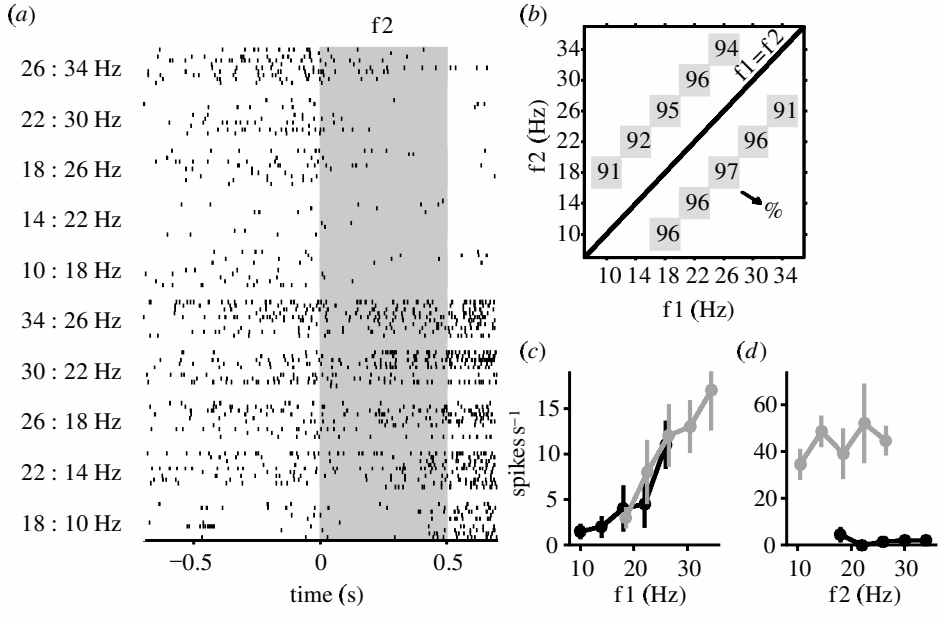

Figure 6. The extracellularly recorded responses of a typical stimulus-dependent neuron in cortical area S2, during and around stimulus f2. (*a*) Spike train rasters are arranged into blocks according to both f1 and f2; labels on the left indicate f 1:f2. The black symbols indicate f2 = f1 + 8 Hz trials; the grey symbols indicate f2 = f1 − 8 Hz trials. (*b*) The typical stimulus set used during these recordings. Each grey box indicates an f1 : f2 pair used, and the number inside the box indicates the overall per cent correct trials performed by the monkey. (*c*) The average firing rate of the neuron, as a function of f1, during the first 200 ms of f2. Trials with f2 = f1 + 8 Hz (black symbols) are shown separately from trials with f2 = f1 − 8 Hz (grey symbols). (*d*) Average firing rate as a function of f2 during the first 200 ms after the end of f2.

In the stimulus set most commonly used (figure 6*b*), f1 and f2 are very far from being independent of each other. Could this introduce a bias in the coefficients found by the linear fits? If the response properties of a neuron are independent of the stimulus set used to study it, the result of fitting equation (3.1) to spike rates produced by the neuron should not depend on the particular choice of stimulus set used. A direct check of this can be carried out by fitting equation (3.1) to data for which we know the result a *priori*. For example, no responses from time

