Dynamics of Neural Population Responses

in Prefrontal Cortex Indicate

Changes of Mind on Single Trials

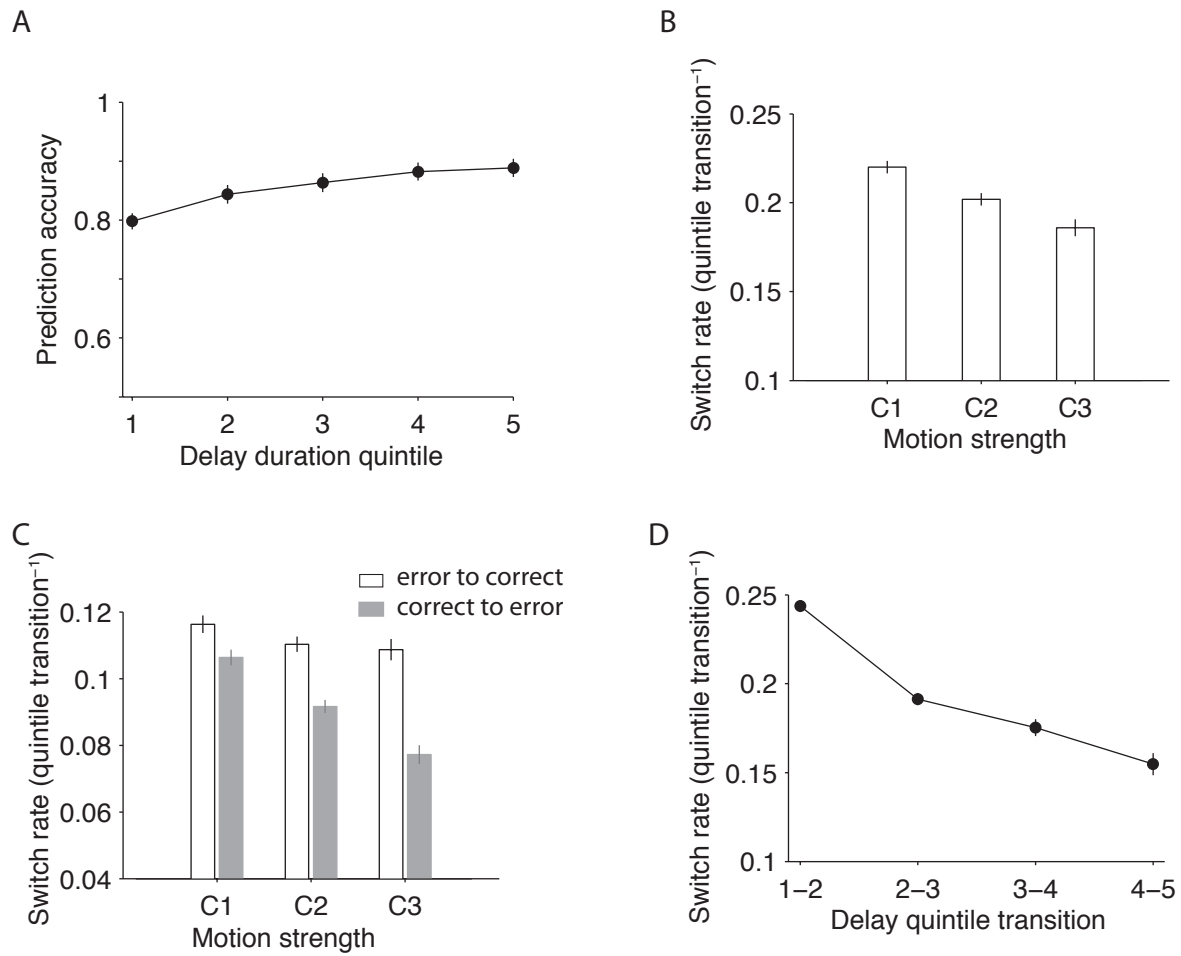**Roozbeh Kiani, Christopher J. Cueva, John B. Reppas, and William T. Newsome**

