

FLUTTER DISCRIMINATION: NEURAL CODES, PERCEPTION, MEMORY AND DECISION MAKING

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Recent studies combining psychophysical and neurophysiological experiments in behaving monkeys have provided new insights into how several cortical areas integrate efforts to solve a vibrotactile discrimination task. In particular, these studies have addressed how neural codes are related to perception, working memory and decision making in this model. The primary somatosensory cortex drives higher cortical areas where past and current sensory information are combined, such that a comparison of the two evolves into a behavioural decision. These and other observations in visual tasks indicate that decisions emerge from highly-distributed processes in which the details of a scheduled motor plan are gradually specified by sensory information.

COGNITIVE NEUROSCIENCE

The problem of neural coding has stimulated a large amount of research in neuroscience. The underlying belief is that unravelling the neural representations of sensory stimuli from the periphery to early stages of cortical processing is key to addressing brain function, be it local or distributed. Investigations in several systems have shown how neural activity represents the physical parameters of sensory stimuli in both the periphery and central areas. These results have paved the way for new questions that are more closely related to cognitive processing. For example, how are the neural representations of sensory stimuli related to perception? What attributes of the observed neural responses are relevant for downstream networks and how do these responses influence decision making and behaviour? To understand the neuronal dynamics of decision making we first need to know how the physical variables on which a decision is based are encoded. One of the main challenges of this approach is that even the simplest cognitive tasks engage a number of cortical areas, and each one might render sensory information in a different way, or combine it with other types of stored signals representing, for example, past experience or future actions. Recent studies in behaving monkeys that combined

psychophysical and neurophysiological experiments have provided new insights into this problem. In particular, there has been important progress about how neural codes are related to perception and decision making in the somatosensory system. The basic philosophy of this approach has been to investigate a non-trivial cognitive task — sensory discrimination — using highly simplified stimuli, so that diverse cortical areas can be examined during the same behaviour. The idea is that if the neural codes for such simple stimuli are readily identifiable, then determining the individual functional roles of those areas should become less difficult. Here, we review the recent literature on this work and compare these observations with those on different experimental models and sensory modalities.

Optimal conditions for exploring neural codes. Nowadays, experiments that combine neurophysiological recordings and psychophysical measurements are relatively common. Mountcastle and colleagues pioneered this approach in the 1960s (REFS 1–3) and made a number of important observations in a sensory submodality called the sense of flutter. Flutter is felt when touching an object that vibrates at frequencies between

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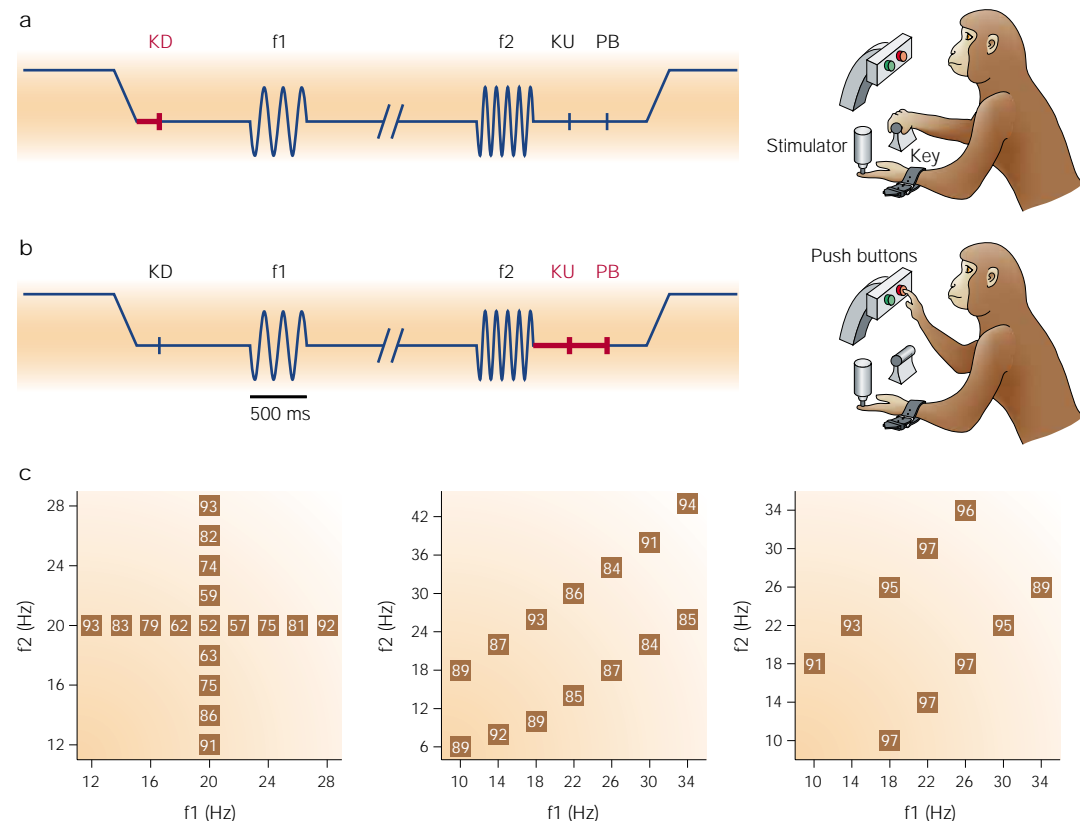


Figure 1 | **Flutter discrimination task.** **a, b** | Sequence of events during discrimination trials. The mechanical stimulator is lowered, indenting the fingertip of one digit of the restrained hand. The monkey places its free hand on an immovable key (**a**, red line; KD). The probe oscillates vertically at the base stimulus frequency (f1). After a delay, a second mechanical vibration is delivered at the comparison frequency (f2). The monkey releases the key (**b**, red line; KU), and presses either a medial or a lateral push button (**b**, red line; PB) to indicate whether the comparison frequency was lower or higher than the base frequency. **c** | Stimulus sets used during recording sessions. Each box indicates a base/comparison frequency pair. The numbers inside the boxes show the overall percentage of correct discriminations. The stimulus sets shown here were used to determine discrimination thresholds (left), and to study working-memory (middle) and comparison (right) processes during the task. The three sets were often used during any given recording session. Modified, with permission, from REF. 42 © (2002) Elsevier Science.

~5 and ~50 Hz¹⁻³. Mountcastle and his colleagues showed that flutter is primarily mediated by rapidly-adapting cutaneous mechanoreceptors^{2,3}, and found that humans and monkeys have similar abilities for detecting and discriminating the frequencies of mechanical sinusoids delivered to the hands³⁻⁵. These authors also tried to determine how the neural activity triggered by flutter stimuli is related to psychophysical performance^{3,5}. In their discrimination task⁵, animals had to indicate whether the frequency of a comparison stimulus was lower or higher than the frequency of a base stimulus that had been presented earlier (FIG. 1). In principle, the task can be conceptualized as a chain of neural operations or cognitive steps: encoding the first stimulus frequency (f1), maintaining it in working memory, encoding the second frequency (f2), comparing it with the memory trace that was left by the first stimulus, and communicating the result of the comparison to the motor system. The flutter task offers several advantages as a model for sensory processing in the brain⁶ — not only do humans and monkeys perform similarly, but the items to be compared are temporally spread and always activate the same well-defined population of primary receptors^{2,3,7-9}. So, spatial

variations are essentially removed. Spatiotemporal integration of tactile input, as in texture discrimination or recognition of Braille characters, is certainly an interesting problem¹⁰⁻¹², but it complicates the neural codes considerably¹³⁻¹⁶ without necessarily adding any essential features to the memory or decision-making steps of a discrimination process. However, for the flutter task to be a useful model, it is essential that it generates a reliable sequence of cognitive events, such as the one described earlier. How do we know this is the case?

A crucial step is to scrutinize the psychophysics¹⁷. Importantly, in the original flutter discrimination task, f1 did not vary from trial to trial during a run. When we re-examined the design of the task¹⁸ we found it to be ambiguous — when the f1 is kept constant, the task can be solved either by comparing the two stimuli or by categorizing the second stimulus as 'high' or 'low', ignoring the base stimulus. What were the monkeys actually doing? When f1 was kept constant during long blocks of trials, as done originally, the measured DIFFERENCE LIMENS and WEBER FRACTIONS were, as expected, similar to those reported before. But if the monkeys had been evaluating the difference between f1 and f2, they would

DIFFERENCE LIMEN
In flutter discrimination, the difference limen is a measure of how small an increase in the frequency of a vibrotactile stimulus can be detected when compared to a standard stimulus frequency. A smaller difference limen implies a higher discrimination capacity.

WEBER FRACTION
Weber made the observation that, within a fairly large range, the increase in a stimulus that is just noticeable (ΔI) is a constant proportion of the initial stimulus (I) for any one sense. The proportion $\Delta I/I$ is the Weber fraction.

also have been able to discriminate when f1 changed from trial to trial. But this was not the case — their performance under this condition dropped to chance levels¹⁸. It seemed that the monkeys were paying attention only to the second stimulus and categorizing it as low or high with respect to an internal reference, perhaps f1, the frequency used during training. Indeed, if single stimuli were delivered in each trial, and the monkeys were rewarded for correctly categorizing a stimulus frequency as lower or higher than an arbitrary reference, the resulting PSYCHOMETRIC CURVES¹⁸ were practically identical to those measured during the classical discrimination task⁵.

For true discrimination, the key was to vary f1 in each trial such that each frequency was followed either by a higher or by a lower comparison (FIG. 1c) — this forced the subjects to compare¹⁸. Performance in this situation attained the same levels as performance in the classical discrimination task, making it almost certain that the animals truly learned to discriminate between frequencies on a trial-by-trial basis. The lesson is that, although monkeys can learn to discriminate, they can also develop alternative strategies to solve a task, as hypothesized earlier based on theoretical arguments¹⁹. In particular, in the classical flutter discrimination task, monkeys tend not to compare the two stimuli at every trial. Instead, they classify the second stimulus, possibly setting the limits of each category during the first few trials in a run¹⁸. Whenever animals are assumed to discriminate, this problem should not be underestimated, regardless of sensory modality^{19–21}.