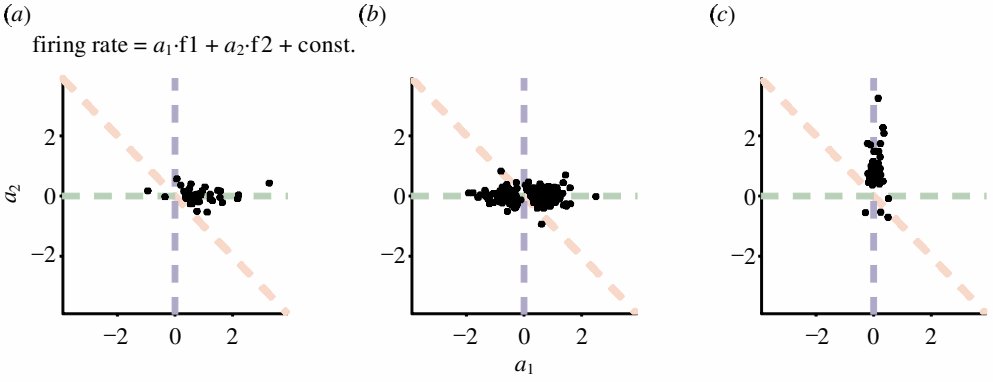

Figure 7. Controls using the planar fit method. In each panel, each data point corresponds to one neuron, and shows the a_1 and a_2 coefficients of fitting equation (3.1) to the firing rate of the neuron. (*a*) Coefficients of fits for the firing rate, averaged over the 500 ms of the first stimulus period, of neurons recorded in area S1. (*b*) Same analysis as in (*a*) for neurons of area S2. (*c*) Same analysis as in (*a*) for neurons of area S1 during the 500 ms of the second stimulus period.

periods before f2 is applied should depend on f2. We therefore fit equation (3.1) to the responses of neurons from area S1 during stimulus f1. Figure 7*a* shows the result of such fits, for firing rates averaged over the entire first stimulus period. Each dot represents the (a_1,a_2) coefficients for one neuron; 44 neurons recorded in area S1 were used for this analysis. As can be seen, the results cluster closely around the $a_2 = 0$ line, correctly indicating dependence on f1 only.

We note that three lines are of particular significance in the types of panels displayed in figure 6. Points that fall on the $a_2 = 0$ axis (dashed green horizontal) represent responses that depend on f1 only; points that fall on the $a_1 = 0$ axis (dashed blue vertical line) represent responses that depend on f2 only; and points that fall on the $a_2 = -a_1$ line (dashed red diagonal) represent responses that are a function of f2 − f1 only. These last are of particular importance for our ordinal comparison task, since correct behaviour depends only on the sign of f2 − f1: the neural computation and representation of f2 − f1 are thus of direct relevance to the monkey's task.

A further control was carried out by analysing data from S2 during the first stimulus period (figure 7*b*). Once again, data points are correctly clustered along the $a_2 = 0$ line, indicating that responses depend only on f1, not on f2. Finally, figure 7*c* shows that responses in area S1 during the second stimulus period do not depend on f1, but are, as expected for a purely sensory area, dependent only on f2, the sensory stimulus being applied.

We now turn to using equation (3.1) to describe the responses of the neuron of figure 6. As can be seen in figure 6, the response properties are not static throughout f2. We therefore used a time-dependent version of equation (3.1)

$$\text{firing rate} \approx a_1(t)\cdot\text{f1} + a_2(t)\cdot\text{f2} + \text{const.}(t). \qquad (3.3)$$

This equation was fit to time-dependent firing rates estimated by convolving the spike trains with Gaussian kernels with a standard deviation of 45 ms. The results are shown in figure 8. Consistent with the observations based on the analysis of figure 6, the current analysis shows that the neuron's firing rate initially depends on f1 (green points near $t = 100$ ms), but later switches to depending only on f1 − f2 (red points near $t = 400$ and $t = 600$ ms).

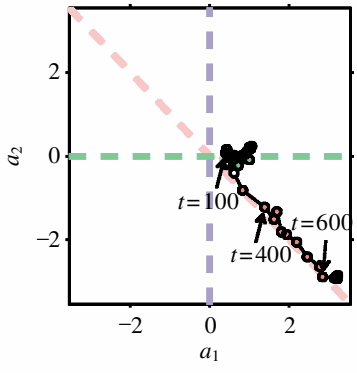

Figure 8. The results of the time-dependent planar fit method using equation (3.3). See § 3 for an explanation.

Thus, not only does f1 modulate the response to f2, but it does so in a way that exactly balances f2, resulting in responses that depend only on the difference between f1 and f2.