Figure S1. A single discriminant hyperplane is adequate to achieve reliable prediction of choices and changes of mind for all delay quintiles, Related to figure 4. (**A-D**) Same as Fig. 4A-D but for a single logistic model trained and cross-validated for the last 87-100 ms of the delay period of all trials. See Experimental Procedures for details.
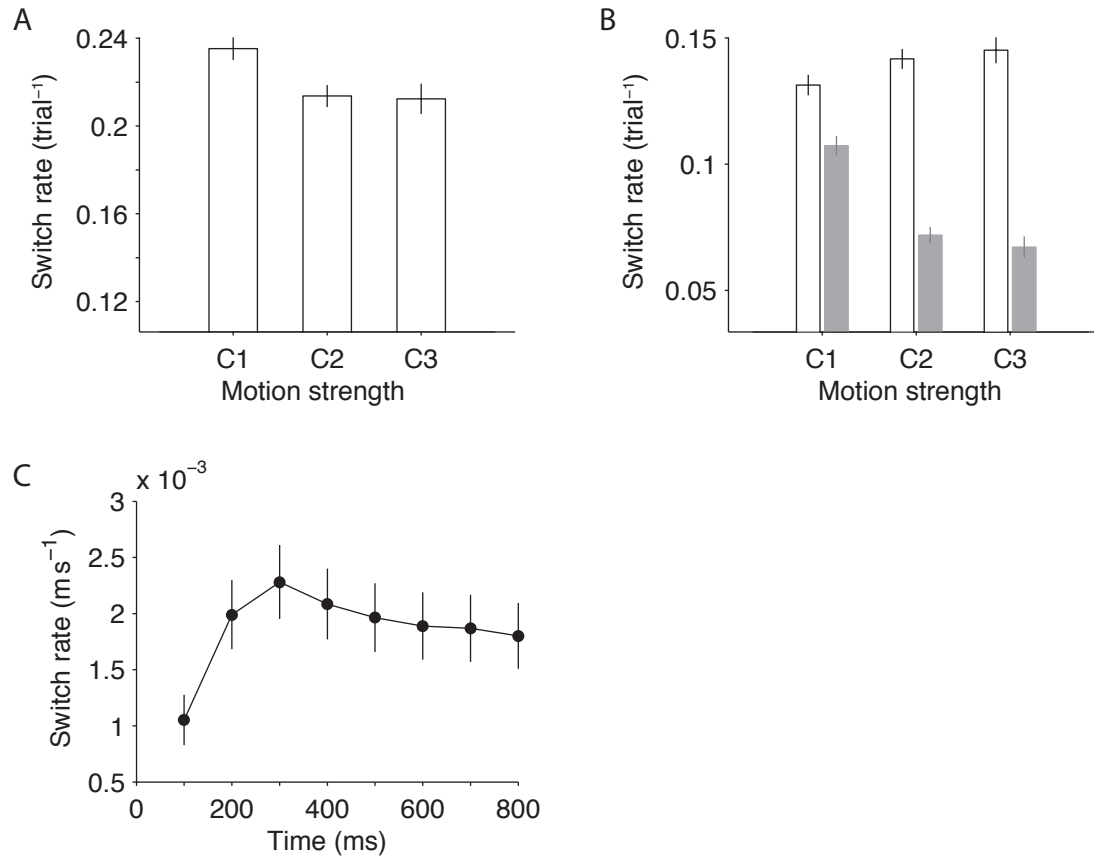
Figure S2. Changes of model DV during motion viewing conform to expected behavioral properties of changes of mind, Related to figure 4. (**A-C**) Same as Fig. 4B-D but for the motion-viewing period. See Experimental Procedures and Results for details.

Supplemental Experimental Procedures

We recorded from populations of neurons in the prearcuate gyrus of two macaque monkeys while they performed a direction discrimination task. All training, surgery, and recording procedures conformed to the National Institutes of Health Guides for the Care and Use of Laboratory Animals and were approved by the Stanford University Animal Care and Use Committee. Due to the similarity of results across the monkeys we pooled the data for all analyses to increase statistical power.

Behavioral task. Figure 1A illustrates the sequence of events on each trial. Each trial began with the appearance of a central fixation point (FP; 0.3° diameter) at the center of the display monitor. The monkey was required to maintain gaze within ±1.5° of FP as long as it was visible on the screen. Eye position was measured with a scleral search coil (CNC Engineering, Seattle, WA), and inappropriate fixation breaks resulted in termination of the trial.

