whether the monkey was fixating on a central point or sitting quietly in the postfixation period. Monkey 2 usually fidgeted during the postfixation period; thus, for this monkey, only data from the fixation period were used in the analysis. Similar effects of the position of the fake and real arms were found for both monkeys.
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20. In addition to responding to passive proprioceptive and visual signals, neurons in area 5, especially in the intraparietal sulcus, also respond when the monkey reaches toward visual targets (*17–19, 36*). In a delayed reaching task, the neurons respond during the delay period before the reach (*37*).
21. Of 126 cells significantly affected by the position of the real (contralateral) arm, 53 fired at a higher rate when the arm was on the contralateral side, and 73 fired at a higher rate when the arm was on the ipsilateral side.
22. Seventy-nine cells (46%) showed a significant effect for the real arm only, 3 (2%) showed a significant effect for the fake arm only, and 47 (27%) showed a significant effect for both arms. The remaining 44 (25%) showed no significant effect for either variable. Of the 47 cells significantly affected by both real and fake arm positions, 27 (57%) showed a significant interaction between the two variables.
23. Cells significantly affected by the position of the fake arm were found both in the surface part of area 5 anterior to the intraparietal sulcus (31 of 116 cells, 27%) and in the anterior bank of the intraparietal sulcus (19 of 57 cells, 33%). Though the proportion was higher in the intraparietal sulcus, this difference was not significant ($\chi^2 = 0.52$, $P = 0.47$). Each cell was also tested with a handheld visual stimulus (a ball on the end of a long rod) to determine if it had any explicit responses to moving visual stimuli. Such responses were found in high concentration in the intraparietal sulcus (31 of 57 cells, 54%) and rarely in the part of area 5 anterior to the sulcus (5 of 116 cells, 6%). This relative concentration of visual cells in the intraparietal sulcus was significant ($\chi^2 = 55.16$, $P < 0.0001$) and has been observed before (*38*). Cells that had an explicit visual response to moving stimuli were not necessarily sensitive to the position of the fake arm. Only nine cells shared both properties. This overlap is no greater than that expected by chance ($\chi^2 = 0.14$, $P = 0.71$). Thus, a visual response to the movement of external objects and a response to the visual position of the limb appear to be independent properties encoded by neurons in area 5.
24. On average, for the sample of 173 neurons, the effect of the fake arm (change of firing rate caused by a change in arm position) was 21% of the effect of the real arm. For those 50 neurons significantly affected by the position of the fake arm, on average, the effect of the fake arm was 44% of the effect of the real arm.
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Neurons in Monkey Prefrontal Cortex That Track Past or Predict Future Performance

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Although frontal cortex is thought to be important in controlling behavior across long periods of time, most studies of this area concentrate on neuronal responses instantaneously relevant to the current task. In order to investigate the relationship of frontal activity to behavior over longer time periods, we trained rhesus monkeys on a difficult oculomotor task. Their performance fluctuated during the day, and the activity of prefrontal neurons, even measured while the monkeys waited for the targets to appear at the beginning of each set of trials, correlated with performance in a probabilistic rather than a determinist manner: neurons reflected past or predicted future performance, much more than they reflected current performance. We suggest that this activity is related to processes such as arousal or motivation that set the tone for behavior rather than controlling it on a millisecond basis, and could result from ascending pathways that utilize slow, second-messenger synaptic processes.

A hallmark of primate behavior is the sophistication of its planning across long periods of time, a function for which prefrontal cortex has been suggested to be critical. Nonetheless, all neurophysiological studies of prefrontal cortex have restricted their analysis to neuronal activity during the brief period of the current trial (*1*). In these experiments, we trained monkeys on a difficult oculomotor task, and the monkeys' behavior tended to fluctuate during the day, from streaks in which performance was perfect to streaks in which the monkey's behavior approached chance. Because of this behavioral fluctuation, we were able to ask if prefrontal neuronal activity correlated not only with the monkey's performance on the current trial, but with the monkey's probability of success over a number of trials.