This seems to be a simple observation, but it might reflect the operation of fundamentally different mechanisms. Consider a task that involves variations in a single feature across trials. To identify or classify a current sensory stimulus, it must be compared to a reference stored in long-term memory, but it is not clear how the process of comparison can be studied in this situation. How is the information in long-term memory retrieved and made comparable to current sensory events? Where is this information stored and how does it differ from the original sensory-evoked activity? By contrast, in discrimination tasks in which two stimuli are sequentially presented in each trial, the comparison is made against the short-term memory trace that was left by the first stimulus. This means that if we can identify the neural correlate of the short-term memory, it might be possible to study the comparison or decision-making mechanisms that underlie task performance. Indeed, such a neural correlate has been recently reported²². But before addressing this issue, we must discuss how flutter stimuli are encoded.

encode features of stimuli that do not vary in time is intensely debated^{23–25}. In the case of tactile discrimination, however, the stimuli themselves typically vary in time, so some temporal processing must take place^{26,27}.

Early work^{1,3} showed that, when stimulated by trains of mechanical sinusoids, rapidly adapting primary afferents have a certain probability of firing in each cycle — and when they do fire, the evoked spike occurs at a specific phase. This takes place with high precision, on the order of 1 ms (in general, primary afferent populations can represent complex spatiotemporal patterns with extremely high fidelity^{28,29}). It was also shown that, in contrast to the responses of other fibres that are activated at higher frequencies, the mean firing rate of rapidly adapting receptors — that is, the mean number of spikes evoked during a fixed time interval that encompasses various stimulus cycles — varied little as a function of stimulus frequency³. This led to the idea^{2,3} that, because the firing rate did not carry information about frequency, a downstream structure would have to extract this information by reading out the time intervals between afferent spikes, which were highly reliable. The possibility that cortical neurons could be sensitive to small time differences was exciting, and theoretical work had supported the feasibility of this concept^{30,31}. Further experiments^{2,5,32,33} showed that primary somatosensory cortex (S1) neurons that respond to flutter have similar characteristics to those of rapidly adapting afferents; they adapt rapidly and, although their spikes are not as strongly PHASE-LOCKED to the stimulus as the firing of neurons in the periphery, they still have a high degree of temporal accuracy (FIG. 2a). Furthermore, these studies found no evidence for the modulation of firing rate as a function of frequency in S1. This was a crucial observation because it meant that the proposed time-sensitive mechanism had to be downstream from this area^{2,5,32,33}.

Although there were some conflicting observations⁸, these results remained unquestioned for several years. However, recent work³⁴ has shown that variations in firing rate do occur at the level of S1 during flutter stimulation. The key findings are as follows: first, how do firing rates change in S1? In the flutter range, mean responses typically increase monotonically with stimulus frequency (FIG. 2d). These responses can be described reasonably well as linear functions³⁴. For example, during the first stimulation period, firing rate equals $a1 \times f1 + b$, where $a1$ and b are constants. The coefficient $a1$ is the slope of the rate–frequency function, and is a measure of how strongly a neuron is driven by changes in frequency. In S1, most slopes are positive, but many are close to zero³⁴. This means that S1 firing rates usually increase with increasing stimulus frequency, but that just a small fraction of all responsive neurons show strong frequency modulation. This could explain why, in previous studies^{5,32,33} that were based on small samples or used a limited frequency range, significant variations in rate were not observed. FIGURE 3a shows the firing rate of an S1 neuron as a function of time, with different traces corresponding to different stimulation frequencies. FIGURE 4a shows slope distributions derived

PSYCHOMETRIC CURVE

A plot of the percentage of correct behavioural responses as a function of changes in the properties of the test stimulus.

PHASE LOCKING

The preferential firing of neurons at a certain phase of an amplitude-modulated stimulus.

Firing rate versus spike timing

How is the frequency of flutter stimuli represented? What is it about the neural activity that is triggered by these stimuli that conveys information about frequency? Do fluctuations in this neural code reflect fluctuations in behaviour? These questions touch on the possible roles of spike timing versus firing rate in encoding sensory information. The use of temporal synchrony to

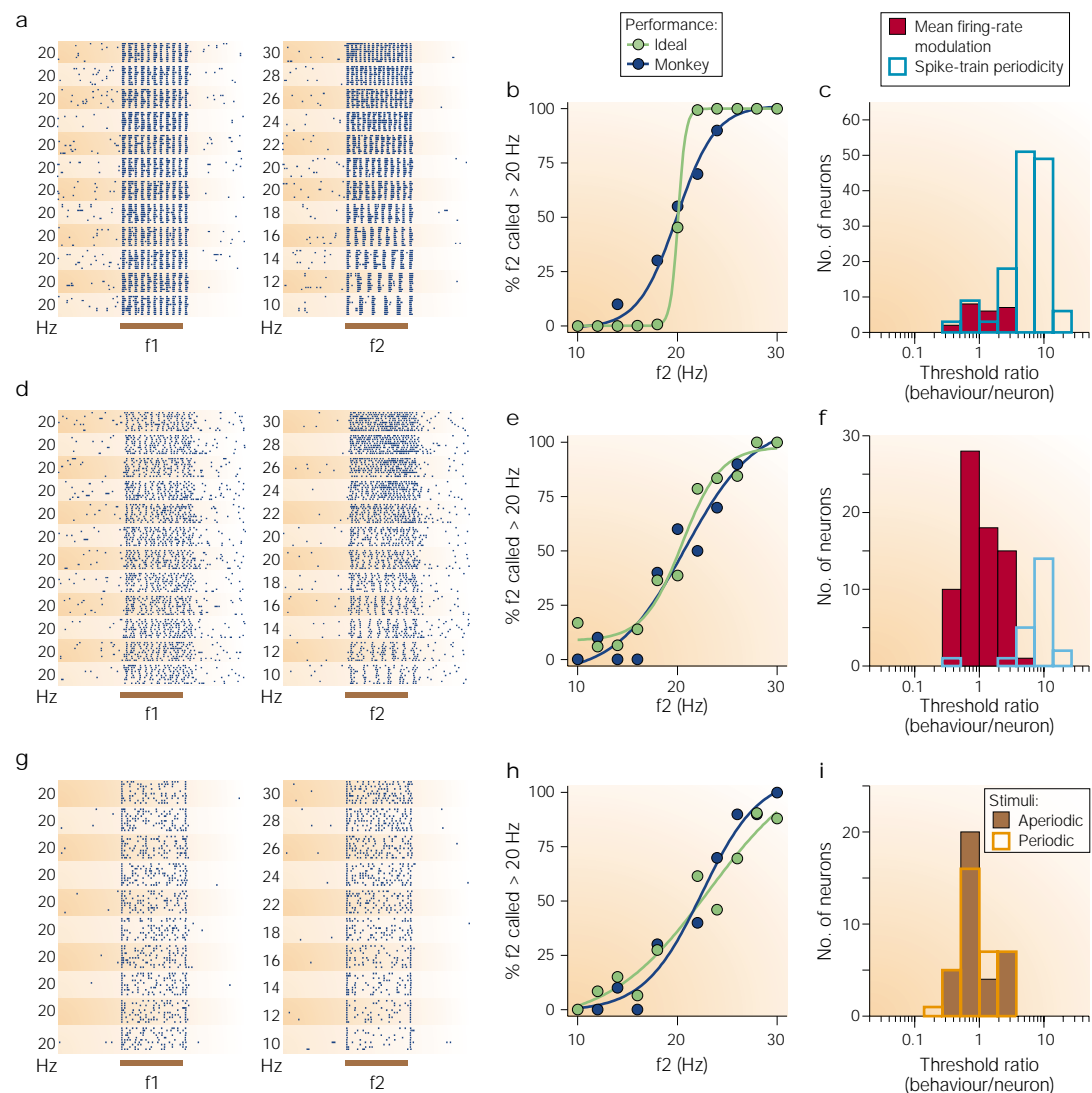


Figure 2 | **Comparison between S1 activity and psychophysical performance in the flutter discrimination task.** Responses of three neurons from the primary somatosensory cortex recorded during discrimination tasks. Each line represents a trial and each dot an action potential. Trials were delivered randomly. Brown bars indicate stimulation periods, and base (f1) and comparison (f2) stimulus frequencies are indicated. **a** | Responses showing weak rate modulation but faithfully reflecting the periodicity of the stimuli. **d** | Responses showing strong rate modulation but little regularity in spike timing relative to the periodic stimuli. **g** | Responses to aperiodic stimuli. **b, e, h** | Psychometric and neurometric curves. The y axis is the percentage of trials in which f2 was assessed as higher than f1, where f1 = 20 Hz. Blue dots and lines correspond to the monkey's performance. Green dots and lines indicate performance of an ideal observer that based his decisions on the responses of a single neuron. Continuous lines are sigmoidal fits to the data — the discrimination threshold is inversely proportional to maximum steepness. Part **b** shows the performance of the ideal observer on the basis of the periodicity of the neuron in **a**. Parts **e** and **h** show the performance of the ideal observer on the basis of the firing rates of the neurons in **d** and **g**, respectively. **c, f, i** | Numbers of S1 neurons with the indicated threshold ratios. In **c** and **f**, neurometric thresholds based on spike-train periodicity (open bars) were much smaller than those that were based on mean firing-rate modulation (filled bars), which matched the behavioural thresholds. Part **i** shows that threshold ratios based on mean firing rates were similar for aperiodic stimuli (filled bars) and periodic stimuli (open bars). Modified, with permission, from REF. 51 © (2000) National Academy of Sciences.

from S1 responses. There are two numbers, a1 and a2, indicating how strongly the neurons are driven by f1 and f2, respectively (see figure legend for details). To get an idea of modulation strength, a value of 1, which is fairly typical, means that the rate increases by 1 spike per second when frequency increases by 1 Hz.

