The sensory nature of mnemonic representation in the primate prefrontal cortex

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A long-standing issue concerning the function of the primate dorsolateral prefrontal cortex is whether the activity of prefrontal neurons reflects the perceived sensory attributes of a remembered stimulus, or the decision to execute a motor response. To distinguish between these possibilities, we recorded neuronal activity from monkeys trained to make a saccade toward the brighter of two memoranda, under conditions of varied luminance. Our results indicated that during the delay period when sensory information was no longer available, neuronal discharge was modulated by the luminance of the stimulus appearing in the receptive field, and was directly correlated with psychophysical performance in the task. The findings suggest that although prefrontal cortex codes for a diversity of representations, including the decision for an impending response, a population of neurons maintains the dimensional attributes of remembered stimuli throughout the delay period, which allows for flexibility in the outcome of a mnemonic process.

The primate prefrontal cortex (PFC) is a critical node of the network that mediates working memory, one component of which is the ability to retain and mentally manipulate a stimulus over the time scale of seconds[1,2]. Prefrontal lesions in humans[3,4] and monkeys[5,6] produce severe deficits in tasks that require mnemonic representations. Electrophysiological[7–10] and imaging[11–14] experiments confirm prefrontal cortical activation during working memory tasks.

The nature of neuronal activity in PFC during working memory tasks, and whether this activity represents a remembered stimulus or preparation for a response has been a matter of debate. Although neurons in the primate prefrontal cortex discharge while a stimulus is maintained in memory, it has been argued that temporal correlation does not necessarily imply involvement of this activity in perceptual memory[15–17]. Indeed, evidence from recordings in posterior parietal and dorsolateral prefrontal cortex using a delayed discrimination task raises the possibility that neurons represent not the remembered stimulus itself but the decision that determines a motor command[18,19]. The discharge rate of individual neurons in the primate visual cortex correlates well with psychophysical performance in behavioral tasks[20,21], suggesting that sensory representations are mediated by the activity of the neuronal population. No such link between behavior and discharge rate has yet been established for neurons in areas active during the maintenance of visual stimuli in memory.

To explore the relationship between neuronal activity and behavioral performance, we recorded from the dorsolateral prefrontal cortex of monkeys trained to perform a delayed discrimination task. Animals were briefly shown two stimuli of varied luminance, and after a delay period, they made a saccade to the remembered location of the brighter stimulus, which could appear inside or outside the neuron's receptive field. This protocol allowed us to determine whether activity in the delay period, after all sensory information for the formation of a perceptual decision had been provided, was modulated by the sensory attributes of the remembered stimulus, or represented the outcome of the animals' choice[19]. If mnemonic activity represents sensory attributes, firing rates in the delay period should reflect variations in the luminance of the stimulus to be recalled. Our results indicate that mnemonic neuronal responses were not only graded by the sensory attributes of the stimulus, but were also directly correlated with psychophysical performance.

RESULTS

We analyzed activity from 52 isolated neurons in the prefrontal cortex (areas 8 and 46) of two rhesus monkeys (Fig. 1a). The animals were trained to perform a variant of the oculomotor delayed response (ODR) task that has been used to characterize neuronal responses in the prefrontal cortex[9,22,23]. The monkeys fixated on a central spot on a screen, and were presented with two stimuli appearing simultaneously, at diametric positions (Fig. 1b). The stimuli remained on the screen for 0.5 second and were followed by a delay period of 3 seconds. Subsequently, the fixation point turned off, and the animals were trained to make a saccade to the location of the brighter of the two stimuli, which could appear inside or outside the neuron's receptive field. The relative contrast of the two stimuli differed randomly in each trial. The luminance of one stimulus (target) remained fixed in all trials, whereas the luminance of the second stimulus (distractor) varied between the background and the luminance of the target. The animals' percentage of correct responses depended on the contrast ratio of the two stimuli (Fig. 1c and d). They achieved 75% correct responses when the contrast ratio of the distractor relative to the target was 1 to 4%. We selected a range of stimulus luminance over which performance varied in an essentially linear fashion when plotted against the logarithm of the contrast ratio (linear regression, $R^2 = 0.99$, 0.97 for the two animals respec-

