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ORIGINAL ARTICLE

From Prior Information to Saccade Selection: Evolution of Frontal Eye Field Activity during Natural Scene Search

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Abstract

Prior knowledge about our environment influences our actions. How does this knowledge evolve into a final action plan and how does the brain represent this? Here, we investigated this question in the monkey oculomotor system during self-guided search of natural scenes. In the frontal eye field (FEF), we found a subset of neurons, "Early neurons," that contain information about the upcoming saccade long before it is executed, often before the previous saccade had even ended. Crucially, much of this early information did not relate to the actual saccade that would eventually be selected. Rather, it related to prior information about the probabilities of possible upcoming saccades based on the presaccade fixation location. Nearer to the time of saccade onset, a greater proportion of these neurons' activities related to the saccade selection, although prior information continued to influence activity throughout. A separate subset of FEF neurons, "Late neurons," only represented the final action plan near saccade onset and not prior information. Our results demonstrate how, across the population of FEF neurons, prior information evolves into definitive saccade plans.

Key words: Bayesian, frontal eye field, planning, prior, saccades

Introduction

Deciding where to look next in the real world is a complex process, as we must rapidly decide between countless options. Prior knowledge about the environment and past behavior can facilitate decisions by focusing finite computational resources on options that have a higher probability of success. For example, if you are currently looking on the left side of the desk for a pencil, it will be most useful to look rightwards next. Using prior information to make preliminary plans about upcoming saccades could be an efficient use of neural resources in the oculomotor system.

To be more precise, in visual search, we define prior information about the upcoming saccade as anything that can influence the saccade decision before the subject has access to new visual

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information. In a Bayesian framework, we can think of the new visual information as the "likelihood," and this likelihood is combined with the prior information to make a saccade decision. In classic neuroscience visual search tasks (Bichot and Schall 1999, 2002), where stimuli are flashed onto the screen, prior information can be any knowledge or biases that can affect the upcoming saccade prior to the stimuli being displayed. In more natural visual foraging (Burman and Segraves 1994; Phillips and Segraves 2010), where a subject is making continuous saccades around a scene, prior information is anything that could affect saccade planning prior to processing the new visual information at each new fixation location. This could include general information about the task or environment, information gathered during previous saccades, search strategies and biases, and more. There are likely many ways in which prior information could affect saccade planning.

Several previous studies have shown that oculomotor structures in the brain utilize prior information for planning saccades (Basso and Wurtz 1998; Dorris and Munoz 1998; Bichot and Schall 1999; Everling et al. 1999; Everling and Munoz 2000; Bichot and Schall 2002; Mirpour et al. 2009). In macaque superior colliculus (SC), neurons show increased pretarget activity (Basso and Wurtz 1998; Dorris and Munoz 1998) when there is an increased probability that a target will be placed in the neurons' receptive fields. For SC neurons (Everling et al. 1999) as well as for frontal eye field (FEF) corticotectal neurons (Everling and Munoz 2000), prior information about the task (whether it is a prosaccade or antisaccade task) affects pretarget activity. Additionally, the identity of targets on previous trials can affect the response of FEF neurons to targets on the current trial (Bichot and Schall 1999, 2002). Thus, there is evidence that prior information affects neural activity at cortical and midbrain levels of the oculomotor system.

However, unlike unconstrained, natural eye movement behavior, most tasks used in previous studies imposed substantial limitations on the available prior information. Rather than eliciting self-guided search behavior, these tasks elicited single saccades instructed by a target. This approach eliminated the ongoing planning of sequences of saccades, which is a function of FEF neurons in natural search conditions (Phillips and Segraves 2010; Zhou and Desimone 2011). For example, monkeys might carry over upcoming saccade plans from previous saccades. Conventional tasks also remove the possibility of ruling out saccade targets based on previous saccades (Mirpour et al. 2009). Finally, these tasks often removed starting fixation locations as a variable. The oculomotor system is modulated by eye position in a manner that favors movement toward the center of the oculomotor range (Paré and Munoz 2001). Thus, by ignoring fixation location, these previous studies also removed a significant source of prior information for constraining the range of potential eye movements. In naturalistic settings, much therefore remains unknown about how the oculomotor system represents prior information and how this representation evolves into a definitive saccade plan.

Here, to explore how prior information affects saccade planning in more naturalistic conditions, we recorded from macaque FEF during a natural scene search task. A subset of neurons, "Early neurons," reflected the probabilities of upcoming eye movements based on the current fixation location, regardless of the actual selected saccade direction. As time elapsed toward the upcoming saccade, the activity of these neurons began to relate more to the impending saccade direction, although the prior information continued to influence activity throughout. There was another subset of neurons, "late neurons" that only coded for the selected action plan shortly before the upcoming saccade and did not represent prior information. Thus, across the population of FEF neurons, we observe how prior information evolves into definitive saccade plans.

Materials and Methods

Many of the methods here, especially for neural data analysis, are the same as in our other recent manuscripts (Glaser et al. 2016; Glaser et al. 2017) and are described in the same way.

Behavioral Paradigms

Experiment

Two monkeys (Monkeys J and K; in previous papers referred to as M15 and M16 (Glaser et al. 2016; Ramkumar et al. 2016)) freely searched for an embedded Gabor target in a grayscale natural scene background, as in (Glaser et al. 2016; Ramkumar et al. 2016). They were rewarded for fixating near the target for 200 ms. If they did not find the target after 20 saccades, the trial ended.

Eye Tracking

Eye movements were tracked with an infrared eye tracker (ISCAN Inc., Woburn, MA, http://www.iscaninc.com/) at 60 Hz.

Saccade Detection

The start of saccades was determined by when the velocity of eye movements went above 80 degrees/sec. The end of saccades was marked by when the velocity fell below 100 degrees/sec. Saccades could only be detected after an intersaccadic interval (latency) of 90 ms. To be conservative about saccades, we only included saccades of at least 5 degrees (so that noise in the eye tracker was not classified as a saccade). Saccades longer than 80 degrees or with duration longer than 150 ms were discarded as eye blinks or other artifacts.

Neural Data Acquisition and Preprocessing

Monkeys J and K were implanted with a 32 channel chronic electrode array (Gray Matter Research) over the FEF. The depth of each individual tungsten electrode (Alpha-Omega) could be independently adjusted over a range of 20 mm. Details about recording locations can be found in Glaser et al. (2016). While discussing recording locations, we want to briefly note that there were many instances in which both Early and Late neurons (see Results) were recorded from the same electrodes at the same depths.

Automatic spike sorting with some manual correction was performed offline using the Plexon Offline Sorter (Plexon, Inc., Dallas). Because any given electrode was often left in place for multiple days, we often recorded from the same neuron across sessions. To make use of this, we combined data from units that persisted across recording sessions on different days. To do this, we manually compared spike waveforms from units recorded at the same site on different days. Generally, we merged units sharing waveform shape (rise/fall characteristics, concavity/convexity, etc.) and time course. Ambiguous cases were not combined.

In Monkey K, we stimulated with the electrodes to verify FEF location (details in (Glaser et al. 2016)). Monkey J continues to be used in ongoing experiments. Since microstimulation would lower the impedance of the array electrodes and harm our ability

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to record neurons, we have not yet administered microstimulation in this animal. While we were not able to confirm the electrode placement for Monkey J, the array was in the same stereotactic location as for Monkey K, and the response patterns were very similar. Thus (in addition to having the array stereotaxically above FEF), we used functional measures to include neurons that were likely in FEF (as in Ramkumar et al. [2016]). We only included neurons that either had visual onset activity or movement activity. To determine whether there was visual onset activity, we compared neural activity in the 100 ms prior to image onset with activity 50 to 150 ms after image onset and to see whether there was a significant difference (Wilcoxon rank-sum test; $P < 0.005$). To determine whether there was movement activity, we looked at perisaccadic time histograms aligned to the start of the upcoming saccade, binned into 8 angular directions (according to saccade direction), with each bin spanning 45 degrees. In any bin, we tested whether there was a significant difference between activity in the 100 ms around saccade onset and a baseline period 300–200 ms before saccade onset (Wilcoxon rank-sum test; $P < 0.005$). In sum, while most of the neurons were likely in FEF, it is possible that some neurons were in nearby areas. After following the above inclusion criteria, we had 104 neurons from Monkey J and 76 neurons from Monkey K.