We taught two rhesus monkeys an oculomotor version of the self-ordered task (Fig. 1A) (*2*), which is useful in the diagnosis of frontal deficits in humans (*3*). The task consisted of a set of three increasingly difficult steps (trials). Although the monkeys never performed the task perfectly throughout the day, they reached a plateau on average that made it clear that they had learned the task (monkey #1, around 65%; monkey #2, around 55%; Fig. 1B). The monkeys did not perform uniformly. Instead, their performance fluctuated, with streaks of as many as six to eight consecutive correct sets alternating with epochs of far less accurate performance. We calculated a performance fluctuation function to provide a smoothed estimate of the monkeys' performance over a number of sets (Fig. 1C). The probability of making eight successive correct third-step choices is <0.000006. This high frequency of successful consecutive correct sets reassured us that even when the monkeys' performance approached chance on the average, their poor performance had to do more with disinterest, fatigue, or lack of enthusiasm than with their performing near chance in a random manner. The monkeys worked at a constant rate, with a mean duration for each set of trials of 23 s for monkey #1 and 26 s for monkey #2. We excluded all data after epochs in which the monkey took breaks longer than 2 min, and we only used data for which there were more than one cycle of behavioral fluctuation.

We recorded the activity of neurons in prefrontal cortex, on both sides of the principal sulcus (*4*). Neurons responded to various aspects of the current trial (*5*). A more unusual

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class of neurons had activity in a given epoch which was not related to the current trial, but which correlated with the performance on past sets of trials. Neuronal activity even in the fixation period of the first step reflected the monkey's past performance (Fig. 2). The neuron gave a transient biphasic response to the appearance of the visual cues (Fig. 2A) but was not selective for a given object or a given spatial location. We calculated a neuronal fluctuation function, which did not resemble the performance fluctuation function, but matched the performance fluctuation function shifted five sets earlier (Fig. 2B). We plotted the neuronal fluctuation function for each set against the performance fluctuation function shifted five sets in the past (Fig. 2C) and found a significant linear regression ($r = 0.81$). We analyzed the correlation of this neuron with the monkey's performance shifted in time from eight sets before the current set to eight sets after (Fig. 2D), using a permutation method to determine significance (*6*). The maximum correlation occurred at a shift of −5, i.e., five sets of trials in the past, but the neuron also showed significant correlation with behavior from −6 to −4 shifts. The activity of the neuron did not correlate with the monkey's performance in the current set of trials. Another class of neurons predicted future performance (Fig. 3). The neuron illustrated also had a cue-related response (Fig. 3A), although it did not show any selectivity for object or location. Analysis similar to that for Fig. 2 (Fig. 3, B through D) shows that its activity during the fixation period of the first step correlated best with performance four sets into the future ($r = 0.78$), exceeding the criteria of permuted data. It is important to emphasize that although this neuronal activity correlates with the monkey's performance, the activity predicts the probability of the monkey's successful or unsuccessful behavior rather than determining on a trial-by-trial basis what that behavior will be.

We analyzed the activity of 171 prefrontal neurons from two monkeys (84 from monkey #1; 87 from monkey #2). The activity during the fixation period of the first step of 28/171 (16%) of the neurons showed a significant correlation (14/84, 17% from monkey #1; 14/87, 16% from monkey #2) (Fig. 4A). The probability of 28 neurons each of which has a false significant correlation ($P < 0.05$) occurring in a sample of 171 neurons is $<10^{-10}$ (*7*). Of 14 neurons with significant correlations in monkey #1, eight were "past" neurons and five were "future" neurons, and one had a maximum correlation at 0. Of 14 significant neurons in monkey #2, four were "past" neurons and 10 were "future" neurons. It was striking that only one neuron had a peak correlation at −1, one had a peak correlation at 0, and none at +1, although five neurons did show significant but not maximal correlations at those times. Instead, there was a trend toward bimodality: one population tracked past performance with an average of 4.0 sets before the current, and a second population predicted future performance with an average of 4.6 sets after the current (Fig. 4A). A correlation of five sets implies a correlation with an event that will occur nearly 2 min in the future (23 s per set × 5 sets = 115 s in monkey #1).

We also investigated whether any of the neurons had a significant negative correlation. We examined the minimum (e.g., most negative) correlation at any shift. The distribution of maximum and minimum correlation coefficients for the permuted data was symmetric: the distributions of absolute values of minimum and maximum correlations were identical. The real data were not symmetric: only 6/171 neurons passed our criterion for significance of negative correlations (Fig. 4B) and this is within chance ($P = 0.19$). We therefore cannot assert that there are anticorrelated neurons, and this asymmetry, in turn, provides further evidence for the validity of our results.