The points in figure 8 have been colour coded according to their proximity to one of the three dashed lines. Error bars were first estimated for each point. We then found all the $(a_1(t),a_2(t))$ coefficients that were statistically significantly different from (0,0). Neuronal responses were then defined as unambiguously f1, f2 or (f2 − f1) dependent if the (a_1,a_2) coefficients were within two standard deviations of one of the corresponding three lines ($a_2 = 0$, $a_1 = 0$ or $a_2 = -a_1$, respectively), and more than 2.5 standard deviations from the other two lines. Points not satisfying these criteria were classified as 'ambiguous.' In figure 8, points have been colour coded according to this classification (green for $a_2 = 0$, blue for $a_1 = 0$, red for $a_2 = -a_1$ and white for ambiguous).

To display the variety of responses found in area S2, in figure 9 we illustrate the result of applying the time-dependent analysis of figure 8 to a further eight neurons. The response of some neurons depends purely on f2 (figure 9*a*,*b*). Other neurons can initially respond to either f2 or f1, yet later become (f2 − f1) dependent (figure 9*c*,*e*, respectively). Still others depend strictly on (f2 − f1) throughout the second stimulus period and into the reaction time after it (figure 9*d*). Finally, a substantial number of neurons have time-dependent responses that defy sim-

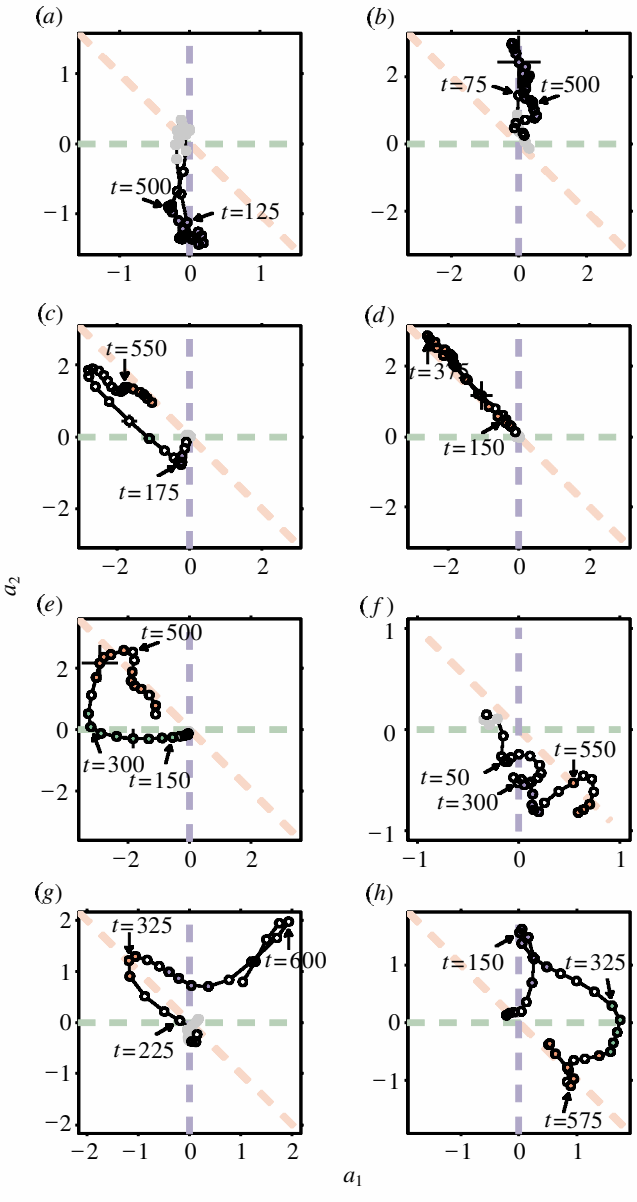

Figure 9. Analysis as in figure 8 for a further eight representative neurons.

ple interpretation (figure 9*f*,*g*,*h*). However, when the set of neurons was analysed as a whole, we found that (f2 − f1)-dependent responses came to dominate the population response, doing so gradually over the course of a few hundreds of milliseconds (R. Romo *et al.*, unpublished data).