Second, how do rates change downstream of S1? In FIG. 4a, S1 activity is easy to interpret; neurons respond

to f1 during the first stimulation period, and to f2 during the second. However, more centrally located areas show more complex patterns (discussed later in this review). Similar variations in rate are also observed^{34,35} in the second somatosensory cortex (S2). Whether this reflects serial or parallel organization is not clear. There is strong evidence^{36–39} that S2 is directly driven by S1, but other observations^{40,41} contradict this view. In any

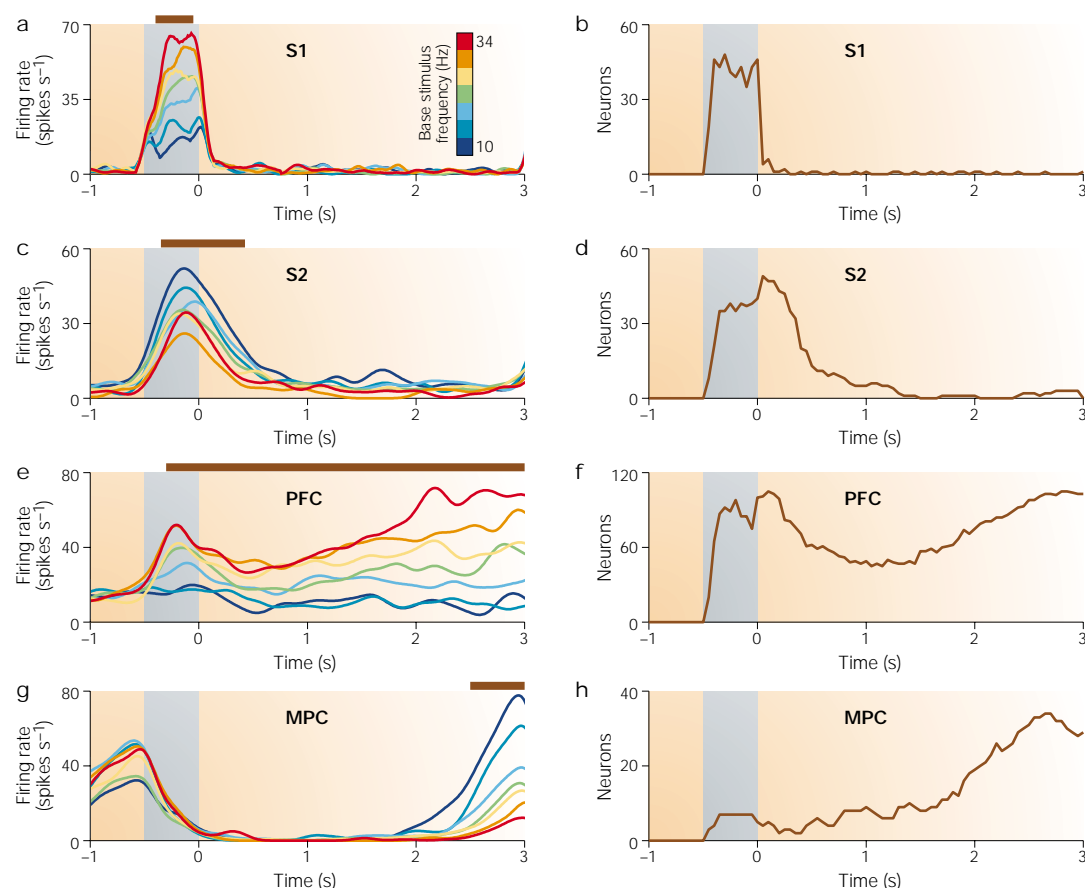


Figure 3 | Neuronal responses evoked by the base stimulus in four brain areas during the flutter discrimination task.
a, c, e, g | Spike density functions from four single neurons. Brown bars above each plot indicate times during which the neuron's firing rate carried a significant monotonic signal about the base stimulus. Colours are used to sort responses according to base frequency, as indicated by the scale gradient in **a**. Parts **a** and **e** show neurons that fired most strongly with high stimulus frequencies. Parts **c** and **g** show neurons that fired most strongly with low frequencies. **b, d, f, h** | Numbers of recorded neurons carrying a significant signal about the base stimulus, as a function of time relative to the beginning of the delay period. Only data collected from runs with a fixed delay of 3 s are included. MPC, medial premotor cortex; PFC, prefrontal cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex. Grey area indicates base stimulation period. Parts **a–d** show unpublished data. Parts **e** and **f** were modified, with permission, from *Nature* REF. 22 © (1999) Macmillan Magazines Ltd. Parts **g** and **h** were modified, with permission, from REF. 42 © (2002) Elsevier Science.

case, there are various differences between S1 and S2 activity during flutter discrimination³⁴. With regard to the neural code for frequency, two of these differences stand out. First, ~40% of the neurons in S2 have negative slopes. The firing rates of these units decrease as a function of increasing stimulus frequency in a roughly linear manner^{34,35}. The responses of one S2 neuron that reacted most intensely to low frequencies are illustrated in FIG. 3c, and the distribution of S2 slopes is shown in FIG. 4b. All areas downstream of S1 that have been examined so far and that are active during flutter discrimination show similar monotonic responses and similar proportions of positive and negative slopes (REFS 22,34,35,42 and R.R., unpublished observations). Interestingly, similar complementary populations of S2 units with positive and negative slopes have also been observed with other types of tactile stimuli such as GRATINGS^{43,44}, again with few negative slopes found in the S1 region⁴⁵. The second important difference

between S1 and downstream areas is that the latter show minimal or no traces of periodic activity in spite of the periodicity of the stimulus and of the evoked S1 discharges^{22,34,35,42}.

Third, is there any indication that firing rate modulations or spike timing in S1 are directly related to behaviour? There are three lines of evidence that provide some insight into this question. One important clue is that there are significant covariations between evoked firing rates and psychophysical responses in single trials³⁴, which is consistent with studies of vision⁴⁶. This means that the firing rate of some S1 neurons predicted to a significant extent whether the monkey would discriminate correctly or incorrectly in any given trial. Similar but stronger covariations were also observed^{34,35} in S2, in agreement with experiments based on the classification of surface roughness⁴⁷. By contrast, no such association was found between spike timing, which was quantified in various ways and

GRATING

An arrangement of parallel bars. The roughness of a surface may be varied by adjusting the width and spacing of the bars of an embossed grating.