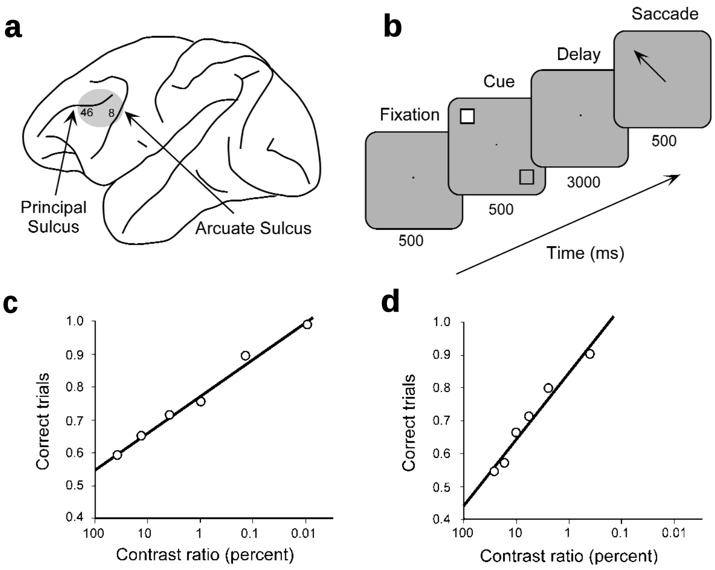


Fig. 1. Macaque brain and behavioral task. (**a**) Recordings were focused on the posterior third of the principle sulcus and the anterior lip of the arcuate sulcus. (**b**) Successive frames represent appearance of the fixation point, presentation of the two stimuli, delay period and saccade. (**c**, **d**) Psychophysical performance of the two monkeys in the behavioral task. Percentage of correct saccades toward the target as a function of contrast ratio between target and distractor. Conditions corresponding to 0% contrast ratio (no distractor) and 100% contrast ratio (equal luminance of the two stimuli) are not shown.

tively). This linear relationship was exploited to determine whether psychophysical behavior was correlated with neuronal activity.

Responses from one prefrontal neuron are shown in Fig. 2. The neuron exhibited a phasic response during the cue presentation followed by a tonic response during the delay, when the target appeared inside the receptive field (Fig. 2a, c and e). The neuron was also active when the distractor appeared in the receptive field, and moreover, its activity was graded based on the distractor luminance (Fig. 2d and f). In each case, the neuron's activity in the delay period represented the stimulus that appeared in its receptive field, regardless of whether the animal made a saccade toward it or away from it. This was representative of our population, although we did observe some neurons, particularly those with strong pre-saccadic responses, that only reflected the animal's motor response. Most neurons in our sample maintained activity above the baseline during the delay period when a distractor appeared in the receptive field, although the animal made a saccade away from the receptive field (Fig. 3). The effect was statistically significant for 42% of the neurons (45% and 25% for the two animals respectively; *t*-test, $p < 0.05$).

We tested the effect of stimulus luminance on neuronal responses by performing a regression analysis (Fig. 4). The delay period activity of each neuron was normalized to the average response to the target in the receptive field, then responses from all neurons were used for the regression. Delay period activity was not significantly modulated by the presence of a distractor outside the receptive field, when the target appeared inside (Fig. 4a; regression analysis, $p > 0.3$). However, delay period activity was significantly dependent on contrast ratio when the distractor appeared in the receptive field (regression analysis, $p < 10^{-5}$). To ensure that this effect was not due to eye-movement parameters, we repeated our analysis after including saccade metrics in the regression model. The effect of contrast ratio remained highly