Behavioral Analysis

We excluded saccades that started or ended outside of the boundaries of the screen. Behavioral data were combined across all sessions.

Statistics of Movement

We defined the angular fixation location, Φ_L, as the initial fixation location (prior to a saccade) relative to the center of the screen (Fig. 1C). We defined Φ as the angular difference between the upcoming saccade direction, Φ_S, and the angular fixation location (Fig. 1), that is, $\Phi = \Phi_S - \Phi_L$.

Latency Effects

Latency was defined as the time from start of fixation to saccade onset. Latencies greater than 400 ms were excluded as outliers, as latencies of this duration could have been due to an undetected saccade.

We computed the mean latency of movements as a function of Φ. When claiming that latencies were lower when making saccades opposite the angular fixation location (when Φ is close to 180°), we did the following test: We calculated the Pearson's correlation between latency and $\left|\Phi - 180^\circ\right|$. We then calculated the P-value associated with the correlation (using a 2-sided one-sample t-test).

We also analyzed differences in latencies between saccades that returned toward the center ($|\Phi - 180^\circ| < 60^\circ$) and saccades away from the center ($|\Phi - 180^\circ| > 120^\circ$), based on the distance of the fixation location from the borders of the screen. To test whether the latency difference between toward-center and away-from-center saccades depended on the distance from the border, we used linear regression to fit the latency of saccades as a function of distance from the center. We then did a 2-sided unpaired t-test with unequal sample variances to analyze whether the slope was less (more negative) for toward-center saccades compared with away-from-center saccades.

Neural Data Analysis

As in our behavioral analyses, we only included saccades that remained on the screen. Additionally, except when noted otherwise, we excluded the first saccade of each trial to remove the confound of the large visual onset activity driven by the appearance of the image.

Smoothed Maps of Neural Activity

For many aspects of the following neural data analysis, we computed smoothed maps of neural activity in relation to some variable (fixation location, previous movement, or the upcoming movement). For instance, we created a map of how neural activity varied over all locations on the screen (see Supplementary Fig. 1 for examples), and a map of how neural activity varied in response to all upcoming saccade vectors. For our maps, we estimated the average firing rate at each point in space using weighted k-nearest neighbor smoothing. As an example, for the saccade variable (previous or upcoming), for each saccade, we found the k nearest saccade vectors (based on Euclidean distance). We then averaged the firing rates associated with each of the k saccades, but with each weighted in proportion to its distance from the given saccade to the d power.

The parameters (k and d) we used to generate the smoothed maps of neural activity are as follows. For the smoothed maps used in the generalized linear models (see section below), k = the smaller of 30% of the number of data points (used in fitting the smoothed map) and 500, $d = 0$. These parameters were found using cross-validation on held out data sets, in order to not inflate the number of significant neurons in the generalized linear model (GLM) analysis. For all other times, k = the smaller of 30% of the number of data points and 400, $d = -0.5$. These parameters were found using cross-validation on the current data sets in order to create as accurate maps as possible. Importantly, all results were robust to a wide range of smoothing parameters.

For any single variable (e.g., fixation location), we can get the associated estimated firing rate, θ_P, by looking up the firing rate for that location on the smoothed map. If, for instance, we want to get the estimated firing rates due to location in a time interval before every saccade, we would get a vector $\boldsymbol{\theta_P}$, which contains the estimate before each saccade. The same can be done to estimate the firing rates due to the upcoming saccades, $\boldsymbol{\theta_{US}}$, or previous saccades, $\boldsymbol{\theta_{PS}}$.

Determining Preferred Directions of Neurons

When determining the preferred direction (PD), we used the 100 ms preceding saccade initiation. Let $\mathbf{Y}$ be the vector of firing rates in that interval for every saccade. We fit a von Mises function to relate the movement directions to the firing rate due to movement:

$$\mathbf{Y} = \alpha \exp\left[\beta \cos\left(\boldsymbol{\Phi}_S - {\Phi_S}^*\right)\right]$$

where $\boldsymbol{\phi}_S$ is the vector of upcoming saccade directions, and α, β, and ${\Phi_S}^*$ are the parameters that get fit. ${\phi_S}^*$ is the PD of the neuron.

When estimating the PD, we only used the time period prior to the first saccade of each trial, when the fixation location was in the center and there was not a previous saccade that was just ending, so these were not confounding factors. Moreover, this makes it so saccades used for estimating the PD were not included in the actual data analyses.

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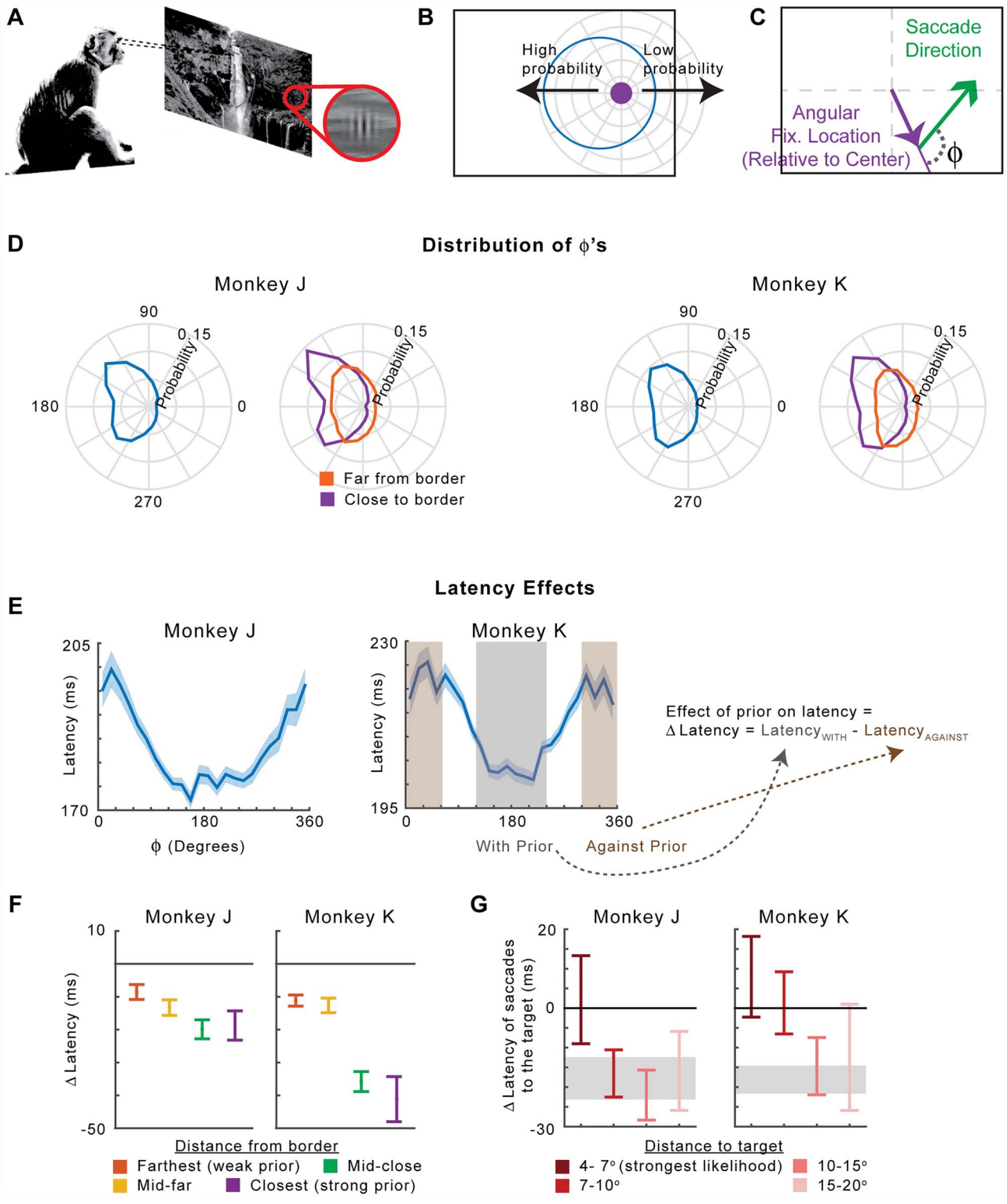