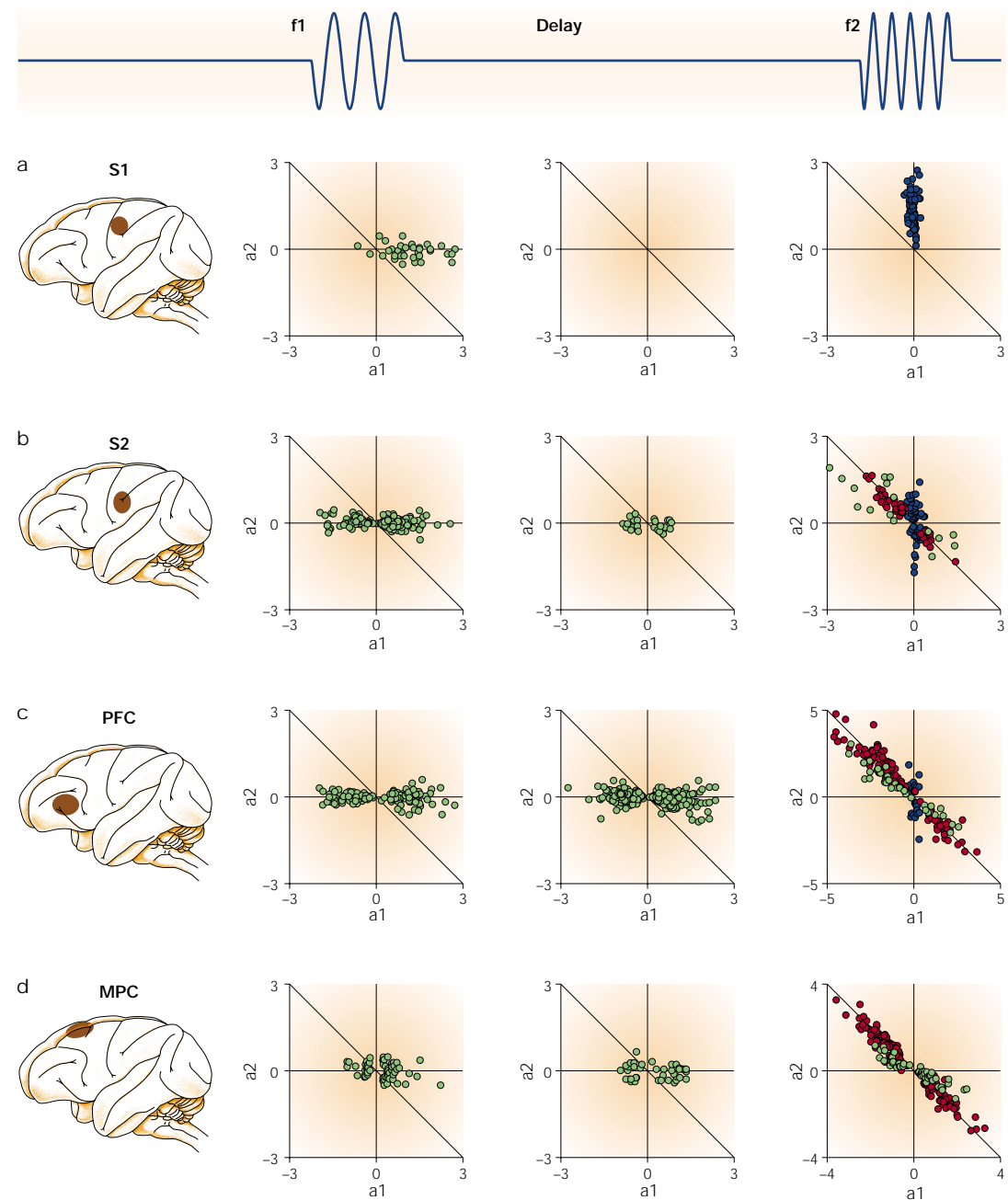


Figure 4 | Population dynamics in four cortical areas during the flutter discrimination task. Each data point represents one neuron. For each neuron, responses were fitted to the equation: firing rate = $a_1 \times f_1 + a_2 \times f_2 + b$, where f_1 is the base stimulus frequency, f_2 is the comparison stimulus frequency, and a_1 , a_2 and b are coefficients. The coefficients a_1 and a_2 were computed from responses at different times during the task. Points that fall on the $a_1 = 0$ axis represent responses that depend on f_2 only; points that fall on the $a_2 = 0$ axis represent responses that depend on f_1 only; points that fall on the $a_2 = -a_1$ line represent responses that are functions of $f_2 - f_1$. Green dots indicate neurons with significant a_1 coefficients (regardless of a_2); blue dots indicate neurons with significant a_2 coefficients only; red dots indicate coefficients computed during the last 300 ms of the second stimulus. **a** | Primary somatosensory cortex (S1) responses during the base stimulation period (f_1 ; left column), the inter-stimulus period (delay; middle column) and the comparison stimulation period (f_2 ; right column). These neurons were active only during stimulation — most of them increased their rates with increasing frequency (positive a_1 and a_2). **b** | Secondary somatosensory cortex (S2) neurons respond to f_1 and show a modest but significant amount of delay activity. Positive and negative coefficients indicate rates that increase and decrease as functions of frequency, respectively. During the initial part of f_2 , neurons might have significant a_1 coefficients or might respond exclusively to f_2 , as computed from the first 200 ms after stimulus onset. Later, the coefficients cluster around the line $a_2 = -a_1$, as computed from the last 300 ms before stimulus offset. The schematic of the brain shows the region of approach to S2, which is hidden in the lateral sulcus. **c**, **d** | Data from the prefrontal (PFC) and medial premotor cortices (MPC), respectively. The coefficients were calculated as in **b**. Parts **a** and **c** show unpublished data. Part **b** was modified, with permission, from *Nature Neuroscience* REF. 35 © (2002) Macmillan Magazines Ltd. Part **d** was modified, with permission, from REF. 42 © (2002) Elsevier Science, and unpublished data.

behaviours³⁴. In other words, although the time intervals between evoked spikes (or more precisely, their phases within a sinusoidal cycle) also fluctuated from trial to trial, these variations did not predict the monkey's behaviour. This indicates that the total number of spikes fired by an S1 neuron during the stimulation period is more important than the exact times at which those spikes are fired.

Another way of comparing a subject's behaviour to a neuron's activity is to construct a **NEUROMETRIC CURVE**^{48–51}. This corresponds to the psychophysical behaviour of an ideal observer that performs the discrimination task only on the basis of the responses of the chosen neuron. This ideal observer uses an optimal strategy to generate its choices, so a subject's actual behaviour can be compared to the best possible behaviour on the basis of the activity of a single cell. Neurometric curves can be constructed from any quantity that is considered as a response. The approach of Hernández and colleagues⁵¹ was to compute two types of neurometric curves: one on the basis of a neuron's firing rate and another on the basis of its periodicity, or the phase difference between emitted spikes. Examples of such curves are shown in FIG. 2b,e. What these authors found was that neurometric curves that were based on firing rate typically matched the behavioural or psychometric data, whereas neurometric curves that were based on periodicity did not — these typically predicted much more accurate performance than was actually observed⁵¹ (FIG. 2c,f). This confirms that the timing of S1 spikes is very precise, but indicates that this regularity is not exploited by the cortical circuitry, at least not to its full capacity. The same conclusion was reached on the basis of an **INFORMATION-THEORETIC** analysis³⁴.

Last, there is another observation that indicates that firing rates might be used to encode stimulus frequency. This is based on the use of aperiodic stimuli^{34,52}, which do not generate regular time intervals between spikes. An example of the spike trains that are evoked in this condition is shown in FIG. 2g. In this case, the stimulus consists of a train of mechanical pulses that are separated by pseudo-random intervals, and stimulus frequency is defined in an average sense using the total number of pulses delivered during the fixed stimulation time-window. Although this manipulation eliminated any regularity in spike timing from one trial to the next, the monkeys were able to adjust to these stimuli quickly — within a few trials their performance became as consistent as with sinusoidal vibrations⁵², which was unexpected. Furthermore, periodic and aperiodic stimuli evoked almost the same modulations in firing rate³⁴ and, consequently, the corresponding neurometric curves were also similar⁵¹ (FIG. 2e,h). This is consistent with the idea that, in both cases, stimulus frequency is encoded through a mean-rate code.

In summary, firing rates that vary as a function of stimulus frequency operate in several areas that are activated during the flutter discrimination task, particularly in S1, and there is evidence that these rate variations have an important impact on behaviour. By contrast, there is no indication that the high periodicity that flutter elicits

in S1 contributes to frequency discrimination, although it is difficult to entirely rule out this possibility.

Clearly, the brain must be able to extract at least some information from the precise timing of S1 spikes. For example, humans can easily distinguish periodic from aperiodic stimuli. Furthermore, temporal cues have a strong influence on the perception of roughness in humans^{26,27}, and this influence might change according to task requirements and experience²⁶. How central regions determine which features to extract and which to ignore from a given input is an important and challenging problem.

Generating artificial percepts

How can we be sure that the activity from any given cortical area is actually related to perception and behaviour? **INTRACORTICAL MICROSTIMULATION** is a powerful technique that can establish a causal link (not just a correlation) between the activity of localized neuronal populations and specific cognitive functions^{52–56}. For flutter discrimination, this approach has provided compelling evidence that all the cognitive processes of the task can be triggered directly by the rapidly adapting neurons in S1. This approach has also allowed us to explore questions about the neural code for flutter stimuli.

FIGURE 5 summarizes results from several microstimulation experiments. Initially, the idea was to manipulate only the comparison stimulus^{52,57} (FIG. 5a,b). The monkeys first learned to discriminate the frequencies of two sinusoidal vibrations delivered successively to the fingertips. Once they mastered the task, clusters of rapidly adapting neurons with receptive fields that had been activated by the mechanical stimulating probe were identified in S1, and the comparison stimulus was substituted with microstimulation in half of the trials (FIG. 5a). Artificial stimuli consisted of periodic current bursts delivered at the same comparison frequencies as mechanical stimuli. Remarkably, the monkeys discriminated the mechanical (base) and electrical (comparison) signals with performance profiles that were indistinguishable from those obtained with only natural stimuli (FIG. 5a). The most direct interpretation of this finding is that the artificially induced sensations closely resembled natural flutter⁵², although it is difficult to rule out the possibility that the sensations were different but still comparable. For example, sounds from a flute and a guitar are quite distinct, but their pitches can be compared.

As the intensity of the microstimulation current was varied, an interesting effect was observed⁵². At very low intensities, artificial stimuli were not detected — the monkeys simply kept waiting. At intermediate intensities, the monkeys detected the stimuli — they reacted and pushed a button — but their psychophysical behaviour was at chance levels, as if they could determine the presence but not the frequency of the artificial stimuli. At higher intensities, the monkeys discriminated normally. These transitions parallel those that are observed when the amplitude of mechanical vibrations is gradually increased. In particular, there is an 'atonal interval'

NEUROMETRIC CURVE

A plot of the percentage of correct behavioural responses that an ideal observer would make on the basis of observing the neuronal responses that are elicited by a given test stimulus.

INFORMATION THEORY

Shannon introduced the term 'mutual information' in a strict mathematical sense within a framework for studying communication channels. Mutual information is a statistic that measures the degree of association between any two quantities or sets of quantities. It is useful because it requires no assumptions about their mathematical form or behaviour, so it is in some sense objective.

INTRACORTICAL MICROSTIMULATION

A neurophysiological technique that is used to activate a population of neurons within a restricted cortical locus. Pulses of electric current delivered through a microelectrode drive the activation.