These results differ from most neurophysiological studies in two ways: their absence of direct task-related aspects and their time course. Neuronal activity is usually correlated with the current behavior, or some aspect of the current trial. Activity occurring before stimulus presentation has usually been dismissed as background, and often subtracted from task-related responses, although recent studies have begun to emphasize the importance of this "background activity" (*8, 9*). In particular, prestimulus activity in the superior colliculus (*10*) and the frontal eye field (*11*) correlates with the direction of the saccade on the previous trial. Although we have seen correlations with aspects of the current trial in these experiments, the neurons described here correlate in a general way with the animal's performance over a number of trials, past or future, but not present. This activity is consistent with the neurons tracking or predicting the monkey's probability of success that may be closely related to attentional, arousal, or motivational level, but not with a specific required component of the trial such as memory load or reward expectation. Note that we used only activity during the first step of each set, a trial in which the monkey could make any saccade and could only expect a small reward. It is apparent that the activity

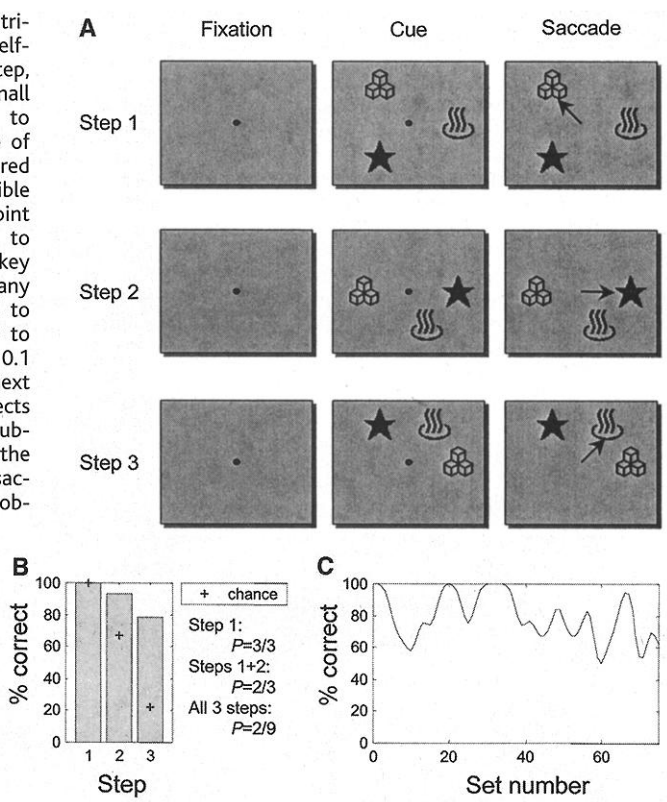

Fig. 1. (**A**) Representative trials of the oculomotor self-ordered task. In the first step, the monkey fixated a small fixation point for 800 to 1200 ms, and then three of six different objects appeared at any of three of six possible positions. The fixation point disappeared after 600 to 1000 ms, and the monkey made a saccade to fixate any of the three. It then had to hold fixation for 680 ms to receive a liquid reward, 0.1 ml in volume. In the next step, the same three objects appeared, but at a new subset of positions, and the monkey had to make a saccade to one of the two objects that it had not chosen in the first step in order to receive a slightly larger reward, 0.2 ml in volume. In the third and final step, the same objects appeared again at a new subset of positions, and the monkey had to make a saccade to the one remaining object that it had not chosen on the previous steps, for a much larger reward, 0.4 ml in volume. If the monkey made a mistake on any step of the task, a new subset of three objects was chosen pseudorandomly from the six and a new set of steps began. (**B**) An example of one monkey's average performance on 75 consecutive sets of trials on one day. Bars depict performance in steps 1, 2, and 3. The plus within the bar shows chance level. (**C**) Performance fluctuation function computed over the same trials as those averaged in (B). To compute the function, we constructed an impulse function for each set (1 for a successful set, 0 for an unsuccessful set) and convolved it with a Gaussian of mean = 0 and $\sigma = 2.0$. For display purposes, we multiplied this value by 100, thus yielding the percentage of responses that would be correct at any given time.

we have described here has little effect on the specifics of the current trial, or on the specifics of the trial in the epoch with which the activity is best correlated.

The self-ordered task is useful for the analysis of frontal deficits (*12*). The interpretation of this deficit is not clear: it could be related to the failure of a memory mechanism as memory load increases throughout the set of trials or to the failure of a self-monitoring mechanism. It could merely be related to the tendency for perseveration, exhibiting the same behavior repetitively rather than changing it to fit the context of the current task, well-described in frontal deficits. Alternatively it could be related to the increased arousal or attention necessary to perform the task as its difficulty increased. The neurons that we have described must be related to some general aspect of the task. Their activity could be related to the motivation or even an emotional correlate of the performance, or to the associated increased demands of arousal or attention in a difficult task with a significant memory load. Neurons that track past performance and success may be useful for monitoring and/or setting the necessity for current performance in the task; neurons that predict future performance may well determine the likelihood of distractibility or changes in behavioral plan.