Figure 1. Experiment and behavior. (*A*) Monkeys freely searched for a Gabor target embedded in natural scenes. (*B*) The probability of the direction of the upcoming saccade is dependent on the fixation location on the screen. This is an example where the fixation location is to the right of the screen. (*C*) We quantify the relationship between the upcoming saccade direction and fixation location using Φ, the angle between the angular fixation location (the fixation location vector relative to center) and the upcoming saccade vector. (*D*) The distribution of Φ's for all saccades (blue), and split according to whether the starting fixation location was close (purple) or far (orange) from the border. The close/far distinction was based on being less/more than the median distance from a border. (*E*) The mean latency of saccades as a function of Φ. Saccades back toward the center ("with prior") have $|\Phi - 180°| < 60°$. Saccades away from the center ("against prior") have $|\Phi - 180°| > 120°$. We use ΔLatency (the difference between latencies with and against the prior) as a behavioral metric of the effect of the prior. (*F*) ΔLatency as a function of the starting fixation location's distance from a border. The distance from the border was divided into quartiles. (*G*) ΔLatency for saccades that end near the target, as a function of the initial distance to the target. The shaded area represents the mean +/− SEM of the latency difference for saccades not to the target. In panels *E*–*G*, all error bars represent SEMs.

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Peri-event Time Histograms (PETHs)

When plotting PETHs of individual neurons, we plotted the mean firing rate across saccades. The error bars on PETHs are the standard error of the mean (SEM) across saccades. When plotting the PETHs averaged across neurons, we first calculated the mean firing rate (across saccades of the given condition) over time for each neuron. We then normalized this activity trace for each neuron by dividing by the maximum firing rate of the average trace (across all conditions). We then show the average of these normalized firing rates across neurons. Error bars are the SEM across neurons. The traces in Figs 2, 3, and 7 (and corresponding supplemental figures) are smoothed using a 10-ms sliding window. The traces in Figs 5 and 6 (and corresponding supplemental figures) are smoothed using a 30-ms sliding window, as there are fewer saccades in the conditions in those PETHs. For the PETHs aligned to fixation, only data obtained before the onset of the saccade are included.

PETHs were made for different categories of movements. For the PETHs, saccades toward the PD were defined as those that were within 60° of the PD. Saccades away from the PD were defined as those greater than 120° from the PD. Fixation locations opposite the PD were defined as angular fixation locations greater than 120° away from the PD. Fixation locations near the PD were defined as angular fixation locations less than 60° away from the PD.

Generalized Linear Model

To determine which variables were reflected in the neural activity, we used a Poisson GLM. Let $\mathbf{Y}$ be a vector containing the number of spikes in the time interval we are considering, for every saccade. It has size $m \times 1$.We aimed to predict $\mathbf{Y}$ based on several factors. Unless otherwise noted, we used the fixation location, the previous saccade vector, the upcoming saccade vector, the peak velocity of the upcoming saccade, and a baseline term. More specifically, the covariate matrix $\mathbf{X}$ was:

$$\mathbf{X} = \begin{bmatrix} | & | & | & | & | \\ \mathbf{1} & \boldsymbol{\theta}_{\mathbf{P}} & \boldsymbol{\theta}_{\mathbf{US}} & \boldsymbol{\theta}_{\mathbf{PS}} & \mathbf{v}_{\mathbf{max}} \\ | & | & | & | & | \end{bmatrix}$$

where $\boldsymbol{\theta}_{\mathbf{P}}$, $\boldsymbol{\theta}_{\mathbf{US}}$, and $\boldsymbol{\theta}_{\mathbf{PS}}$ are generated from the smoothed maps (see Smoothed Maps of Neural Activity above). Essentially, these covariates are the expected firing rates from fixation location, upcoming saccade, and previous saccade (respectively) by themselves. Note that these covariates are not just based on angle, as they were when making PETHs—saccade amplitudes and the distance of the fixation location from the center matter. $\mathbf{v}_{\max}$ is the vector of peak velocities of movements. The peak velocity was relative to the expected velocity given the main sequence (Bahill et al. 1975), to control for the changes of velocity with saccade amplitude (as in Glaser et al. [2016]). When we run GLMs during different time intervals, we make separate smoothed maps for these time intervals. Note that when determining whether neurons were "Early" or "Late" (and Supplementary Fig. 13), we only used the previous and upcoming saccade vectors (and a baseline term) as covariates.

Overall, the model that generates the firing rate ($\boldsymbol{\lambda}$; also known as the conditional intensity function) can be written as:

$$\boldsymbol{\lambda} = \exp(\mathbf{X}\boldsymbol{\beta})$$

where $\boldsymbol{\beta}$ is a vector of the weights for each covariate that we fit, and $\mathbf{X}$ is the matrix of covariates, which is z-scored before fitting. If there are j covariates, then $\boldsymbol{\beta}$ has size $j \times 1$. $\mathbf{X}$ has size $m \times j$. Note the use of an exponential nonlinearity to ensure that firing rates are positive. The model assumes that the number of spikes, $\mathbf{Y}$, is generated from the firing rate, $\boldsymbol{\lambda}$, according to a Poisson distribution.

We fit the model weights to the data using maximum likelihood estimation. That is, we found $\boldsymbol{\beta}$ that was most likely to produce the true spike output (assuming spikes were generated from the firing rate in a Poisson nature). Critically, we used (5-fold) cross-validation, meaning that the model was fit to the data using one set of data (the training set), and model fits were tested with an independent set of data (the testing set). Similarly, when calculating the test set covariates for saccade and fixation location (described in Smoothed Maps of Neural Activity), we only used k-nearest neighbors from the training set, to avoid overfitting.

The general approach to determine if an individual covariate influenced neural activity was to test whether model fits significantly decreased when that covariate was removed from the model. First, we ensured that the full model with all covariates had significant predictive power. To determine the value of a model fit, we used pseudo-R^2 (Waldhör et al. 1998; Fernandes et al. 2013), a generalization of R^2 for non-Gaussian variables, which is defined as:

$$R_D{}^2\,(\text{model}) = 1 - \frac{\log L(n) - \log L(\hat{\lambda})}{\log L(n) - \log L(\overline{n})},$$

where $\log L(n)$ is the log likelihood of the saturated model (i.e., one that perfectly predicts the number of spikes), $\log L(\hat{\lambda})$ is the log likelihood of the model being evaluated, and $\log L(\overline{n})$ is the log likelihood of a model that uses only the average firing rate.

Then, to compare the fits between the reduced model where the individual covariate is left out (model 1) and the full model (model 2), we used relative pseudo-R^2, which is defined as:

$$R_D{}^2\,(\text{model 1}, \text{model 2}) = 1 - \frac{\log L(n) - \log L(\hat{\lambda}_2)}{\log L(n) - \log L(\hat{\lambda}_1)},$$

where $\log L(\hat{\lambda}_2)$ is the log likelihood of the full model, and $\log L(\hat{\lambda}_1)$ is the log likelihood of the reduced model.