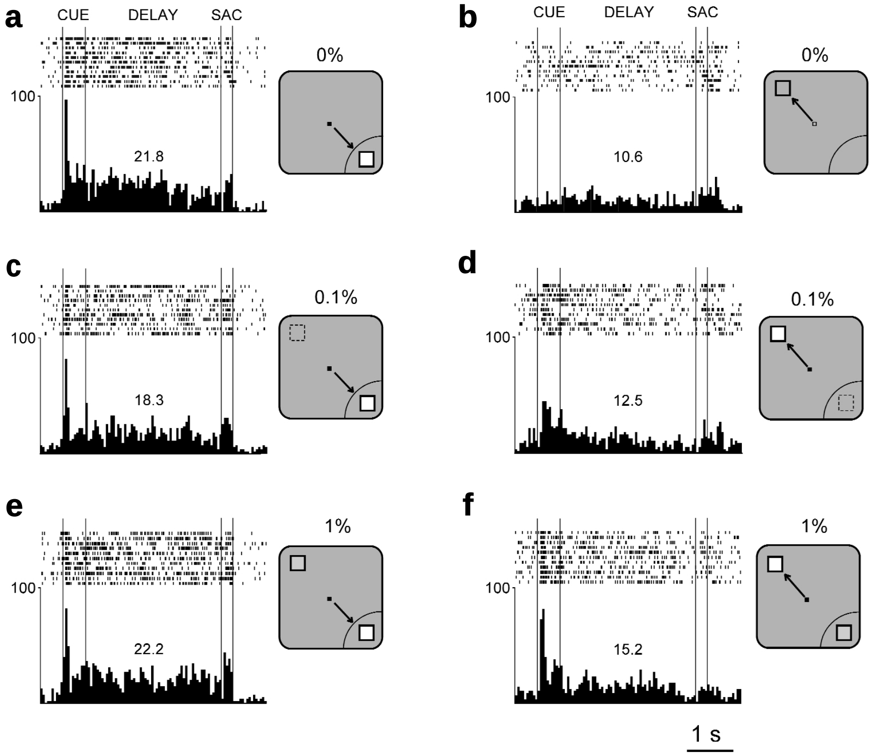


Fig. 2. Single neuron responses were modulated by stimulus contrast. (**a–f**) Rasters and PST histograms represent responses of a single prefrontal neuron to six stimulus conditions (right). Only correct trials are shown. Higher contrast ratios represent brighter distractors. The average discharge rate during the delay period is indicated above each histogram. The neuron is active during the cue and delay periods when a stimulus appears in its receptive field, whether the animal makes a saccade toward it (**a**, **c**, **e**) or not (**d**, **f**). Values of contrast ratios were rounded; actual values, 0.13% and 0.96%.

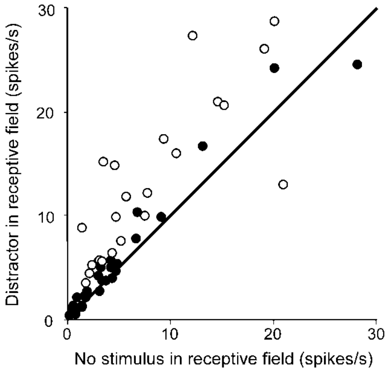


Fig. 3. Distractors evoked delay-period responses for most neurons tested. Each point represents responses of one neuron in the delay period. Abscissa, activity recorded during the presentation of a sole target stimulus outside the receptive field. Ordinate, activity recorded during the presentation of the brightest distractor in the receptive field. White circles, neurons with significantly different responses in the two conditions (*t*-test, $p < 0.05$).

significant ($p < 10^{-5}$), indicating that the modulation was independent of the motor response.

This analysis indicated that the average activity in the delay period was modulated by the contrast ratio of a remembered stimulus. It is possible, however, that this sensory representation is transient and that the outcome of the perceptual decision is reflected in neuronal activity later in the delay period. To test this hypothesis, we quantified the probability that neuronal responses can distinguish between a target and a distractor by doing a receiver-operating characteristic (ROC) analysis in successive time windows. The area under the ROC curve was calculated in 250-ms intervals for each neuron and then averaged across all neurons. Our results indicated that the ability to discriminate between a target and distractor was dependent on the contrast ratio throughout the delay period (Fig. 5). A gradual increase in predictive activity as a function of time was also apparent. The effects of both contrast and time on the probability value were highly significant (regression analysis, $p < 10^{-5}$). The interaction between time and contrast was not significant (two-way ANOVA, $F_{66,4284} = 0.57$, $p > 0.9$), although the ANOVA test confirmed that the main effects of both contrast and time were significant (contrast, $F_{6,4284} = 12.7$, $p < 10^{-5}$; time, $F_{11,4284} = 5.1$, $p < 10^{-5}$). This result suggests that discrimination probability can be represented as a linear function of contrast and time.

The results presented so far were based on the analysis of trials with a fixed delay interval. It is possible that the sensory attributes of remembered stimuli modulate responses in the delay period only under these conditions. Neurons may instead represent a motor response if the delay varies randomly, forcing the animal to form a motor plan after the offset of the cue. To test this hypothesis, we recorded activity from 24 additional neurons, tested with a delay period that could vary between 0.15 and 3 s in each trial. The neuron depicted in Fig. 6 was active during the delay period following presentation of a target in the receptive field (Fig. 6a) but not if the target was outside the receptive field (Fig. 6b). The same neuron continued to discharge in the delay period following presentation of a distractor in the receptive field (Fig. 6c) even though the duration of the delay varied randomly from trial to trial. The effect of stimulus contrast across the population was statistically significant when the distractor appeared inside the receptive field (two-way ANOVA, $p < 10^{-5}$) but not significant when the target appeared in the receptive field ($p > 0.3$) as was the case when using a fixed delay interval (Fig. 7).