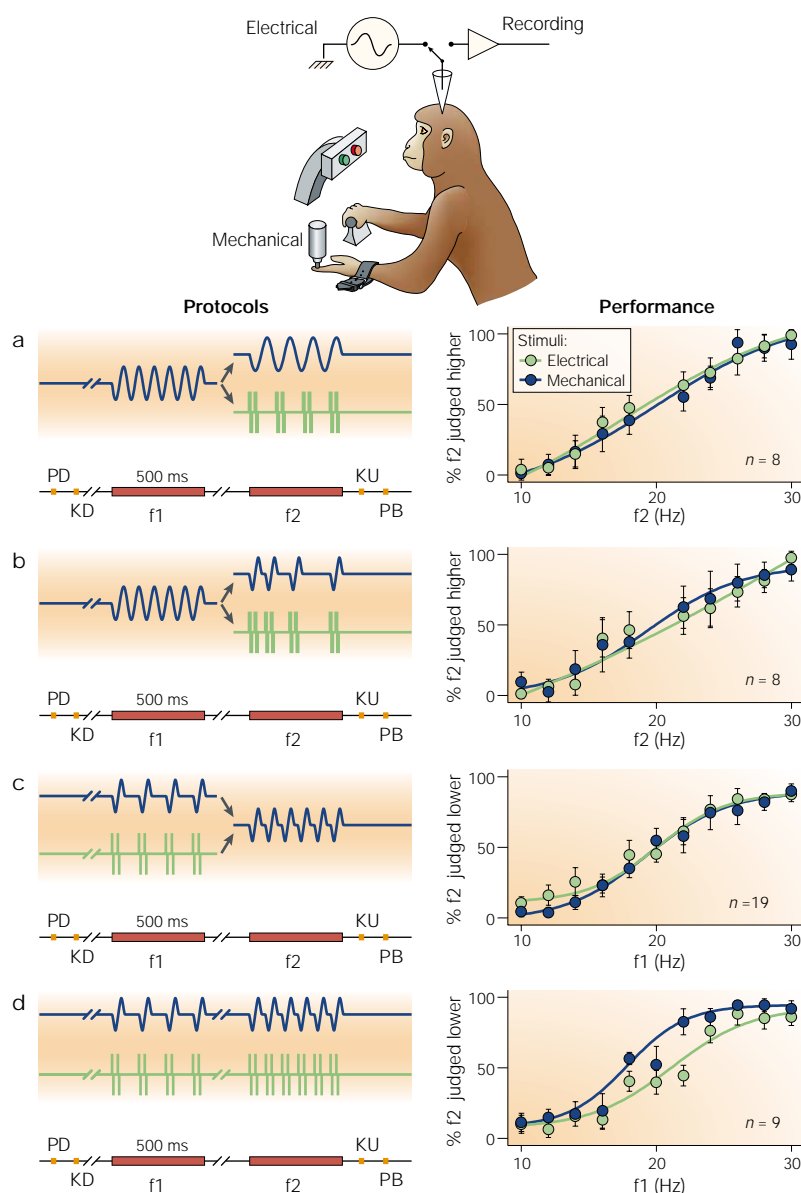


Figure 5 | Psychophysical performance in frequency discrimination with mechanical stimuli delivered to the fingertips, and with electrical stimuli delivered directly to primary somatosensory cortex (S1) neurons. Monkeys were first trained to compare two mechanical stimuli presented sequentially to the fingertips. Some of the mechanical stimuli were then replaced by trains of electrical current bursts that were microinjected into clusters of rapidly adapting neurons in area 3b of S1. Each burst consisted of two biphasic current pulses (green). Current bursts were delivered at the same comparison frequencies as natural stimuli. In half of the trials, the monkeys compared two mechanical vibrations delivered to the skin. In the other half, one or both stimuli were replaced by microstimulation. The two trial types were interleaved, and frequencies always changed from trial to trial. The diagrams on the left show four of the protocols used. The curves on the right show the monkey's performance in the situations illustrated on the left. Blue and green circles indicate mechanical and electrical stimuli, respectively. Continuous lines are fits to the data points. **a** | All stimuli were periodic. The comparison stimulus could be either mechanical or electrical. **b** | The base stimulus was periodic and the comparison stimulus was aperiodic. The comparison could be either mechanical or electrical. **c** | All stimuli were periodic. The base stimulus could be either mechanical or electrical. **d** | All stimuli were periodic. In microstimulation trials, both base and comparison stimuli were artificial. Vibrotactile stimuli were either sinusoids or trains of short mechanical pulses, each consisting of a single-cycle sinusoid of 20 ms. The monkey's performance was essentially the same with natural and artificial stimuli. f1, f2, first and second stimulus frequency, respectively; KD, hand on key; KU, key released; PB, button pushed; PD, mechanical probe down. Parts **a** and **b** were modified, with permission, from *Nature* REF. 52 © (1998) Macmillan Magazines Ltd. Parts **c** and **d** were modified, with permission, from *REF.* 53 © (2000) Elsevier Science.

in which stimuli can be detected but their frequencies cannot be ascertained⁴.

Because of the design of the task, the comparison of the second stimulus is made against a memory trace of the first stimulus¹⁸. So, monkeys could interpret an artificial stimulus during the comparison, but could they use an electrical stimulus delivered during the base period? In experiments in which the base stimulus consisted of electrical microstimulation, the monkey's psychophysical behaviour was again indistinguishable from that observed with only natural stimuli⁵³ (FIG. 5c), indicating that the signals evoked by mechanical and artificial stimuli could be stored and recalled with roughly the same fidelity. Moreover, monkeys could perform the entire task, with little degradation in performance, on the basis of purely artificial stimuli⁵³ (FIG. 5d).

A couple of additional observations from these experiments are noteworthy. First, early experiments with primary afferents showed that the flutter sensation is specifically mediated by rapidly adapting fibres^{3,8,9}, but this was more difficult to test at the level of S1. When microstimulation was applied to clusters of neurons that were identified as having slowly adapting properties, the monkeys could barely discriminate, if at all. As the electrode was advanced to the border between slowly adapting and rapidly adapting clusters, performance improved, and reached its usual degree of accuracy when rapidly adapting properties became most evident in the recordings⁵³. So, rapidly adapting and slowly adapting units are still functionally segregated in the primary cortex, consistent with previous observations^{32,58–61}. This is key to the success of these experiments. Last, returning to the question of whether periodicity is crucial for frequency discrimination, we applied aperiodic microstimulation patterns that mimicked the pseudo-random trains of mechanical pulses that were discussed earlier (FIG. 5b). From the initial trials, the animals could discriminate both mechanical and electrical aperiodic signals with nearly the same performance level that they reached with periodic vibrations⁵².

These experiments show that activating clusters of S1 neurons with rapidly adapting properties is sufficient to drive the full cascade of cognitive events leading to flutter discrimination.

Sensory versus mnemonic activity

One of the key features of the flutter discrimination task is that it requires short-term storage of information about the first stimulus. Where and how does this happen? And how does this mnemonic trace compare with the sensory-triggered activity that is evoked during stimulation? So far, the clearest neural correlate of the working-memory component of the task has been found in the prefrontal cortex (PFC)²², an area implicated in working memory in numerous experiments^{62–65}. The inferior convexity of the PFC contains neurons that increase their activity in a frequency-dependent manner during the delay period between base and comparison. An example is shown in FIG. 3e, in which the mean firing rate of a neuron that has a preference for high frequencies

is plotted as a function of time for various base frequencies. As in the S2 region^{34,35}, the dependence of firing rate on base frequency is monotonic — slightly less than half of the neurons have negative slopes and fire more intensely for low stimulus frequencies, whereas the remainder have positive slopes and fire most strongly at high stimulus frequencies²² (FIG. 4c).

This mnemonic representation is not static, in the sense that the intensity of the persistent activity varies throughout the delay²². This is evidenced in two ways. First, not all neurons are activated at the same time. Some prolong the responses evoked during the base stimulus into the first part of the delay, becoming silent before the comparison (early neurons). Other neurons do the opposite — they are initially silent but their activity increases towards the end of the delay period (late neurons). Another class of neurons (FIG. 3e) spans the full interval between stimuli (persistent neurons). As a result of this diversity, the total number of activated neurons changes with time, as shown in FIG. 3f. In all of these cases, the firing rate depends on base frequency, as evidenced by the separation between traces in FIG. 3e. For a single neuron, the frequency representation is clearly dynamic because the degree of separation — or signal strength, which is quantified by the magnitude of the coefficient a_1 — changes with time. The second phenomenon that underscores the flexibility of PFC activity is its capacity to adapt to changes in delay interval. When the interstimulus interval is increased from 3 to 6 s, the activation profiles of late neurons shift in proportion to the delay period²². So, these units always begin firing towards the end of the delay period, regardless of its duration. This is consistent with previous observations using visual stimuli⁶⁶.

A key question — especially for the units that are activated late in the delay — is whether the persistent activity truly encodes f_1 or, instead, reflects preparatory activity that is related to impending motor behaviour. This is an important issue whenever there is sustained activity that is to some extent uncoupled from sensory or motor events. Activity recorded during delayed-response tasks might often be interpreted as either sensory- or motor-dependent — that is, as either mnemonic or anticipatory^{62,67–70}. In the flutter task, the observed graded activity could be related to the probability of making a specific movement, such as to the left button. For example, with the stimulus set shown in FIG. 1c (left panel), the probability that a specific movement is made varies monotonically with f_1 . However, this interpretation is unlikely to be correct because the same repertoire of graded responses is seen²² even with stimulus sets in which, for each base frequency, the probability of making a given movement is kept constant at chance levels ($p = 0.5$) as in FIG. 1c (middle panel). Therefore, the delay activity in the PFC resembles a copy or extension of the sensory-triggered activity in S2 during stimulation; it seems to maintain the information about f_1 'online'.

Although the PFC shows the clearest neural correlate of working memory during the flutter discrimination task, it is almost certainly not the only area involved in this function — delay-period activity has

been found both in areas closer to the periphery and in areas closer to the motor output. In S2, about one-third of the neurons that are significantly modulated by stimulus frequency prolong their responses by at least a few hundred milliseconds beyond the end of the base stimulation period^{34,35}. The neuron illustrated in FIG. 3c is an example. Its response decays over a relatively long timescale, which is evident when compared to the S1 neuron in FIG. 3a, which has a sharp offset. FIGURE 3b,d shows the same contrast at the population level. Most S2 neurons with sustained activity become silent within the first second of the delay period. These units are similar to the early neurons found in the PFC, which also have relatively short-lived responses. At the other end of the delay interval, responses similar to those of the late neurons in the PFC were found in the medial premotor cortex (MPC)⁴², which comprises the supplementary and pre-supplementary motor areas^{71,72}. The example in FIG. 3g shows delay activity that has a preference for low frequencies. As can be seen from FIG. 3h, some MPC neurons are active during the entire delay period, but the activity of the population mostly increases towards the end. In general, MPC firing rates during the delay are monotonic functions of f_1 , with positive and negative slopes (FIG. 4d), and their onset shifts as a function of delay duration⁴², as in the PFC. A comparison across areas (FIG. 4) shows that, although each area seems to have its own functional identity, there is considerable overlap between the types of responses, possibly reflecting tight interconnectivity^{73–78} and dynamic cross-talk between the areas.