To determine significance, we bootstrapped the fits to create 95% confidence intervals, and checked whether the lower bounds of these confidence intervals were greater than 0. Note that the pseudo-R^2 and relative pseudo-R^2 values can be less than 0 due to overfitting.

Population Activity over Time Averaged Across Trials

For each neuron (of the category we were plotting), we calculated the firing rate as a function of the relative angular fixation location (Fig. 4). We defined the relative angular fixation location as the difference between a neuron's PD and the fixation location (the PD minus the angular fixation location). We then normalized each neuron by dividing by its mean firing rate, and then averaged the normalized activity across neurons. We then smoothed the activity for plotting using the parameters from the smoothed maps. As with the PETHs, only data obtained before the onset of the upcoming saccade are included.

We also made variants of the above plot. We made plots in which only saccades near or far from the border (split based

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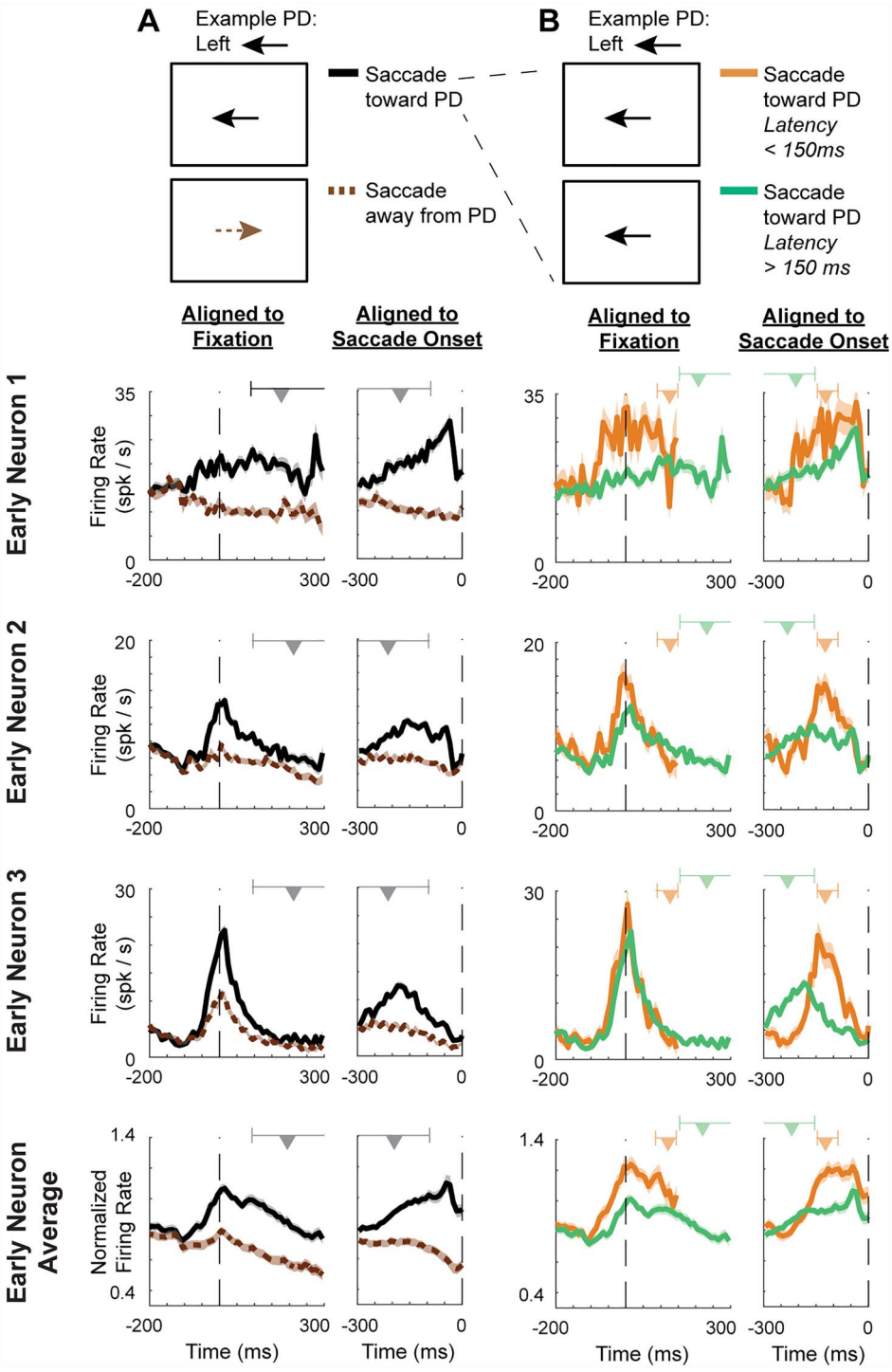

Figure 2. Early times of saccade selectivity, and neural differences related to saccade latencies. PETHs, aligned both to fixation (left part of each column) and the upcoming saccade onset (right part). Rows 1–3 of PETHs: Example Early neurons. Bottom row: Normalized averages of all Early neurons. (A) PETHs of saccades toward the PD (black, solid) versus away from the PD (brown, dashed). Above the PETHs aligned to fixation, we show the range of 95% of saccade initiation times (the upper end of this range is larger than the *x*-axis limit). Above the PETHs aligned to saccade onset, we show the range of 95% of fixation onset times (the lower end of the range is below the *x*-axis limit). The triangles represent the median times. (B) PETHs of saccades toward the PD (like the black trace in panel A), divided further based on saccade latency. Saccades with latencies less than 150 ms are shown in orange, while saccades with latencies greater than 150 ms are in green. Above the PETHs, ranges of fixation/saccade times are shown separately for the separate traces. In all figures, for the plots aligned to fixation, only data obtained before the onset of the saccade are included in the PETHs.

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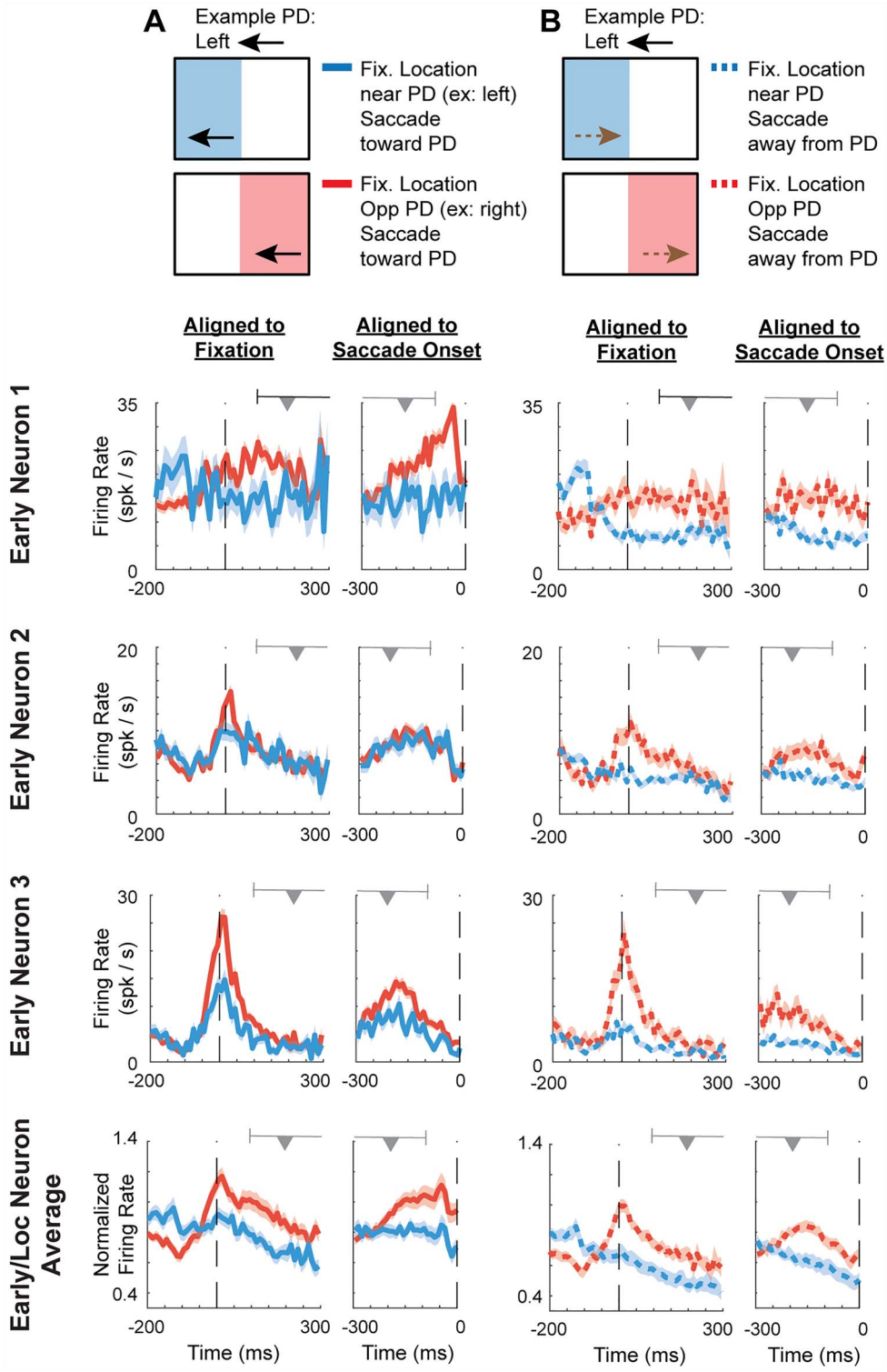