DISCUSSION

Activity of neurons in the dorsolateral prefrontal cortex during the delay period of a mnemonic task was modulated by the perceived sensory attributes of remembered stimuli, and correlated directly with psychophysical performance in the task. This response pattern cannot be accounted for by factors such as task difficulty or reward expectation, which modulate the firing rate of prefrontal neurons[24–26]. The average population response was not significantly modulated by the difficulty of the discrimination when the target appeared inside the receptive field (Fig. 4a). Indeed, neurons discharged more vigorously when the distractor appearing in their receptive field was identical to the target, the condition that represented the minimum reward expectation (Fig. 4b).

Our experiments addressed whether prefrontal cortical activity represents the formation of a decision to execute a particular response. If that were the case, neural activity should reflect sensory attributes early in the decision process, but only a stereotyped outcome of the animal's choice after all sensory information had been accumulated[19,27]. Responses to all contrast levels should therefore be identical and not differentiable during the delay period (Fig. 8, top). Contrary to that prediction, our results indicated a graded pattern of responses related to luminance throughout the delay.

The present findings are in agreement with previous experiments in the dorsolateral prefrontal cortex suggesting that neuronal activity in a mnemonic task represents the remembered visual stimulus, as demonstrated by the anti-saccade paradigm, spatial match-to-sample and conditional response tasks[10,28,29].

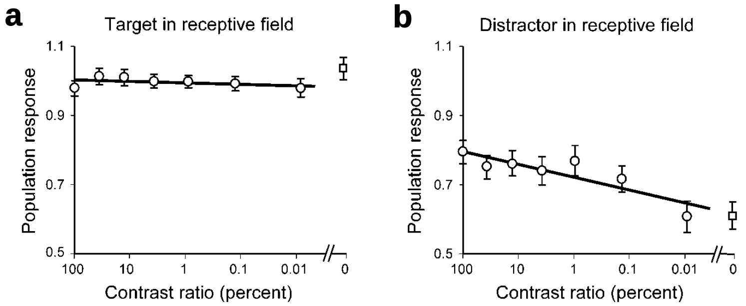
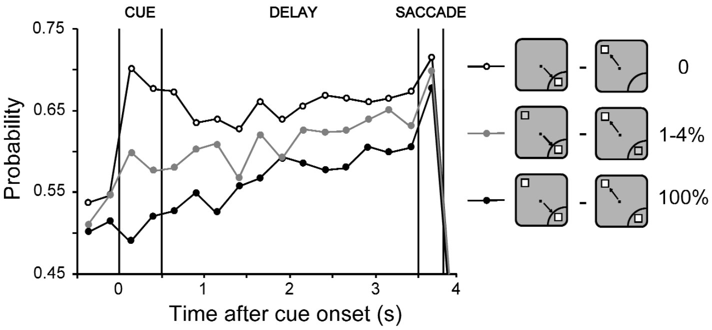


Fig. 4. Population responses were modulated by the luminance of the stimulus in the receptive field. Average normalized responses for neurons tested with the range of contrasts shown in Fig. 1c ($n = 39$, from one monkey). Line, regression of discharge rates on the logarithm of contrast ratio. (**a**) Trials with the target appearing inside the receptive field. Regression slope was not significantly different from zero (–0.004, $p > 0.3$). (**b**) Trials with the distractor appearing in the receptive field. The regression slope was significantly different from zero (–0.037, $p < 10^{-5}$). Squares, responses to the target alone (not included in the regression analysis).

Fig. 5. Probability of discrimination between a target and distractor was graded as a function of their contrast ratio. Probability values were computed as the area under the ROC curve in 250-ms windows, then averaged across all neurons. The three curves represent stimulus presentations with no distractor (0% contrast ratio), distractor equal in luminance to the target (100% contrast ratio) and distractor of near-threshold luminance (1–4% contrast ratio).