The correlation of neuronal activity in the prefrontal cortex with general probabilities of behavior with significant time lags, rather than with the details of the current trial may provide the cortical neurophysiological function of ascending pathways such as the modulatory dopaminergic and/or noradrenergic pathways. Usher *et al.* (*13*) showed that the activity and synchrony of neurons in the locus coeruleus correlate with the monkey's performance. The ascending pathways are clearly important to prefrontal function. Subcortical aminergic areas project diffusely to prefrontal cortex and receive input from it (*14*). A few studies suggest a functional role for them on prefrontal activity: antagonists change the properties of prefrontal

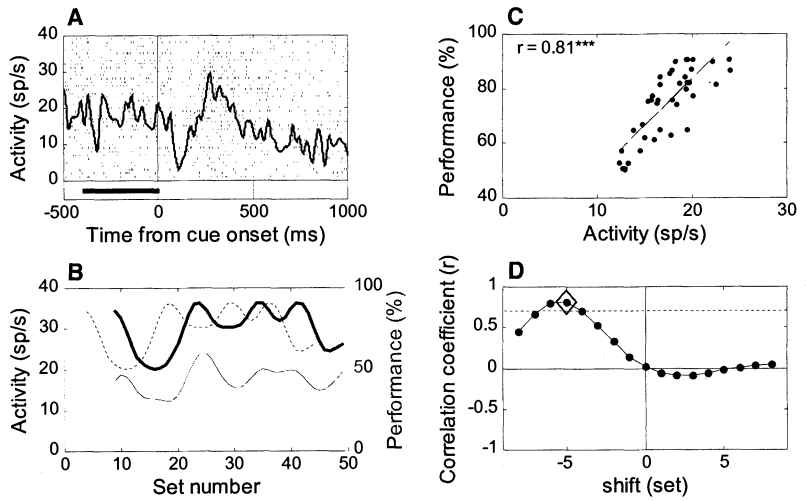

Fig. 2. An example of prefrontal neuron reflecting previous performance. (**A**) Peristimulus raster and spike probability density histogram (solid line) of unit activity, synchronized on cue appearance. There is a weak biphasic response to the cue onset that is not specific for object or spatial location. Horizontal bar delineates fixation period. (**B**) Neuronal and performance fluctuation functions plotted against set number. Thin solid line: Neuronal fluctuation function, computed by convolving mean activity in the fixation period of the first step of each set with a Gaussian of mean = 0 and σ = 2.0. Dotted line: Original performance fluctuation function. Thick solid line: Performance fluctuation function shifted five sets in the past. Note the striking similarity between the neuronal and the shifted performance fluctuation functions. (**C**) Average activity in the fixation period of the first trial of each set (ordinate) plotted against the performance fluctuation function (abscissa) shifted five sets before the neuronal activity. Straight line is the linear regression of the data (r = 0.81). (**D**) Correlation of neuronal activity with data shifted in time. Each point represents the correlation coefficient of neuronal activity with behavior shifted the number of trials at that point on the ordinate. The diamond is the maximum correlation coefficient. The dashed line defines the one-sided 95% confidence limit for the set of random shuffles by the permutation method.

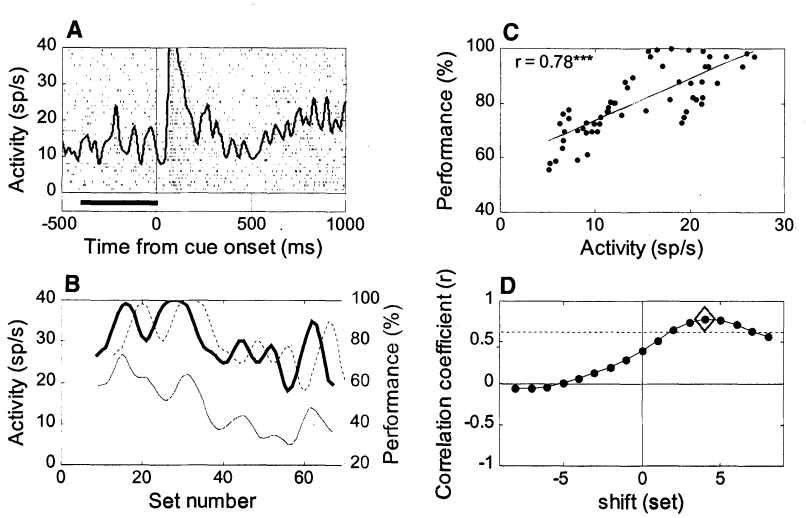

Fig. 3. An example of prefrontal neuron predicting future performance. (**A**) Raster and histogram synchronized on cue onset. (**B**) Neuronal (thick solid line), actual performance (dotted line), and shifted (thin solid line) performance fluctuation functions. The shifted function is shifted four sets into the future. (**C**) Neuronal activity plotted against correlation four sets in the future. (**D**) Correlation of neuronal activity with data shifted in time. Symbols for all panels are identical to those in Fig. 2.