Figure 3. Increased activity in fixation locations that are more likely to result in saccades toward the PD. PETHs, aligned both to fixation (left part of each column) and the upcoming saccade onset (right part of each column). Ranges of saccade/fixation onset times are shown above the PETHs as in Fig. 2. Rows 1–3 of PETHs: Example Early/Loc neurons. Bottom Row: Normalized averages of all Early/Loc neurons. (*A*) PETHs of saccades toward the PD, with a starting angular fixation location near the PD (unlikely that upcoming saccade will be toward PD; blue) versus an angular fixation location opposite the PD (likely that upcoming saccade will be toward PD; red). For example, if the PD is to the left, locations near the PD will be on the left side of the screen (see Methods for details). (*B*) PETHs of saccades away from the PD, with a starting angular fixation location near the PD (blue, dashed) versus an angular location opposite the PD (red, dashed).

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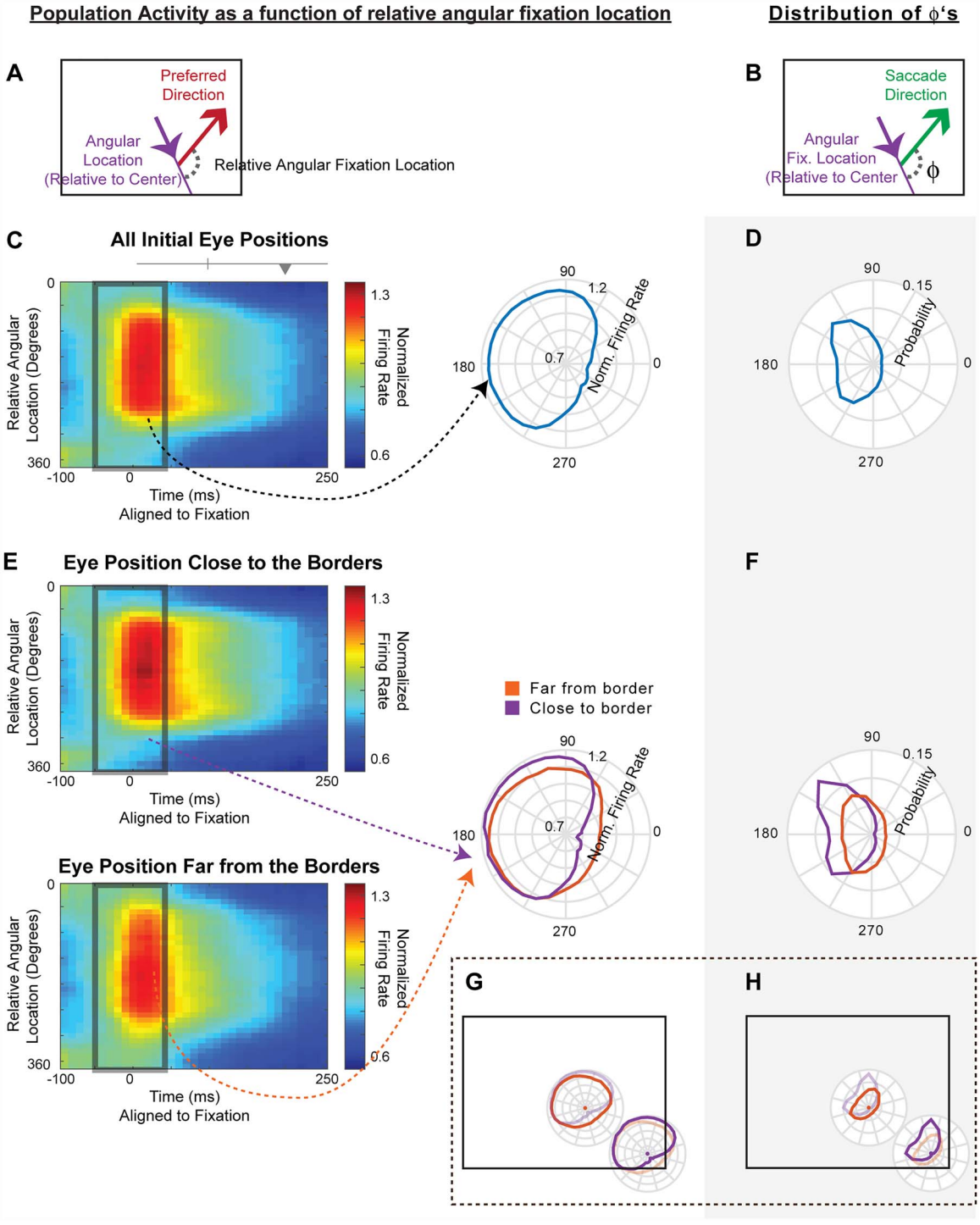

Figure 4. Early population activity reflects the probabilities of upcoming saccades. On the left, we plot the population activity of Early/Loc neurons as a function of the relative angular fixation location. On the right, with a gray background, we show how this relates to the behavioral distribution of Φ's. (*A*) The relative angular fixation location is the difference between a neuron's preferred direction and the angular fixation location (the vector from the screen center). (*B*) Copied from Fig. 1C, Φ is the difference between the upcoming saccade and the angular fixation location. (*C*) On the left, a heat map of normalized activity over time, as a function of relative angular location, averaged across neurons. Ranges of saccade onset times are shown above, as in Fig. 2. On the right, the normalized average activity in the 100 ms surrounding fixation, plotted as a function of the relative angular location. Only saccades away from the PD are included. (*D*) The distribution of Φ's across all saccades combined across monkeys. (*E*) Same as panel *C*, but now separated for initial fixation locations close to the borders (top left, right in purple) and far from the borders (bottom left, right in orange). Only saccades away from the PD are included. (*F*) The distribution of Φ's combined across monkeys, separated by initial fixation locations close to the borders (purple) and far from the borders (orange). (*G*,*H*) The distributions from panels *E* and *F*, respectively, are plotted on set locations, rather than as a function of relative angular fixation location. The distribution corresponding to the set location (e.g., purple when close to the border) is darker.

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on median distance to the nearest border) were included. To control for the correlation between the previous and upcoming saccades, we made a plot where saccades were only used if the angle between previous and upcoming saccades was less than 90°.