In each case, most neurons reflect the position of the remembered stimulus rather than the direction of response. Similar conclusions are drawn from experiments in the posterior parietal cortex[30,31], an area that provides direct anatomical input to dorsolateral PFC (but see refs. 32, 33). Studies in the inferior convexity of the PFC also indicate that neurons respond based on the identity of a remembered visual stimulus[34–37], although task demands may modulate the level of activity evoked by the stimulus[38,39]. Experiments using a tactile task further indicate that sensory information is represented in a parametric fashion in the PFC, reflecting the frequency of a remembered vibratory stimulus[40]. A direct link between the sensory attributes of stimuli, delay-period activity of prefrontal neurons, and behavioral performance in a mnemonic task, as established here, provides compelling evidence that dorsolateral prefrontal neurons can mediate the mental representation of sensory information in working memory.

In contrast to these results, previous studies analyzing activity in the delay period of a discrimination task concluded that neuronal responses best correlate with the outcome of a perceptual decision[18,19]. An important caveat in these experiments is that, in an attempt to separate sensory and motor responses, stimuli were always placed outside the neuron's receptive field and instructed a saccade toward or away from it. Therefore, it is possible that the potential of prefrontal neurons to represent the remembered visual stimulus was not assessed in these studies. Neurons presented with stimuli outside their receptive fields may be active in the delay period if the animal is planning a response toward the neuron's receptive field[41]. However, it is questionable whether the activity of neurons with no access to the relevant sensory information is pooled toward the formation of a decision.

How can the results of these discrimination experiments be reconciled with our own? It is likely that the earlier studies recorded from the population of neurons that reflected a motor response[10,29]. We observed such neurons in our own sample, and their activity is reflected in the population average (Figs. 4 and 5). Motor-related neurons represent the impending response as well as the perceptual decision about the brightness of the two stimuli. These neurons tend to discharge in an accelerated fashion before the onset of movement[42], which could account for the fact that the population of PFC neurons best discriminated between the target and distractor at the time interval immediately preceding the eye movement, for each contrast level (Fig. 5). Based on these considerations, we propose that dorsolateral PFC encompasses neurons engaged in at least two separate processes: a sensory representation that remains fairly constant or slowly decays during the delay period, and a response preparation that increases toward the onset of the saccade (Fig. 8). Our present findings favor the view that a motor plan is an emergent property of a network composed in part by neurons sustaining sensory information, rather than involving a discrete decision stage in which sensory parameters are transformed into motor variables by single neurons[43,44].

Our task did not explicitly require the animals to remember the luminance of the stimuli; the subject needed only to discriminate between their relative difference. However, delay period activity did maintain a faithful representation of the perceived sensory attributes of the stimuli, evidenced by its strong correlation with the animals' performance. In this context, delay-period responses to a distractor can be thought of as short-term memory traces for an unattended stimulus. This point is important in interpreting the results of imaging studies that often rely on the comparison of

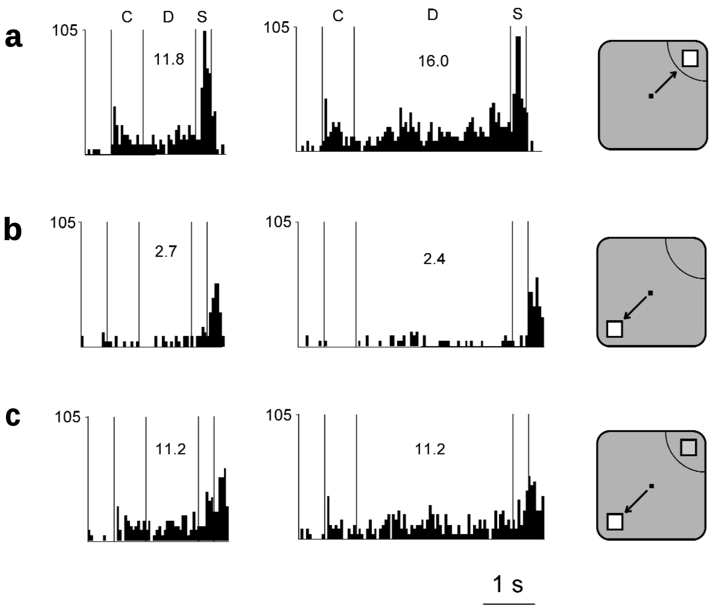
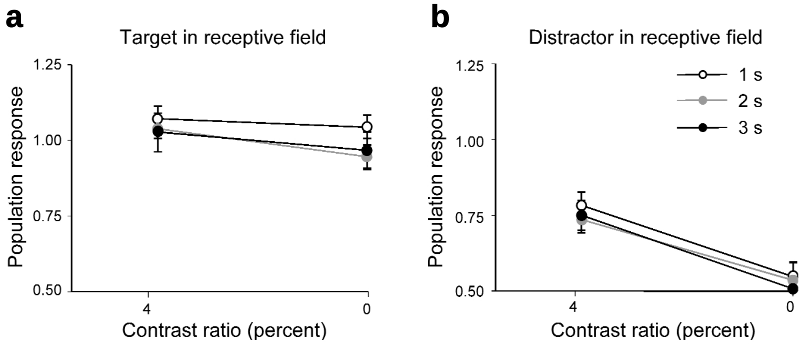