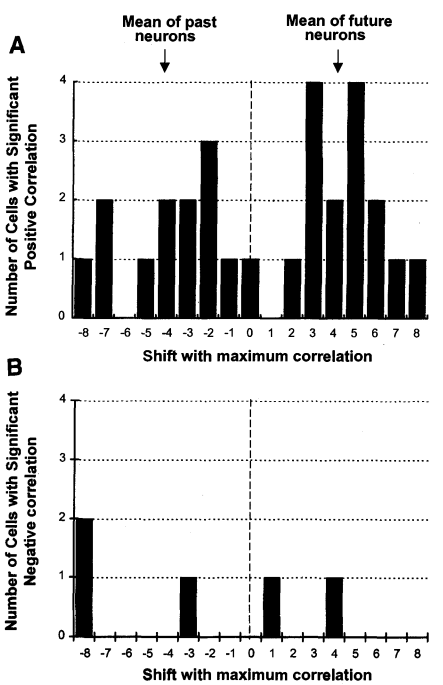

Fig. 4. Distribution of significant maximum correlations as a function of shift. Each bar has the number of neurons whose maximum correlation occurred at a given shift level. (**A**) Neurons with significant positive correlation coefficients in the fixation period. (**B**) Neurons with significant negative correlations.

neurons in monkeys performing memory tasks (*15–17*); extracellular dopamine increases when a monkey performs a delayed alternation task, a classic task which has been shown to require the prefrontal cortex (*18*). Because these ascending systems work through second-messenger pathways, these synaptic effects can take place over minutes rather than the few milliseconds needed for direct short-term synaptic processes and may explain the time lags seen in our data (*19*). One can easily postulate that our "past" neurons receive feedback from the task-related neurons that accomplished the task, and we can also easily postulate that our "future" neurons feed forward to neurons that will be responsible for accomplishing the task. If those projections include a second-messenger step, then we would expect to see the delays that we have demonstrated.

The activity that we have demonstrated in the prefrontal cortex may set the tone for behavior in a general way, similar to that accomplished by stimulants, fatigue, enthusiasm, arousal, or other influences through ascending pathways. The critical result of these experiments is the demonstration of a tonic signal in prefrontal cortex that changes across minutes rather than milliseconds, and which predicts or tracks the probability of past or future success rather than the actual details of the behavior itself.

References and Notes

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2. We prepared two rhesus monkeys (*Macaca mulatta*) weighing 7 to 11 kg, using standard sterile surgical techniques and isoflurane/ketamine anesthesia, for head restraint and physiological recording. The National Eye Institute Animal Care and Use Committee approved all animal protocols, which were in compliance with the NIH/ILAR/PHS *Guide on the Care and Use of Laboratory Animals* (National Academy Press, Washington, DC, 1996).
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5. Current trial-related neurons included visual neurons selective for stimulus location and/or target pattern, movement neurons selective for saccade direction, and neurons whose activity was modulated by the current step level [R. Hasegawa, A. M. Blitz, M. E. Goldberg, *Soc. Neurosci. Abstr.* **25**, 366 (1999)].
6. To adjust the significance for the 17 correlation coefficients (one for each shift), we convolved 500 random permutations of the impulse function for each set with the same Gaussian distribution used to calculate the real fluctuation functions, and determined the maximum correlation of the neural data with each permuted fluctuation function. A histogram of these values provides the permutation distribution of the maximum correlation under the null hypothesis of no effect. Only when the maximum correlation coefficient of the original performance fluctuation function and neural data exceeded 95% of the permutation distribution values did we declare a peak correlation coefficient to be significant. This method is called the permutation method and carefully avoids the multiple hypothesis tests that 17 correlation coefficients on each neuron would ordinarily generate.
7. If the probability of a false significant correlation coefficient is 0.05, the probability obtaining at least 28 false significant correlations out of 171 independent neurons is $<10^{-10}$ by the normal approximation to the binomial probability distribution.
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