Visual Activity

For Supplementary Fig. 14A, we determined whether cells had "visual" activity based on the response when the visual scene was first displayed. For this analysis, for each neuron, we only included trials in which the first saccade after scene onset was away from the neuron's PD, to remove the potential confound of upcoming movement activity. Neurons were classified as "visual" if they met two criteria. First, activity from 50 to 150 ms after scene onset had to be significantly different ($P < 0.05$ using a Wilcoxon Rank Sum test) than activity in the 100 ms before scene onset. Second, to ensure a relatively sharp rise in activity after scene onset, neurons' activities needed to increase by at least 35% within a 50-ms window (e.g., from 40 to 90 ms after scene onset, or 50 to 100 ms).

Results

Behavior

To better understand the evolution of saccade plans during self-guided eye movements, we recorded single units from the FEF while head-fixed monkeys freely searched for a target embedded in natural scenes (Fig. 1A) (Glaser et al. 2016; Ramkumar et al. 2016). Trials either ended when the monkeys made 20 saccades without finding the target, or when they made a saccade to the target and held gaze there to receive a reward. During such a self-guided search, monkeys could use prior information to start planning saccades before they have new detailed visual information at each upcoming fixation location.

One easily quantifiable factor that could provide prior information is the fixation location on the screen. For instance, when the monkey is fixating on the right side of the screen, there are more possible saccadic opportunities to the left, and thus, the monkey might make preliminary plans to go left (Fig. 1B).

To explore this idea, we defined a quantity Φ, which was the angle between the angular fixation location (the fixation location vector relative to the center of the screen) and the upcoming saccade vector (Fig. 1C). When going back toward the center, Φ = 180°, and when going away from the center, Φ = 0°. We found that monkeys are more likely to look approximately opposite of their current angular fixation location (away from the borders of the screen), and the effect is stronger when closer to the border of the screen; Fig. 1D. This is in line with the known finding of center bias in eye movement behavior (Buswell 1935; Tseng et al. 2009; Bindemann 2010). Interestingly, the peak of Φ is not at exactly 180° (i.e., going back toward the exact center). In both monkeys, there is a higher probability of Φ = 135° or Φ = 225° than Φ = 180°. This is because these statistics do not simply reflect the on-screen saccades that are possible (which would be centered on 180°); they also reflect any other strategies and biases of the monkeys.

If prior information based on fixation location matters for saccade planning, we would expect higher probability saccades to have shorter latencies. This was the case; latencies were shorter for saccades made approximately opposite of the angular fixation location (at Φ close to 180°; both monkeys, $P < 1e\text{-}10$; Fig. 1E; see Supplementary Fig. 2 for the distribution of all latencies). This finding is consistent with several previous studies showing that saccades back toward the center have shorter latencies (Zambarbieri et al. 1995; Fuller 1996; Paré and Munoz 2001).

We used this finding to create a behavioral metric for the effect of the prior on behavior. We defined ΔLatency as the latency difference between saccades going "with" the prior (Φ close to 180°) and saccades "against" the prior (Φ far from 180°; Fig. 1E). If the prior is having a stronger effect on behavior, then there should be a larger magnitude latency difference. Indeed, for fixation locations closer to the border, when prior information was more informative, the magnitude of ΔLatency was larger (Monkey J, $P = 4.9e-4$; Monkey K, $P = 7.9e-10$; Fig. 1F). Overall, the monkeys' behaviors suggest that the oculomotor system became more prepared to look in a given direction as the probability of a saccade in that direction increased.

We can also analyze the behavior from a Bayesian perspective, in which prior information is combined with a likelihood (here, the new visual information) to form a decision. When there is strong likelihood information, the prior information should have less influence on the final decision. In our task, when the next saccade is to the target, we can assume that the likelihood was generally very informative, as visual information about the target is driving the decision. Thus, when the next saccade is to the target, we would expect prior information related to fixation location to be less influential.

To test how likelihood information modified the influence of prior information, we again used the ΔLatency metric. For saccades that went to the target, we plotted ΔLatency as a function of the distance to the target. We separated saccades based on the distance to the target, because it is likely that long saccades that landed near the target may have landed there by accident, rather than based on visual information (see Supplementary Fig. 3 for probabilities of making a saccade to the target as a function of distance). We found that for shorter saccades to the target, there was not a significant latency difference between saccades toward and away from the center, suggesting the prior had a limited influence (Fig. 1G). For longer saccades to the target (>7° for Monkey J and > 10° for K), there was a latency difference comparable to saccades not going to the target. This provided behavioral evidence that when there is a strong likelihood (a target nearby that is noticed), location-based prior information is less influential.

Overview of Neural Data Analysis

Next, we analyzed the activity of single FEF neurons while the monkeys performed the natural scene search task. As we were aiming to understand the neural correlates of prior information, we initially focused on activity from around the time of fixation, before new visual information could be gathered. We thus identified "Early" neurons, which were already predictive of the upcoming saccade around the time of fixation. We then determined whether this prior-related activity was based on fixation location in the manner expected by our behavioral results.

We were not only interested in how neural activity related to prior information but also how it related to the final saccade selection. To disentangle between activity related to prior information and saccade selection, we used models that separated activity predicted by fixation location (which was the basis of the prior information) and the actual upcoming saccade. Using these models, we determined how neural activity's relation to prior information and saccade selection evolved as time elapsed

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from fixation to saccade onset. Additionally, as in our behavioral analysis, we took a Bayesian approach to determine the scenarios when early neural activity predicted the final saccade. Finally, we identified "Late" neurons, which were only predictive of the final selected saccade near the time of saccade onset, and not prior information. We have thus shown how natural search behavior can be viewed through the lens of Bayesian integration theory and have mapped it onto subsets of neurons in the FEF.

Early Saccade-Related Neural Activity

To investigate the neural basis of how prior information is used for saccade planning, we first looked at the time at which neurons' activities began to be informative of the upcoming saccades. We used a GLM-based approach (see Methods) to determine how important the upcoming saccade vector was for predicting neural activity, beyond the effects of the previous saccade. We found that 38/180 (21%) of recorded neurons had activity that was significantly modulated by the upcoming saccade in the 50 ms around fixation (before new visual information could be processed), and we classified these as "Early neurons."

We investigated these neurons with PETHs that compared neural activity prior to saccades toward the neurons' PDs versus away from the PDs (Fig. 2A and Supplementary Fig. 5A). When looking at individual neurons' responses (Fig. 2, rows 1–3; see Supplementary Fig. 4 for all Early neurons) and the average across Early neurons (Fig. 2, bottom row, and Supplementary Fig. 5), it was clear that the activity traces began to differentiate early, even before fixation onset. As Early neurons had predictive activity that preceded new visual information, this demonstrates that those neurons represented prior information about upcoming saccades.

If the Early neurons' activities are involved in saccade planning, then we would expect them to relate to the latency of the upcoming saccade, with higher activity predictive of shorter saccade latency (Hikosaka and Wurtz 1986; Rivaud et al. 1994; Dorris et al. 1997; McPeek and Keller 2004). We found that this is the case; for saccades into neurons' PDs, shorter saccade latencies were associated with greater neural activity (Fig. 2B and Supplementary Fig. 5B). This provides evidence that the prior information represented by Early neurons reflects aspects of the saccade planning process.

Prior Information Based on Fixation Location

Our behavioral results suggested that fixation location provides prior information that affects the planning process. Does the prior information encoded by Early neurons relate to the monkey's fixation location on the screen? We again used a GLM-based approach to determine whether fixation location significantly modulated neurons' activities. This model included fixation location and the upcoming saccade (along with the previous saccade), so we could determine the influence of fixation location beyond the saccade that actually occurs. We found that 28/38 (74%) of Early neurons were significantly modulated by fixation location in the 50 ms around fixation. We will refer to these neurons as "Early/Loc" neurons. Thus, fixation location may be used as a source of prior information within many Early neurons.