Fig. 6. Individual neuronal responses were dependent on contrast in a variable delay experiment. PST histograms represent responses of a single PFC neuron. (**a**) The neuron was active during the delay period of 1 s (left) or 3 s (right) when the target appeared in the receptive field. (**b**) The same neuron did not respond during presentation of the target outside the receptive field. (**c**) The neuron displayed significant delay period activity following presentation of a distractor (contrast ratio, 4%) in the receptive field.

Fig. 7. Population responses for each contrast level in variable delay period experiment. Points, average normalized responses of all neurons tested with the variable delay task (*n* = 24). Black circles, 1-s delay period; gray circles, 2-s delay period; white circles, 3-s delay period. The effect of distractor contrast was significant only when the distractor appeared in the receptive field. The effect of delay duration was not statistically significant.



passive versus active memory tasks to identify brain areas involved in working memory[17,45,46].

Our results demonstrate the functional capacity of PFC neurons to sustain a representation of the perceived sensory aspects of stimuli in working memory that could be potentially used or manipulated flexibly, and that could serve many options. This nature of neuronal representation in prefrontal cortex is compatible with a role for PFC in executive processes. A response code, in contrast, would limit neuronal activity to a cortical reflex, that is, the obligatory outcome of a sensory–motor association.

METHODS

Behavioral task. All neurons were initially tested with the oculomotor-delayed response (ODR) task[9]. Eye position was monitored with a scleral eye-coil[47]. Neurons exhibiting significantly elevated firing rate in the ODR task were further tested with a discrimination task, as follows. Trials began with the appearance of a point on a tangent screen that the animals were required to fixate on throughout the trial. Two stimuli were subsequently presented for 0.5 s at diametric positions around the fixation target. The stimuli were 1° in size, and they appeared at an eccentricity of 14°, making the discrimination very difficult unless the two stimuli differed considerably in luminance. After a delay period of 3 s, the fixation point turned off and the monkeys were trained to make a saccade to the location of the brighter stimulus (target). The target had a luminance of 110 or 150 cd/m^2 (Michelson contrast, 99%) and it could appear randomly on either spatial location. The luminance of the fainter stimulus (distractor) varied between the background (no visible distractor) and the luminance of the target. The monkeys were rewarded randomly for saccades to either stimulus when the two stimuli were equal in luminance.

Electrophysiological recordings. Monkeys were implanted with a head-restraining device, and an MRI-guided craniotomy was done to expose a circular aperture over the prefrontal cortex. Neuronal activity was recorded using varnish-coated tungsten electrodes (1–4 MΩ at 1 kHz). One to four electrodes were placed in stainless steel guide tubes and independently advanced into the cortex through a set of micromotors (Alpha-Omega Engineering, Israel). Neuronal activity was sampled with 30-µs resolution and recorded waveforms were sorted into separate units using a template-matching algorithm (CED, Cambridge, UK). All animal training, surgeries and experimental procedures were done in accordance with NIH guidelines, and approved by the Yale Animal Care and Use Committee.