We have described our data analysis methods here in the context of applying them to responses from cortical area S2. However, the same methods may be applied to responses in other cortical areas. Such an analysis of responses in the MPC has been used in part to provide evidence for decision-related neuronal responses in MPC (Hernández *et al.* 2002). Decision-related responses are also commonly found in PFC (Kim & Shadlen 1999; R. Romo *et al.*, unpublished data).

4. DISCUSSION

When neuronal responses may depend on two separately controlled variables, they must be explicitly analysed with that fact in mind. The analysis method should make as few *a priori* assumptions as possible regarding how the responses depend on the two variables. Here, we have described a method where the analysis relies on the fact that the somatosensory responses to vibrotactile flutter stimuli have been documented as being monotonic in the applied frequencies. This fact makes the simplest possible approximation to an arbitrary function, a linear approximation, an adequate one. (By contrast, for paradigms where Gaussian-shaped tuning is observed, such a linear approximation would not be appropriate.) Using this approximation, which is unbiased with respect to the treatment of f1 and f2 (the two sequentially applied vibrotactile frequencies), and carrying out the analysis in a time-dependent manner, we have shown that somatosensory responses in area S2 gradually become correlated, over the space of a few hundred milliseconds during stimulus f2, with the animal's upcoming behavioural decision regarding the sign of f2 − f1.

Previous work on neural decision processes during well-controlled behavioural tasks has, for the most part, focused on tasks where subjects compare a current sensory stimulus against a fixed standard held in long-term memory (Newsome *et al.* 1989; Britten & Wezel 1998; Shadlen & Newsome 2001). But in the natural world, most decisions are taken in the context of recently experienced and perceived sensory information. Sequential stimulus discrimination experiments, a staple of human psychophysical studies, may be thought of as a well controlled and simplified laboratory approximation to such real-life situations. For example, in the task used here, a decision regarding stimulus f2 must be taken in the context of a previously applied stimulus, f1. By varying f1 in a trial-by-trial manner, we may observe responses that covary with it, and thus study decisions through the interaction of sensations and short-term memory.

A variety of brain regions may participate in such decision-producing interactions between current sensory stimuli and short-term memory. We have focused here on S2, but similar interactions have been observed in other brain areas, such as MPC (Hernández *et al.* 2002) and PFC (R. Romo *et al.*, unpublished data). Preliminary results indicate that responses in PFC may become correlated with the monkey's decision before those in S2. PFC is in addition involved in storing the short-term memory trace of f1 during the delay period between the two stimuli (Romo *et al.* 1999). Thus, there is a rough hierarchy for the neuronal processing required in this task (Pons *et al.* 1987, 1992); this hierarchy is defined anatomically, and in terms of complexity and latency of responses. The hierarchy leads from S1 to S2 to PFC and then to premotor and motor cortices. Guillery & Sherman (2002*a*,*b*; Sherman & Guillery 2002) have suggested a novel role for thalamocortical and corticothalamic connections in the processing hierarchy for the visual sensory modality. These authors have also described specific anatomical features that appear to be signatures of their proposed thalamic role in the way thalamic regions connect together different stages of a cortical sensory hierarchy. An interesting question for future research is whether a similar signature and role might be found for thalamocortical and corticothalamic connections in the somatosensory–motor hierarchy reviewed here for the vibrotactile discrimination task. Some of the first studies of neuronal correlates of

short-term memory (which is one of the important components of the vibrotactile discrimination task) described such responses in both PFC and the nucleus medialis dorsalis of the thalamus (Fuster & Alexander 1971); this suggests that there may be neuronal responses in thalamic regions that actively participate in other complex aspects of the vibrotactile discrimination task. Elucidating whether such thalamic contributions do in fact exist, and if so, what their possible role might be, will be an exciting goal for future research.

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GLOSSARY

f1: first stimulus
f2: second stimulus
KU: key up
MPC: medial premotor cortex
PFC: prefrontal cortex
RA: rapidly adapting
S1: primary somatosensory cortex
S2: secondary somatosensory cortex