Since many Early neurons are modulated by fixation location, it is possible that they use fixation location as prior information to determine which saccades are possible or likely from that location. For instance, when the monkey is fixating on the left side of the screen, it may make preliminary plans to move rightward. Thus, if a neuron with a PD to the right was representing prior information about potential upcoming saccades, we would expect this neuron to have greater activity when the monkey's fixation location was on the left side of the screen. Generalizing this example, we would expect Early neurons to have greater activity when the monkey's fixation locations are such that the next saccade is likely to be into the neurons' PDs. This occurs when the angular fixation locations are approximately opposite of the neurons' PDs. Importantly, we should be able to see evidence of this prior information based on location, regardless of the direction of the actual saccade. That is, we want to determine whether the prior information has its own independent influence upon activity.

Using PETHs, we investigated how the activity of Early/Loc neurons depended on the initial fixation location. Indeed, we found that these neurons did have greater activity when the initial angular fixation location was opposite of the neurons' PDs (Fig. 3 and Supplementary Fig. 6; red trace higher than blue trace), which is when the upcoming saccade is more likely to go into the neurons' PDs. This differentiation of activity based on the initial fixation location began prior to fixation, long before the upcoming saccade. This is around the same time these neurons became predictive of the upcoming saccade (Fig. 2 and Supplementary Fig. 5). Importantly, even when controlling for the direction of the upcoming saccade, Early/Loc neurons still had greater activity when the angular fixation location was opposite the PD (Fig. 3 and Supplementary Fig. 6). In other words, neurons had higher activity when the fixation location made a saccade into the PD likely, even if the saccade didn't actually end up going into the PD (Fig. 3B and Supplementary Fig. 6B). This finding, along with the early timing of these neurons' responses, supports the idea that Early neurons use fixation location as a source of prior information to make initial saccade plans.

Beyond looking at when the angular fixation locations are near vs. opposite neurons' PDs, we want to understand how neural activity more specifically relates to locations across the screen. Does this activity relate to the probabilities of saccades that occur from a given location (Fig. 1D)? To investigate this, we tracked the average activity over time, as a function of the "relative angular fixation location". The relative angular fixation location is the angular fixation location relative to the PD of the neuron (Fig. 4A), and is an analog to the behavioral measure Φ (Fig. 1C, Fig. 4B). Importantly, we only included fixation periods preceding saccades that were made away from the neurons' PDs in order to minimize contamination by neural activity that was related to the actual saccade itself.

In the resulting plot, we observed greater activity when the angular fixation location was approximately opposite the neurons' PDs (Fig. 4C and Supplementary Fig. 7A), which agreed with our PETH results. We ran a control to ensure that this relation was not due to activity from the previous saccade (Supplementary Fig. 7C). By looking more closely at the 100 ms around fixation, we found that the distribution of activity was generally similar to the behavioral distribution of Φ's, although the activity distribution did not have the peaks at 135° and 225° seen in the behavior.

As the probability distributions of upcoming saccades depended on whether the fixation location was close versus far from the border (Fig. 1D), we compared activity between these conditions in the same manner as above. We found that for

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angular fixation locations opposite to the PD, there was greater activity when close to the border (Fig. 4E and Supplementary Fig. 7B). This relates to the behavior, in that the probability of saccades opposite the current angular fixation location is greater when closer to the border (Fig. 4F). For angular fixation locations in the same direction as the PD, there was lower activity when close to the border (Fig. 4E and Supplementary Fig. 7B). This relates to the behavior, in that the probability of saccades in the same direction as the current angular fixation location is smaller when closer to the border (Fig. 4F). Moreover, by plotting the distributions of activity on given locations close or far from the borders (Fig. 4G,H), we can more intuitively see how the activity represents a prior distribution of potential movements from a given starting fixation location. There is a wider distribution when farther from the border, and a narrower distribution when closer to the border. Thus, the early activity of the subset of Early/Loc neurons closely relates to the probabilities of saccades that will later occur.

Evolution of Neural Activity over Time

We have seen that, early on, the activity of Early/Loc neurons represents prior information about potential upcoming saccades. How does the neural activity evolve over time as the upcoming saccade approaches? We first looked at PETHs preceding saccades with latencies in small windows (100–150, 150–200, and 200–250 ms in Fig. 5A). Using specific latencies allowed us to more clearly see neural activity that was aligned to the upcoming saccade. As in Fig. 3, we compared scenarios when there were differing amounts of prior information based on fixation location (angular fixation location is near vs. opposite the PD), and also when the actual upcoming saccade was toward vs. away from neurons' PDs. This allowed us to track how neural activity reflected both prior information and the selected upcoming saccade over time.

We first analyzed how activity reflected the actual upcoming saccade (solid versus dashed lines in Fig. 5A and Supplementary Fig. 8A). Early on, around the time of fixation, there was already a differentiation of activity related to the actual saccade that would occur, when controlling for fixation location. As time progressed toward saccade onset, this activity difference increased. Interestingly, two activity peaks were often visible when the upcoming saccade was into the PD—one peak around the time of fixation and another peak about 50 ms before the upcoming saccade onset.

We then analyzed how activity reflected fixation location over time (red versus blue lines in Fig. 5A and Supplementary Fig. 8A). As we saw before, there was differentiation of activity related to location early on. Interestingly, this differentiation of activity based on location continued until the upcoming saccade. That is, activity near the upcoming saccade reflected a mixture of prior information and information about the saccade that would actually occur.

To be more rigorous, we also used a GLM approach (Fig. 5B and Supplementary Fig. 8B). This model can control for confounding factors in the PETH-based analyses, such as correlations with the previous saccade, and can better disentangle correlations between fixation location and upcoming saccades. Additionally, in the GLM, the saccade and locations are no longer only characterized by angles, as they were in the PETHs. As input variables to the model, we included the fixation locations, upcoming saccade vector, upcoming saccade velocity, and previous saccade vector (see Methods). This model-based analysis allowed us to directly estimate the importance of saccade and location variables for predicting neural activity.

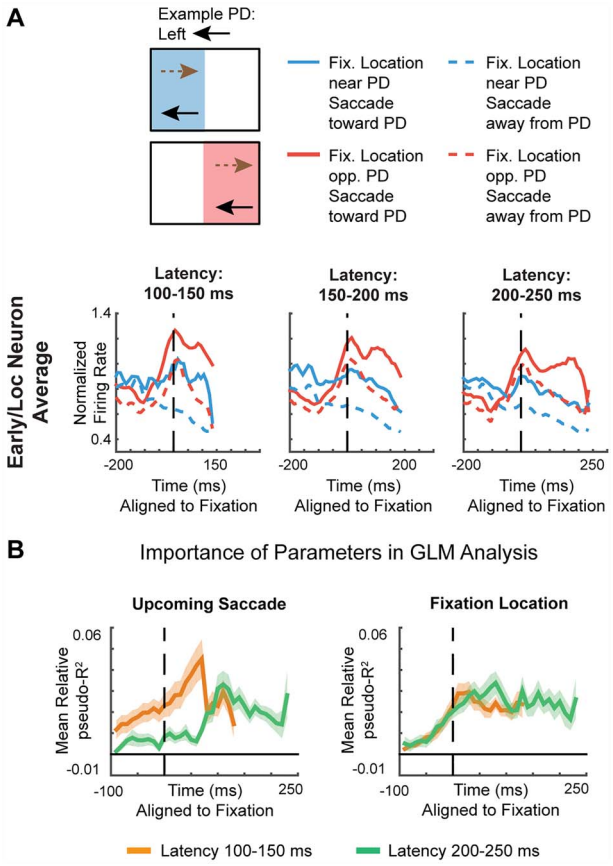

Figure 5. Evolution of activity over time. (*A*) PETHs, aligned to fixation onset, of normalized averaged activity of Early/Loc neurons. Blue lines are those with a starting angular fixation location near the PD (unlikely that upcoming saccade will be toward PD). Red lines are those with a starting angular fixation location opposite the PD (likely that upcoming saccade will be toward PD). Separate PETHs are constructed for saccades with latencies from 100 to 150 ms (left), 150 to 200 ms (middle), and 200 to 250 ms (right). (*B*) Importance of parameters in the generalized linear model, across time, aligned to fixation onset, for Early/Loc neurons. The mean relative pseudo-R^2 (across Early/Loc neurons) of the upcoming saccade (left) and fixation location (right) covariates are shown. We separately determine parameter importance for saccades with latencies of 100–150 ms (orange) and 200–250 ms (green). Shaded areas represent SEMs.