Data analysis. Firing rate was calculated in three epochs: cue (0.5 s), delay (3 s following the offset of the cue) and saccade (0.25 s following the offset of the fixation point). Neurons were included in the analysis if they satisfied two criteria. First, their firing had to be significantly elevated from baseline fixation for at least one task epoch (paired *t*-test, $p < 0.05$). Second, responses to a stimulus presented at the two diametric locations of the discrimination task had to be reliably distinguishable from each other (ROC analysis, see below, probability ≥ 0.9). The latter criterion was necessary because multiple neurons with disparate receptive fields were recorded in each behavioral run, and some neurons were tested with stimuli placed at sub-optimal locations (sometimes both in, or both out of the receptive field). The number of neurons that fulfilled the selection criteria in the cue, delay and saccade periods were 22, 25 and 21 for the 3-s delay experiment and 13, 20 and 17 for the variable delay experiment, respectively. Many neurons with predominantly cue or saccadic responses were active during the beginning or end of the delay period. We based the analysis of our results on the entire sample, rather than ignore the contribution of primarily cue and saccade neurons to the delay period activity.

We defined a contrast ratio C as $\Delta L_d/\Delta L_t$ where ΔL_d is the luminance

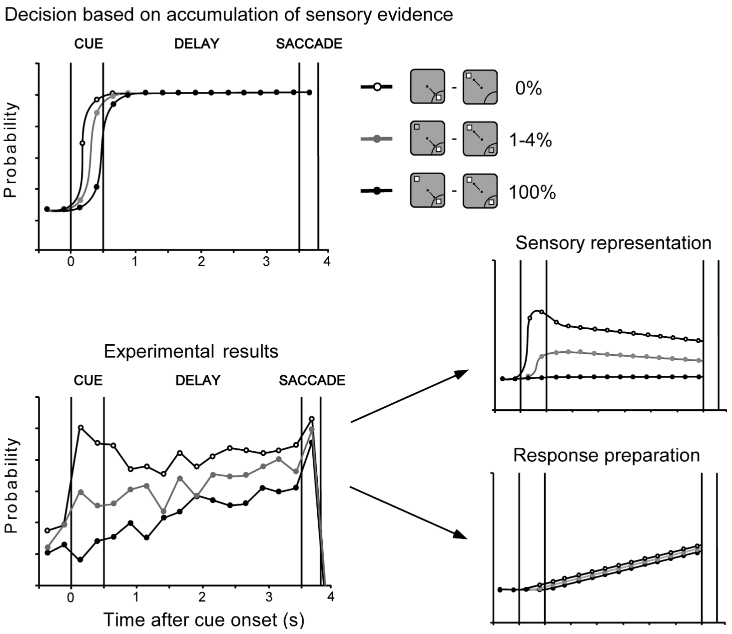


Fig. 8. Model. Top, pattern of ROC probability curves that would be predicted if prefrontal neurons were representing the formation of a decision based on accumulation of sensory evidence. After the presentation of the cue, neuronal responses should only represent the motor decision, and ROC curves should converge. The experimental results (bottom) can be better represented as the sum of two processes: a sensory representation that remains fairly constant or decays slowly during the delay, and a response preparation component reflecting the animal's choice, which increases during the delay.

of the distractor minus the luminance of the background, and ΔL_t is the luminance of the target minus the luminance of the background. We determined the effect of contrast ratio on neuronal firing rate by performing a linear regression using the following model.

$$Y = a + bC \qquad (1)$$

Y represents the firing rate in the delay period of each trial. Firing rates were normalized by the neuron's average firing rate during the delay period following a target stimulus. C represents the logarithm of the contrast ratio. A regression analysis was done separately for the target appearing inside and outside the receptive field. Trials recorded when no distractor stimulus was present were not used for the regression, as they correspond to a contrast ratio of zero, which cannot be transformed into a logarithmic value; all other available trials from all neurons were included in the model.

To ensure that any effect of luminance was not accounted for simply by variations in saccadic eye movements, we repeated the regression analysis including five descriptors of the saccade metrics in the model: latency, amplitude, accuracy, maximal speed and duration. All models were tested with the statistical software SYSTAT (SPSS, Chicago, Illinois).

We used receiver-operating characteristic (ROC) analysis[48] to determine the ability of each neuron to distinguish between a target and a distractor placed in its receptive field. The area under the ROC curve represents the probability that of a given pair of responses, one belonging to a target and one to a distractor, the target will evoke the higher discharge rate. ROC curves were constructed using the spike count in successive 250-ms windows spanning the entire behavioral trial. The time course of the predictive activity was assessed with a linear regression model of the following form.

$$Y = a + b_1C + b_2T \qquad (2)$$

Here, Y represents the area under the ROC curve (probability of correct discrimination) for each neuron, T, the corresponding time from the beginning of the delay period, and C, the contrast ratio, as above.

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