After the monkey fixated on the central fixation point, two targets appeared on the screen (T_1 and T_2). After a 250 ms delay, a random dot motion stimulus was presented for 800 ms and was followed by a delay period of variable duration. At the end of the delay period the FP disappeared (Go cue), instructing the monkey to report the perceived motion direction by making a saccadic eye movement to one of the targets. For a valid response the monkey's saccade was required to land within 2-4° of the target (depending on target eccentricity). In 10 of 15 sessions the two targets were positioned on opposite sides of the screen (T1 contralateral, T2 ipsilateral). On the remaining 5 sessions both targets were positioned contralateral to the recorded hemisphere (T1 and T2 were randomly assigned). On each trial, motion direction was either toward T1 or T2. We controlled the difficulty of the trials by varying the percentage of dots moving coherently in the same direction (motion strength or coherence) as described previously [S1, S2]. The set of motion strengths for each monkey were chosen to afford a wide range of accuracies, from chance to perfection. For monkey 1, the set included 0%, 2.5%, 5%, 10%, 20%, and 40% coherence. For monkey 2, the set included 0%, 1.2%, 2.4%, 4.8%, 9.6%, 19.2%, and 38.4% coherence in most sessions. For two sessions we tested slightly different sets: 0%, 6%, 12%, 24%, and 48% coherence in one session, and 0%, 1%, 2%, 4%, 8%, 16%, and 32% coherence in the other. The motion direction and strength varied randomly from trial to trial, but were fixed within each trial. The monkey received a liquid reward for choosing the target that corresponded to the motion direction. For 0% motion strength the monkey was rewarded randomly on half of the completed trials irrespective of the direction of the choice.

The variability of the delay period duration plays a crucial role in our analyses because it provides an objective means to test the accuracy of our neuronal model predictions about the subject's impending choice. Different delay durations were used in various sessions, permitting useful tests of the robustness of our results. In seven sessions the delay duration of each trial was drawn randomly from these five values: 323 ms, 510 ms, 698 ms, 885 ms, and 1073 ms. In six sessions the delay durations were 673 ms, 760 ms, 848 ms, 935 ms, and 1023 ms. In one session they were 473 ms, 560 ms, 648 ms, 735 ms, and 823 ms; and in the last session they were drawn randomly from several discrete values in the range 300-1500 ms. None of our results strongly depend on the exact delay durations used in each session. We therefore present aggregated results across sessions.

The 15 sessions used in this study were chosen based only on the reliability of recordings, number of trials (>1000), and number of recorded units (>150). The dataset consists of 20938 trials and 3257 units.

Neural recording. The monkeys were implanted with 96-channel microelectrode arrays (electrode length=1.5 mm; spacing=0.4 mm; Blackrock Microsystems, Salt Lake City, UT) in the prearcuate gyrus (Fig. 1B). Neural spike waveforms were saved online (sampling rate, 30 kHz) and sorted offline (Plexon Inc., Dallas, TX). To improve the quality of sorting we used customized algorithms to remove recording artifacts that were registered by a large number of electrodes. Also, we merged redundant spike waveform clusters based on waveform shapes, firing rates and inter-spike intervals. We identified 100-250 single- and multi-units in each session (median=219). Throughout the paper we use the term 'units' to refer to both isolated single neurons and multi-units. All units were retained in our analyses irrespective of their selectivity.

Data analysis. We quantified the time-varying firing rate of each unit on each trial by counting the number of spikes in a sliding 100 ms window (step size=20 ms). We used an L1-regularized logistic regression [S3] to predict the monkey's choice based on neural responses on each trial:

$$Logit\left[P_t(T_1)\right] = \beta_0(t) + \sum_{i=1}^{n} \beta_i(t) r_i(t) \qquad \text{(Equation S1)}$$

where $r_i(t)$ is the firing rate of unit i at time t, n is the number of recorded units and the β coefficients are model parameters. L1-regularization imposes a constraint on the L^1-norm of the coefficients to avoid overfitting. The model was cross-validated by using 90% of trials in each session as 'training set' for fitting the parameters and the remaining 10% as 'test set' to measure the model's prediction accuracy. The best regularization parameter of the model was found by a 10-fold cross-validation within the training set. At any moment in time the model predicts a T_1 choice if $Logit\left[P(T_1)\right] > 0$ and a T_2 choice if $Logit\left[P(T_1)\right] < 0$. The model prediction is correct if it matches the monkey's actual choice at the end of the trial. Fig. 2A shows the model prediction accuracy averaged across sessions. We used a similar logistic regression to gauge the prediction accuracy of individual units:

$$Logit\left[P_{t,i}(T_1)\right] = \beta_0(t) + \beta_1(t) r_i(t) \qquad \text{(Equation S2)}$$