Regarding the organization of memory networks, there is some evidence for the participation of primary sensory areas both in visual^{79,80} and somatosensory^{81,82} modalities. In particular, a study by Harris and colleagues⁸³ in humans is most germane to our discussion, because these authors used roughly the same flutter discrimination task. Their experiment was simple and clever. At different points during the delay interval they delivered a pulse of TRANSCRANIAL MAGNETIC STIMULATION (TMS) to S1 of subjects performing the task. Such a pulse disrupts neuronal activity in a localized area for ~200 ms. These authors found that TMS lowered behavioural performance significantly when it was applied to S1 contralateral to the stimulus and early in the delay (300 or 600 ms after f_1 offset), but it had no effect when it was applied either later or to the ipsilateral S1. The interpretation is that something that contributes to stimulus retention is taking place in the contralateral S1 during the early part of the delay. This is because the hand representation in S1 is strictly contralateral, whereas all downstream areas have bilateral receptive fields. Therefore, any laterality effects must be due to S1 activity⁸³. This seems to be at odds with recordings from S1, which do not show any significant mnemonic activity³⁴ (FIG. 4a). Harris *et al.* suggested that this could be the result of the monkeys being overtrained in the task, as compared to humans⁸³. Another possibility is that after the base stimulus, the rapidly adapting units in S1 might increase or decrease their baseline firing levels for a few hundred milliseconds as a result of adaptation or similar

TRANSCRANIAL MAGNETIC STIMULATION

(TMS). A non-invasive technique that is based on the application of a time-varying magnetic field near the surface of the head. The magnetic pulse generates electrical currents in the brain that affect the activity of the underlying superficial neurons. Pulses are intense but brief and relatively localized because the magnetic field decreases strongly with distance.

changes in excitability⁸⁰. Given that a large population of S1 neurons responds during stimulation with roughly the same intensity for all $f1$ values³⁴, this would result in a small, transient and non-selective change in the firing of many neurons. This uniform signal would not carry information about $f1$, but could have a large functional impact on downstream networks⁸⁴.

Temporal evolution of the comparison process
The core of the discrimination task — the comparison between $f1$ and $f2$ — occurs during presentation of the second stimulus. The responses observed during this interval are often complex, but they generally reflect an active process in which the evoked neural activity eventually encodes the difference between $f2$ and $f1$. Notice that the discrimination task can be thought of as a process by which the sign of this quantity is computed. No evidence of such computation is observed in S1, where neurons simply respond as functions of $f2$ during the comparison^{34,35} (FIG. 4a, right panel), but in S2 there is already a complete rendition of the process³⁵. To quantify the simultaneous dependence of the firing rates on $f1$ and $f2$, these were fitted using the following expression: firing rate = $a1 \times f1 + a2 \times f2 + b$, where b is a constant and $a1$ and $a2$ are the coefficients that measure how strongly $f1$ and $f2$ drive the neurons. Over the course of the comparison period, $a1$ and $a2$ might change. For example, if the $a1$ and $a2$ coefficients for a single S2 neuron are computed at different time intervals, it is possible to observe the following³⁵: within the first 100 ms, the neuron responds as a function of $f2$ — that is, in this time window only the coefficient $a2$ is significantly different from zero. Within the next 100 ms, the response develops a dependence on $f1$, so $a1$ becomes significant. Two to three hundred milliseconds after stimulus onset, $a1$ and $a2$ have roughly the same magnitude but opposite signs, which means that the neuron is responding as a function of $f2 - f1$, that is, it is comparing $f1$ and $f2$. This example is fairly common, but there are several variants. For example, it may be that only the $a1$ coefficient is significant at first — the neuron recalls the frequency presented earlier — and dependence on $f2$ develops later. Also, some neurons end up firing most strongly when $f2 - f1$ is large, whereas others do so when $f1 - f2$ is large. In addition, neurons show different trajectories within the space of $a1$ and $a2$ values, and some simply respond to $f2$ throughout the entire period³⁵.

FIGURE 4b (right panel) summarizes these results on the basis of analysis of two time windows. Blue and green dots show $a1$ and $a2$ values calculated from responses during the first 200 ms of the comparison period. Blue dots correspond to neurons that had a significant $f2$ dependence only, and green points correspond to neurons that had a significant $f1$ dependence (regardless of sensitivity to $f2$). Clearly, S2 neurons first respond as a function of $f2$, or combine $f1$ and $f2$ in a variety of ways. By contrast, the red dots show $a1$ and $a2$ values that were calculated from the same neurons, but using the responses during the last 300 ms of the comparison period. These points cluster along the diagonal $a2 = -a1$, meaning that during that period the neurons respond as

functions of $f2 - f1$. So, the response repertoire in S2 is quite large, but the overall tendency³⁵ is to proceed from encoding either $f1$ or $f2$ to encoding $f2 - f1$.

This pattern of activity indicates that neural representations of $f1$ and $f2$ are combined to generate a comparison signal — the activity encoding $f2 - f1$ — on which the motor action that is used to indicate the discrimination result is based. If this interpretation is correct, the neurons that encode the difference between frequencies should have a sizeable impact on the monkey's decision-making ability^{49,50,85}. This prediction was tested by analysing correct versus error trials, and by calculating for each neuron an index of the probability of predicting the monkey's choice in any given trial on the basis of the neuron's response³⁵. These choice probabilities increased throughout the course of the comparison period, and the highest values were generated by the neurons with responses that depended most strongly on $f2 - f1$. So, consistent with a previous analysis³⁴, there was a measurable association between single-neuron firing and psychophysical behaviour. The strength of this association was comparable to that reported for the PFC⁸⁶, the parietal cortex⁸⁷ and the superior colliculus⁸⁸ in a visual-motion discrimination task.

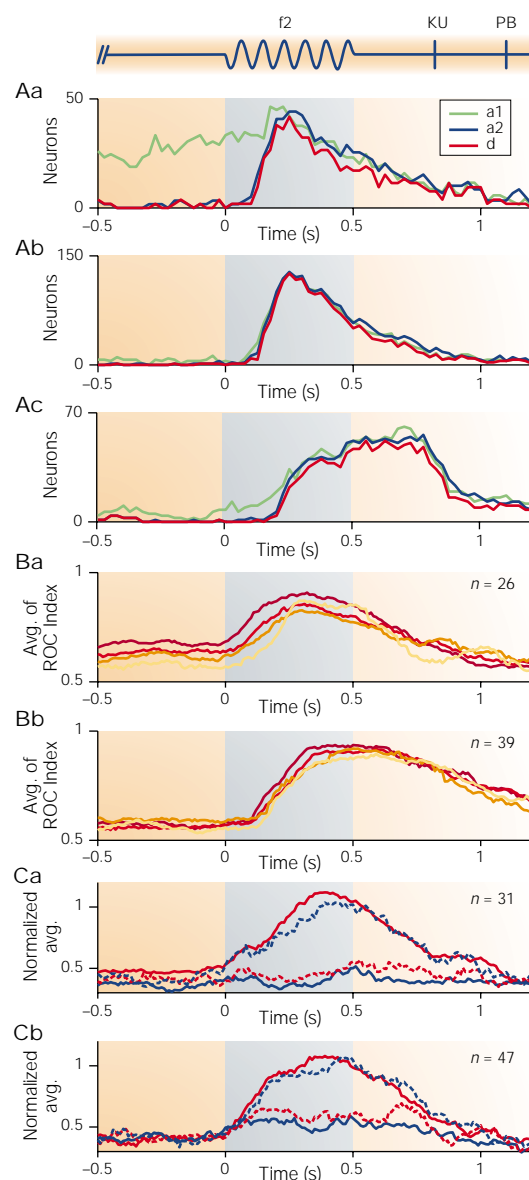
A crucial question about the activity that depends on $f2 - f1$ is whether it feeds into the motor areas to generate the movement that indicates the monkey's choice, or whether it reflects an *REFERENCE COPY* of the associated motor command. In other words, does the $f2 - f1$ -dependent activity drive motor activity or is it driven by motor activity? This was investigated³⁵ by measuring the latencies of S2 responses that depended on $f2 - f1$ throughout the delay, and comparing them to the latencies of neurons in the primary motor cortex (M1) that responded differentially during the task. The responses of these M1 neurons could also be fitted as functions of $f2 - f1$ because the sign of this difference determines the movement to one or other of the push buttons, and the two movements generate differential motor activity^{89,90}. The analysis showed³⁵ that neurons in S2 fired significantly earlier than those in M1.

So, the signal that is observed in S2 towards the end of the comparison period is consistent with the output of a process that compares $f2$ and $f1$ by computing the difference between them. What happens in other areas?

Motor expression of a decision

S2 is not the only part of the cortex that has the dynamic changes discussed above. As with the working-memory component of the task, there is considerable functional overlap between areas. This can be appreciated by comparing FIG. 4b–d (right panels). A few neurons in the PFC also respond as functions of $f2$ during the initial part of the comparison period (FIG. 4c, blue dots) and, as mentioned previously, many PFC neurons show $f1$ -dependent activity before and at the onset of the second stimulus. FIGURE 4c (right panel) shows that this information is quickly combined with information about $f2$. As in S2, PFC responses in the latter part of the comparison were consistent with a role for this structure in encoding $f2 - f1$. As shown in FIG. 4d (right panel), a similar trend

REFERENCE COPY
A copy of a motor command that is sent back to the central nervous system to inform it of the executed movement.



is observed in the MPC. The activity of MPC neurons during the task has been analysed in detail⁴², and several interesting differences and similarities arise with respect to other structures.