To compare individual units with the population (Fig. 2B-C), we analyzed data from the 100 ms window immediately before the Go cue.

The logistic regression of Equation S1 essentially finds the hyperplane that best separates the population response patterns corresponding to the two choices. The population response pattern at each moment can be envisioned as a point in a high-dimensional space whose axes are the firing rates of individual units. The distance of this point from the discriminant hyperplane (the right-hand side of Equation S1) represents the model belief about the

upcoming choice ($Logit\left[P_t\left(T_1\right)\right]$, the left-hand side of Equation S1). A small distance corresponds to a weak belief and a large distance corresponds to a strong belief. We call this distance the 'model decision variable' (DV) and use the changes in the sign of the DV to identify candidate 'changes of mind' (CoM) for the monkey (Fig. 3C). This approximation is valid especially where the model predicts the monkey's choice accurately.

Our criterion for detecting possible CoM—a simply sign change in the DV—is lenient. It ensures that actual CoM's are not missed, but it can include spurious CoM's due to neural noise or the imperfection of the logistic classifier. We have explored more stringent and complex criteria. For example, a change of mind can be defined as a swing from high certainty for one choice (e.g. large positive DV) to another (e.g. large negative DV). These more stringent criteria have additional degrees of freedom (e.g., criterion on the magnitude of DV) and can be fine tuned to reduce the number of detected CoM's. We explored this space, but the results reported in this paper are not critically dependent on the choice of criteria. For all analyses in this paper, therefore, we employed the simple sign change criterion to avoid additional degrees of freedom and fine-tuning of results.

To determine whether putative neural CoM's conformed to properties expected from prior studies of behavioral changes of mind [S4, S5], we analyzed neural CoM statistics during the delay period (after the dots and before the Go cue) when the model prediction accuracy was above 75% (Figs. 2A and 4A). We first divided the trials of each session into quintiles based on the length of the delay period. As explained above, in 14 of the 15 sessions the delay period was chosen randomly from five distinct values. Therefore the trials in each quintile of a session had identical delays and our grouping did not create spurious boundaries or mix trials with variable delay durations. In contrast to the "sliding window" analysis described above (e.g. Fig. 3), here we calculated the predicted decision (sign of the DV) independently for each delay period quintile. We retrained the logistic model (Equation S1) separately for the trials in each quintile using the last 100 ms of their delay period. For the sessions where the time difference between consecutive quintiles was less than 100 ms, we slightly reduced the size of the window for the calculation of firing rates (87 ms) to ensure no overlap between the quintile models. We then calculated the number of neural CoM's observed on each trial. For trials with the shortest delay periods (first quintile) it was impossible (by definition) to detect a CoM since only a single DV was calculated. For trials of the second quintile, a single opportunity for a CoM occurred, two opportunities for trials of the third quintile, and so forth. Importantly, the high overall prediction accuracy of the model (>75% correct) for trials of the shortest duration (first quintile) creates confidence that the DV calculated within each quintile of longer trials accurately estimates the choice the animal would have made had we stopped those trials earlier. It is thus reasonable to consider neural CoM's detected on long trials to be real changes in the decision state of the animal even though we have no direct behavioral readout of the hidden decision state on these trials. Quantitative analyses in Figure 4 (see equations below) measured CoM statistics for those longer-duration trials (second and higher quintiles).

The results presented in this paper were not critically dependent on training separate models for different delay periods. The discriminant hyperplanes calculated for different delay quintiles were closely related to each other. Consequently, training and cross-validating a single model based on the last 87-100 ms of the delay period of all trials replicated all key results (Fig. S1).