Owing to its projections to M1 and the spinal cord, the MPC has traditionally been viewed as a motor area, but recent studies have shown it to be involved in complex cognitive processes such as sensory-motor associations, recall of motor memories and timing of sequential motor actions^{91–93}. The MPC is often subdivided into the supplementary motor area proper, which is more motor, and the pre-supplementary motor area, which is more cognitive^{91,92,94}, but no functional segregation is observed during vibrotactile discrimination⁴². During this task, a significant number of MPC neurons respond to the base stimulus (FIG. 4d, left panel), so this area evidently receives some sensory information. As in other areas, the dependence on f_1 is roughly linear, with positive and negative slopes. As discussed previously,

Figure 6 | Differential activity in the medial premotor cortex (MPC). **A** | Numbers of neurons with significant coefficients a_1 (green) and a_2 (blue), as functions of time; d (red) indicates instances where a_1 and a_2 had similar magnitudes but opposite signs. **Aa** | Data from neurons that carried a significant amount of information about the first stimulus frequency (f_1) during the delay period. **Ab** | Neurons that had no significant delay activity and fired most strongly during the comparison period. The differential response (d) is slightly delayed with respect to the response shown in part **a**. **Ac** | Neurons that fired most strongly after the comparison, during the reaction-time period. The differential response (d) is delayed with respect to the response shown in part **b**. **B** | Y axes show the 'receiver-operating characteristic' (ROC) index averaged across neurons as a function of time. The ROC index measures the average strength of the differential response (that is, one type of arm movement versus the other type) regardless of whether it corresponds to $f_2 > f_1$ or $f_2 < f_1$, where f_2 is the second stimulus frequency. Red-to-yellow levels indicate differences between f_1 and f_2 , from 0 (yellow line) through 2 and 4, to 8 Hz (red line). Traces were computed from trials with different f_1 but fixed f_2 . **Ba** | ROC indices computed from neurons carrying a significant signal about f_1 during the delay. Note that differential activity increases during the comparison period (f_2), and that it increases earlier as the difference between f_1 and f_2 increases. **Bb** | ROC indices for MPC neurons that did not carry a significant signal about f_1 during the delay period. These neurons do not show significant ROC indices during the delay, but later than in **Ba** and with comparable magnitude for various frequency differences. **C** | Analysis of error trials for MPC neurons. Curves show mean normalized responses as functions of time for neurons with (**Ca**) and without (**Cb**) significant delay activity. Separate traces are shown for correct trials in the preferred (solid red line) and non-preferred (solid blue line) condition. Dashed lines correspond to error trials. The preferred condition is either $f_2 > f_1$ or $f_2 < f_1$, whichever produces a stronger response for a given neuron. Traces were calculated from trials with differences of 4 Hz between f_1 and f_2 . Activities were normalized with respect to the highest firing rate during correct trials. Grey area indicates f_2 stimulation period. avg., average; KU, key released; PB, button pushed. Modified, with permission, from REF. 42 © (2002) Elsevier Science.

there is also f_1 -dependent activity during the delay period (FIG. 4d, middle panel), most of it increasing in intensity towards the end of the delay (FIG. 3h). As in S2 and the PFC, responses during the comparison period indicate a dependence on $f_2 - f_1$ (FIG. 4d, right panel).

FIGURE 6A shows, in a different format, the evolution of MPC activity encoding $f_2 - f_1$. The green and blue traces correspond to the numbers of neurons with significant a_1 or a_2 coefficients, respectively, as functions of time. The red traces indicate the number of neurons with significant a_1 and a_2 coefficients of similar magnitude but opposite signs. So, if the three curves lie on top of each other it means that all neurons were responding as functions of $f_2 - f_1$. FIGURE 6Aa presents these quantities only for those neurons that had significant delay activity. FIGURE 6Ab shows them for neurons that did not have delay activity and responded most strongly during the comparison. FIGURE 6Ac corresponds to neurons that did not have delay activity and responded most strongly

after the comparison, during the reaction-time period. The differential signals of the neurons with and without delay activity (FIG. 6Aa, Ab, respectively) differed in onset by ~40 ms, with the delay neurons leading. The neurons that peaked after the comparison had even later onsets (FIG. 6Ac). Whereas the neurons with delay activity seemed to actively combine information about f_1 and f_2 , none of the neurons lacking delay activity were sensitive to f_1 or f_2 alone. So, the responses of the neurons lacking delay activity could be related either to the end result of the comparison process or to the motor command that was associated with the arm movements⁴².

These two possibilities are difficult to distinguish, and it could be that, at some level, there is no actual distinction between them. This is indicated by recent microstimulation studies by Gold and Shadlen^{95,96}. They used a visual-motion discrimination task and showed that, in the frontal eye fields, the accumulation of sensory evidence is equivalent to the process of preparing a motor response. In this experiment, monkeys determined the direction of dynamic RANDOM-DOT STIMULI and indicated their judgement with an eye movement towards one of two possible targets. Motion viewing was interrupted by electrical microstimulation pulses that, in the absence of a sensory stimulus, triggered eye movements towards a certain location. During discrimination, these electrically evoked movements deviated towards a different location, with the magnitude of the deviation depending on motion strength and viewing time, therefore reflecting the accumulation of motion information. Because the deviations were towards a particular location, the degree of accumulation was equivalent to the degree of preparatory motor activity in a population of neurons that generated SACCADIC to that location^{95,96}.

This equivalence is consistent with two complementary analyses of MPC activity in the flutter task⁴². First, as discussed earlier, the units with delay activity seem to carry a sensory signal. More importantly, they seem to reflect the actual comparison process, because the strength of their differential activity varies in a graded fashion with $f_2 - f_1$. In other words, these cells encode not only the sign of $f_2 - f_1$ — which is equivalent to the motor response towards one or other of the push buttons — but they also encode the actual difference $f_2 - f_1$. This is seen in FIG. 6B. The quantity on the y axis is the average 'RECEIVER-OPERATING CHARACTERISTIC' (ROC) index, which measures the difference between the neuronal responses to two combinations of frequencies with identical magnitude $|f_2 - f_1|$. This number is independent of whether a neuron has a preference for $f_2 > f_1$ or $f_2 < f_1$, and its scale is such that a value of 0.5 indicates no statistical difference between responses, and a value of 1 indicates completely non-overlapping responses. The various traces in FIG. 6B correspond to $|f_2 - f_1|$ equal to 0 (yellow), 2, 4 and 8 Hz (red). FIGURE 6Ba shows data from MPC neurons with significant delay activity (as in FIG. 6Aa). The separation between curves indicates that the firing rates are affected by the magnitude of $f_2 - f_1$. That is, the difference in activity between trials resulting in one or other of the arm movements towards a push

button depends on the sensory information. It is also interesting to note that the ROC index increases much earlier for large differences in frequency. FIGURE 6Bb shows data from MPC neurons without delay activity (as in FIG. 6Ab,Ac). Their ROC index has a much longer latency, and they are much less sensitive to the magnitude of $f_2 - f_1$ — they essentially respond to its sign. These results point to both a true comparison between f_2 and f_1 in the delay neurons, and a motor or preparatory signal in the neurons without delay activity.

Second, analysis of error trials^{86,97} points to a predominantly motor response. FIGURE 6C shows average normalized firing rates as functions of time for neurons with (FIG. 6Ca) and without (FIG. 6Cb) significant delay activity. Solid and dashed curves correspond to correct and incorrect discriminations, respectively, and red and blue traces indicate preferred and non-preferred conditions, respectively ($f_2 > f_1$ or $f_2 < f_1$). The figures show that the responses in error trials for the preferred condition are very similar to the responses in correct trials for the non-preferred condition, and vice versa. So, the responses associated with a given arm movement, for example, to the lateral push button, were about the same regardless of whether the discrimination was correct or not⁴² — that is, it is as if MPC activity encoded the motor response.

However, there is an interesting twist to this interpretation. Many MPC neurons were also tested⁴² in an experiment in which the same tactile stimuli were presented (with the same event sequence and identical frequency pairs), but an additional visual cue indicated the correct push button to the monkeys. In this condition, the animals had to ignore the tactile stimuli and simply follow the visual instruction. The key in this case is that the flutter stimuli and arm movements were the same as during regular discrimination, but the cognitive processes — working memory and stimulus comparison — were not. In this condition, the differential activity virtually disappeared. Therefore, the differential activity elicited during discrimination is not simply related to a motor action; either it reflects the final result of the comparison between frequencies or it represents a motor plan that is fully gated by the behavioural context of the discrimination task.

Interestingly, Gold and Shadlen⁹⁶ also observed a strong dependence on behavioural context. The accumulation of motion information was observed in the frontal eye fields only when the discrimination was associated with a specific, predictable movement. When the target location was known only after the discrimination phase, there was little evidence for such an accumulation.

Ubiquity of sensory-motor responses
Shadlen and Newsome⁹⁷ have made an appealing analogy between jury deliberation in a trial and making a motor choice on the basis of sensory input; witnesses present evidence, the members of the jury examine the evidence and reach a decision, and a judge implements this decision. This metaphor is attractive, but are the borders between the sensory, decision and motor stages

RANDOM-DOT STIMULUS
A commonly used visual stimulus that consists of dots randomly moving on a screen. The experimenter can vary the coherence of their movement (the fraction of dots that move in the same direction), and the subjects are asked whether they can detect any movement coherence.

SACCADIC
A rapid intermittent eye movement that occurs when the eyes fix on one point after another in the visual field.