To identify candidate CoM's during the motion-viewing period (Fig. S2) we used the changes in the sign of the decision variable, calculated from the models trained on all trials of a session (Fig. 3). In contrast to the delay period, we could not independently verify the choice-predictive accuracy of CoM's during the motion-viewing period because the motion duration was the same for all trials. A priori, candidate CoM's based on only a DV sign change will be less reliable during the motion-viewing interval due to the lower overall accuracy of the model predictions early in the trial (Fig. 2A). To compensate for this reduced accuracy we used a more stringent criterion. To quantify the frequency and direction of CoM for different motion strengths (Fig. S2A-B), we required the sign of DV to persist for 150 ms before and after a sign change ('persistence window') to qualify as a CoM. To quantify the time course of CoM (Fig. S2C), we reduced this requirement to 75 ms to increase the number of independent estimates of the decision state during motion viewing. The trends in Fig. S2A-B are robust to variations of the persistence window. The trend in Fig. S2C, however, is sensitive to the duration of the persistence window and should be interpreted cautiously; larger windows reduce and even abolish the decline of CoM frequency in the late motion-viewing period. This occurs because long persistence windows impose a sterner criterion for measuring decision states and detecting CoM's, which inevitably delays CoM's to later stages of the motion viewing interval and makes the decision state less likely to change once established. We have observed similar sensitivity to window size in simulations (data not shown).

To test whether the frequency of CoM's during the delay period varied with the stimulus strength we used a linear regression model:

$$\eta = \beta_0 + \beta_1 C + \beta_2 q \qquad \text{(Equation S3)}$$

where η is the number of CoM detected by the model in each trial, C is the motion strength, q is the quintile that the trial delay duration belonged to (2 to 5), and β_i are the regression coefficients. Only trials of the second and higher quintiles contributed to the analysis; as described above, the first quintile could not have a CoM in the delay period. q was included in the regression to control for the increased probability of CoM detection due to increased number of quintile transitions for longer delay periods.

We used a related linear regression to test whether CoM's were more likely to change the monkey's response from an incorrect to a correct choice for stronger stimuli:

$$\Delta s = \beta_0 + \beta_1 C + \beta_2 q \qquad \text{(Equation S4)}$$

where Δs is the difference between the number of CoM's that move the choice prediction from incorrect to correct and vice versa ($\Delta s > 0$ implies more incorrect to correct). This analysis focused on trials with $C > 0$ in which at least one CoM was detected. Trials with $C = 0$ were excluded because of ambiguity in the definition of a correct response. The null hypothesis is that Δs does not change with motion strength ($H_0 : \beta_1 = 0$). After rejecting the null hypothesis via the linear regression analysis, we used a sign rank test to show that the

median of Δs was larger than zero across all trials used in the regression analysis (significant prevalence of incorrect to correct changes).

To test whether the overall probability of being correct was larger on trials in which CoM's were detected we used the following logistic regression:

$$Logit\left[P(cor)\right] = \beta_0 + \beta_1 C + \beta_2 I + \beta_3 q \qquad \text{(Equation S5)}$$

where I is an indicator variable (0 for trials with no CoM and 1 for trials with CoM). C and q are the motion strength and delay duration quintile, respectively (same as in Equation S3). $\beta_2 > 0$ indicates that the subject was correct more frequently on trials in which CoM's were detected.

We tested the dependence of the probability of changes of mind on time using a logistic regression:

$$Logit\left[P(switch)\right] = \beta_0 + \beta_1 C + \beta_2 q' \qquad \text{(Equation S6)}$$

where q' is the delay quintile in which a CoM could be detected minus one. Only trials in the second or higher quintiles contributed to this analysis because at least two delay bins were required to detect a CoM, as described above. Each trial contributed as many data points as permitted by the length of its delay period (maximum=4). The null hypothesis is that the probability of observing a switch does not depend on time ($H_0 : \beta_2 = 0$).

All completed trials (correct and incorrect) were included in the calculation of discriminant hyperplane and subsequent analyses. The grouping of motion strengths to C_1 ($C \leq 6\%$), C_2 ($6\% < C \leq 20\%$), and C_3 ($C > 20\%$) in Fig. 4, S1, and S2 is for illustrative purposes only. All statistical analyses that are mentioned above were performed using the actual motion strengths of the trials.

Supplemental References

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