RECEIVER-OPERATING CHARACTERISTIC INDEX
A measure that allows establishment of the sensitivity and specificity of a given test, enabling us to determine an optimal cut point to distinguish between true and false positives. It is particularly useful when the results of the test are a continuous measure, such as glucose concentration in a blood test.

as clearly demarcated in the primate brain? In the flutter task, the distinction is at best rather unclear, as evidenced by the large overlap between sensory-, decision- and motor-related activity (FIG. 4). Responses during the base stimulation period — arguably the most sensory-dependent phase — have been observed in all areas examined so far, including M1 (R.R., unpublished observations; see also REF. 35). Similarly, responses that correlate with the arm movements after the offset of the comparison stimulus — which are probably related to motor execution — have been observed in all areas except S1. This is not to say that all areas are the same; responses to f_1 are not abundant in M1, just as apparently motor-related activity after the offset of f_2 is not strong in S2. But there is clearly overlap between response characteristics, especially for cortical areas other than S1 and M1. The differences are better characterized as shifts in the distributions of response types.

We have also observed a high degree of functional overlap using a simpler task in which tactile-motion stimuli had to be categorized as either 'fast' or 'slow'. In this case, there were two types of monotonic responses that varied — with positive or negative slopes — as functions of stimulus speed. These differential responses could be interpreted as being either specific for stimulus category or specific for arm movement direction, but the distinction could not be drawn clearly in any of the areas in which they were found, including the MPC^{98–100}, the putamen¹⁰¹ and the M1 region^{90,99,102}. The patterns of hits and errors indicated both sensory and motor involvement^{90,99}, and the differential activity mostly disappeared in experiments in which the same arm movements performed during categorization were guided by visual cues^{90,98–101}. So, either the differential activity reflected the outcome of the categorization process, or it corresponded to motor commands that were gated by behavioural context — the same ambiguity that was found in the discrimination task.

There does not seem to be one specific structure that corresponds to the jury stand in the legal analogy. Furthermore, the responses that correlate best with what could be considered as a decision are difficult to uncouple from either sensory or motor features. During flutter discrimination, the best candidates for decision-related responses are those that represent a processed version of f_1 and f_2 but that do not covary fully with the motor actions. Neurons that carry information about f_1 immediately before the onset of the comparison stimulus and then respond as functions of $f_2 - f_1$ (FIG. 6Aa) seem to reflect the evolution of a comparison process. They show a preference for one motor outcome over the other ($f_2 > f_1$ versus $f_2 < f_1$), but in a way that is sensitive to the strength of the sensory evidence (FIG. 6Ba,Ca). Similar interpretations apply to discrimination in the visual modality, except that behavioural choices in this modality are typically indicated through eye movements. As with the flutter task, activity that predicts a monkey's choice to some extent but also reflects sensory information has been observed in sensory areas^{49,85}, in oculomotor regions of the PFC⁸⁶, and in structures that are traditionally associated with oculomotor control,

such as the lateral intraparietal area^{87,97,103}, the frontal eye fields⁹⁵ and the superior colliculus⁸⁸. The jury seems to be everywhere.

A motor plan modulated by sensory information? Many studies in motor control have focused on relatively small circuits that can generate full behaviours, such as walking, flying, breathing and chewing^{104,105}. Many of these CENTRAL PATTERN GENERATORS (CPGs) have been described in invertebrates and vertebrates. In CPG circuits, sensory input typically serves to modulate behaviours^{104,105} — to turn them on or off, to speed them up or to slow them down. This indicates that the problem with the legal analogy is that it implicitly assumes that when the evidence is ambiguous or when the jury cannot reach a decision, no action is taken. So, generating an action is a sequential process, and the evaluation of sensory evidence is a crucial intermediate step.

In the context of the CPG literature, the generation of motor behaviour is beautifully illustrated by recent neurophysiological work in the leech¹⁰⁶. Esch and colleagues identified a leech interneuron that, when stimulated, triggers one of two locomotor behaviours, crawling or swimming. The type of behaviour that is produced depends on the water level that surrounds the animal, and therefore on the sensory neurons that convey this information. The interneuron signals the command 'let's move', but the actual motion is determined downstream. The authors propose¹⁰⁶ that decisions might proceed in a hierarchical fashion: first an overall goal is set (for example, to go on holiday), and then subsequent aspects are specified sequentially (where to go, what form of transport to use, how long to stay and so on).

In the context of the flutter discrimination task, this idea means that a plan to make an arm movement is first established, and then this plan is modified according to sensory and mnemonic information. Perhaps the underlying neural activity is like a train that is set in motion towards a 'Y' junction, whereby the tracks correspond to neurons and the switch is controlled by sensory and mnemonic activity. When the sensory information is absent or insufficient to move the switch — when $f_1 = f_2$ — the train proceeds as planned, from one area to the next and so on, but one of the two tracks is chosen randomly. Because the train is long and the two paths separate gradually, there is a large temporal and functional overlap in the observed neural activity.

This analogy is roughly consistent with experiments on discrimination and with two other important results. A lesion study¹⁰⁷ investigated the effects of ablating S1 on monkeys trained to categorize the speed of moving tactile stimuli. After the lesion, the animals carried on with the task and were still able to detect the stimuli — they pressed the push buttons after stimulus offset and their reaction times were remarkably normal, as in pre-lesion trials. However, their capacity to categorize decreased, essentially to chance levels¹⁰⁷. Referring to the train analogy, this is as if the motor plan (presumably triggered by the preserved detection mechanisms) proceeded according to schedule, but the switch at the 'Y' junction did not work.

CENTRAL PATTERN GENERATOR (CPG). A circuit that produces self-sustaining patterns of behaviour.

REACTION TIME

The period of time between the detection of a stimulus at a sensory receptor and the performance of the appropriate response by the effector organ.

The second result that fits this analogy comes from the visual discrimination task in which the direction of movement of a random-dot display is determined¹⁰⁸. Seidemann and colleagues applied intracortical microstimulation while monkeys viewed the display. Current was injected in an area that processes visual motion. When microstimulation coincided with the visual stimuli, it biased the monkey's responses, as previously observed³⁴. But when microstimulation was applied slightly late or slightly early relative to the visual stimulus, it had no effect¹⁰⁸. This implies that the task proceeded according to an internal schedule, and that sensory information was blocked or ignored outside a certain time window. In the train analogy, this corresponds to pushing the switch when the train is not there.

A complementary approach to the problem of characterizing a neural population within the sensory-motor spectrum is provided by REACTION-TIME tasks¹⁰⁹. Cook and Maunsell¹¹⁰ recently made recordings from monkeys performing a detection task in which the onset of a visual stimulus triggered a motor reaction. These authors measured the degree to which neuronal responses covaried with the monkey's reaction times — this measure can be used as an indicator of how 'motor' a given area is. They found that the covariance was considerably stronger in the ventral intraparietal area than in the medial temporal cortex, consistent with the conventional characterizations of these areas as integrative and sensory, respectively. These results constitute another addition to the train analogy: there might be some motor-related mechanisms that accelerate or decelerate the train regardless of the state of the switch. These mechanisms would impact reaction time directly but would affect performance only indirectly, possibly by limiting sensory integration time. By contrast, perceptual mechanisms should have a strong impact on performance (that is, which branch of the junction is chosen) but only a minor effect on reaction time. This is consistent with studies indicating that motor, and not perceptual processes, constitute the main source of variability in reaction time^{111,112}. The train analogy also has some features in common with models of motor reaction in which activity increases linearly until it reaches a threshold, at which point a motor action cannot be stopped^{109,112–115} — the linear increase is akin to the progress of the train along the track. Manipulating the trade-off between accuracy

and response time¹¹⁵, or introducing an additional go/no-go instruction at different points in time^{112,114}, could be fruitful approaches for the future study of the mechanisms that underlie somatosensory discrimination and decision making.

This point is worth emphasizing. The difficulty in unravelling the physiological mechanisms of sensory discrimination — exactly how the comparison is implemented — is not so much a matter of designing a circuit that can compare two signals. 'Winner-takes-all' behaviour is well documented in several models^{116–118}, and a recent study¹¹⁹ extends this approach to a high level of realism. In it, two neural populations, each with slow, recurrent excitation and independent sensory input, inhibit each other, producing a binary choice that develops gradually. When applied to data from visual-motion discrimination tasks, this model accounts for psychometric curves, reaction-time distributions and some differences between hit and error trials¹¹⁹. A bigger problem, however, might be capturing the flexibility of sensory-motor associations within a highly-distributed system¹²⁰. How does the circuit that underlies flutter discrimination change when sensory input needs to be ignored, as in the visual-instruction control task^{34,35,42}? Why is it that the MPC activity that is evoked during the base stimulation period⁴² does not generate arm movements? How is the response delayed or accelerated¹¹⁵? What happens when the association between discrimination outcomes and push buttons is reversed, or otherwise dissociated^{120–122}? Answering these questions will probably require not only more experiments, but also theoretical and computational work.

Concluding remarks

Recordings from several cortical areas have provided a fairly complete panorama of the neural activity that underlies discrimination in the flutter submodality. It seems that the comparison between stored and ongoing sensory information takes place in a distributed fashion — no single area can be identified as the unique site of decision making. Similarly, there seems to be a continuum between sensory- and motor-related activity. It might be that the motor plan established to indicate the response after a discrimination trial already contains two possible outcomes, and that sensory information assists in the selection of one of them. Future studies will develop and test this idea more rigorously.

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Acknowledgements

The research of R.R. was partially supported by an International Research Scholars Award from the Howard Hughes Medical Institute, and grants from the Millennium Science Initiative-Consejo Nacional de Ciencia y Tecnología and Dirección General del Personal Académico-Universidad Nacional Autónoma de México. E.S. was supported by startup funds from the Wake Forest University School of Medicine. We appreciate the technical assistance of A. Hernández in preparing the figures.

Online links

FURTHER INFORMATION

Encyclopedia of Life Sciences: <http://www.els.net/> learning and memory | neural networks and behaviour | somatosensory system | touch
Access to this interactive links box is free online.