The GLM analysis confirmed our results from the PETHs. The actual upcoming saccade was already significantly predictive of neural activity at the time of fixation. The importance of the upcoming saccade parameter grew until about 50–100 ms before saccade onset. The importance of the fixation location parameter increased until the time of fixation, and then stayed approximately constant until the time of saccade onset. That is, the prior continued to have an influence on activity throughout the entire saccade planning process. Combining the results from both parameters, while activity continuously relates to both prior information and the actual saccade, as time elapses, a greater proportion of the activity relates to the actual saccade that will occur.

Relationship between Early Activity and the Final Selected Saccade

Above, we observed that early activity around the time of fixation was predictive of the actual saccade that would occur,

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beyond the effects of location (Fig. 5). In order to better understand how early activity relates to the final saccade that is selected, we further examined a few scenarios.

First, we looked at how early neural activity related to the final saccade, depending on the latency of the saccade. PETHs showed that for longer latency (200–250 ms) saccades, there was only a small activity difference between saccades toward versus away from neurons' PDs (when controlling for fixation location; Fig. 5A and Supplementary Fig. 8A). However, for shorter latency (100–150 ms) saccades, there was a larger activity difference based on whether the resulting saccade was into the PD. The GLM analysis confirmed these results. At the time of fixation, the neural activity contained only a small amount of unique information about the upcoming saccade for longer latency saccades, while it contained more information for shorter latency saccades (Fig. 5B and Supplementary Fig. 8B). Thus, when the early neural activity contains more information about the upcoming saccade, it happens faster.

Next, we looked at the scenario when the next saccade is to the target. Behaviorally, we observed that when the next saccade is to a nearby target (meaning there was probably a strong "likelihood"; see Behavior subsection), the prior had less influence on behavior (Fig. 1G). We investigated the neural data to determine whether early neural activity was less informative about the upcoming saccade when there was a strong likelihood. We would expect that if the saccade decision is made based on visual processing that is to occur later, then early neural activity shouldn't be predictive of the actual saccade. PETHs show that this is the case. When the saccade is to a nearby target (<10° away), there is no longer an early activity difference based on whether the upcoming saccade is into the PD (when controlling for location; Fig. 6A and Supplementary Fig. 9A). We find the same conclusion in a GLM-based analysis. When looking at all saccades, we can see that the actual upcoming saccade is predictive of neural activity, beyond the effects of location. However, when going to a nearby target, the actual upcoming saccade is not predictive of early neural activity (Fig. 6B and Supplementary Fig. 9B). That is, the neural activity is not informative about the actual upcoming saccade beyond its information about fixation location. Note that this result is not due to latency differences (Fig. 5), as saccades to the target have shorter latencies (Glaser et al. 2016). Thus, by examining saccades to the target, we observe that neural activity around the time of fixation does appear to act like a Bayesian prior about the upcoming saccade.

Finally, we looked at scenarios when the upcoming saccade is in agreement with the prior information (back toward the center) versus disagreement with the prior information (further away from the center). It is likely that if the saccade ends up going against the prior, that the decision was likely to be primarily based on visual information gathered later (not the prior information). However, if the saccade is in agreement with the prior, then it is possible that this prior information was used in the saccade decision. We analyzed whether the early neural activity was informative about the final saccade decision using a GLM-based analysis. We controlled for latency, given that saccades back toward the center have lower latency. Indeed, we found that neural activity preceding fixation was less informative about the upcoming saccade for saccades away from the center (against the prior; Fig. 6C and Supplementary Fig. 9C). This again supports a Bayesian interpretation of the early activity representing a fixation location-based prior; when the final saccade decision is not based on the prior, this early activity is not very informative about that saccade.

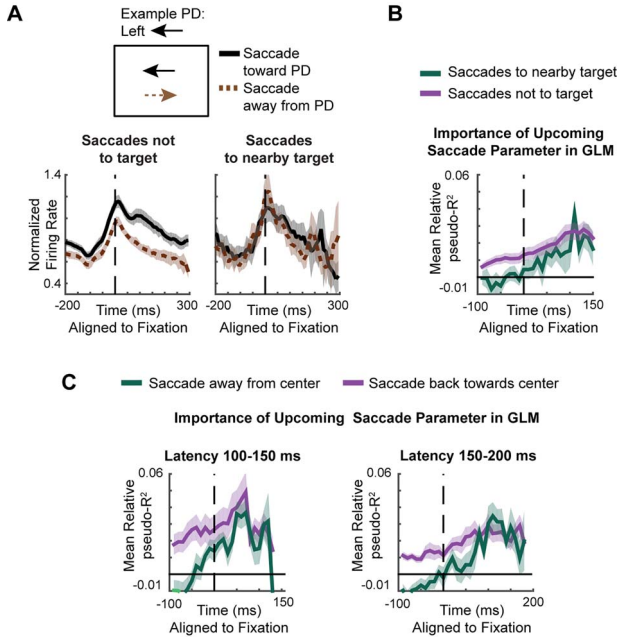

Figure 6. Relationship between early activity and the final selected saccade. (*A*) PETHs of Early/Loc neurons, aligned to fixation, of saccades toward the preferred direction (PD; black) versus away from the PD (brown, dashed). To control for fixation location, we only use saccades starting from locations opposite the PD. On the left, we only include saccades not to the target. On the right, we only include saccades that go to a nearby target (<10°away). (*B*) Importance of the upcoming saccade parameter in the generalized linear model, across time, aligned to fixation. The mean relative pseudo-R^2 (across Early/Loc neurons) was determined for saccades not to the target (purple) and to a target <10° away (gray). Note that the GLM results were only plot until +150 ms, as the results got very noisy since there are limited saccades to nearby targets with latencies >150 ms. (*C*) Importance of the upcoming saccade parameter in the generalized linear model, across time, aligned to fixation. The mean relative pseudo-R^2 (across Early/Loc neurons) was determined for saccades back toward the center (purple) and saccades away from the center (gray). Shaded areas represent SEMs. Note that for this comparison, we cannot do a PETH analysis like in previous scenarios, because saccades back to the center, from an angular fixation location opposite the PD, will always be toward the PD (we can't compare saccades toward versus away from the PD while controlling for fixation location).

"Late" Neurons

While the focus of this paper has been on Early neurons, there were also many "Late" neurons. Late neurons were defined as those significantly modulated by the upcoming saccade in a GLM analysis in the 100 ms before saccade onset, but that were not significantly modulated by the upcoming saccade around the time of fixation (i.e., they were not Early neurons). 51/180 (28%) of recorded neurons were classified as Late neurons. As seen from PETHs (Fig. 7A and Supplementary Fig. 10) and our GLM analysis (Fig. 7D), these neurons' activities start to differentiate based on the upcoming saccade after fixation onset. They also appear to be better aligned to saccade onset than fixation (Fig. 7A and Supplementary Fig. 10). Thus, there is a separate group of neurons with a later time of saccade selectivity.

Do these Late neurons also have prior information related to fixation location? As we did previously for Early neurons, we used a GLM to identify neurons that were significant for fixation location around the time of fixation; these would be candidates for having prior information based on location. We found that 13/51 (25%) of Late neurons were significant for

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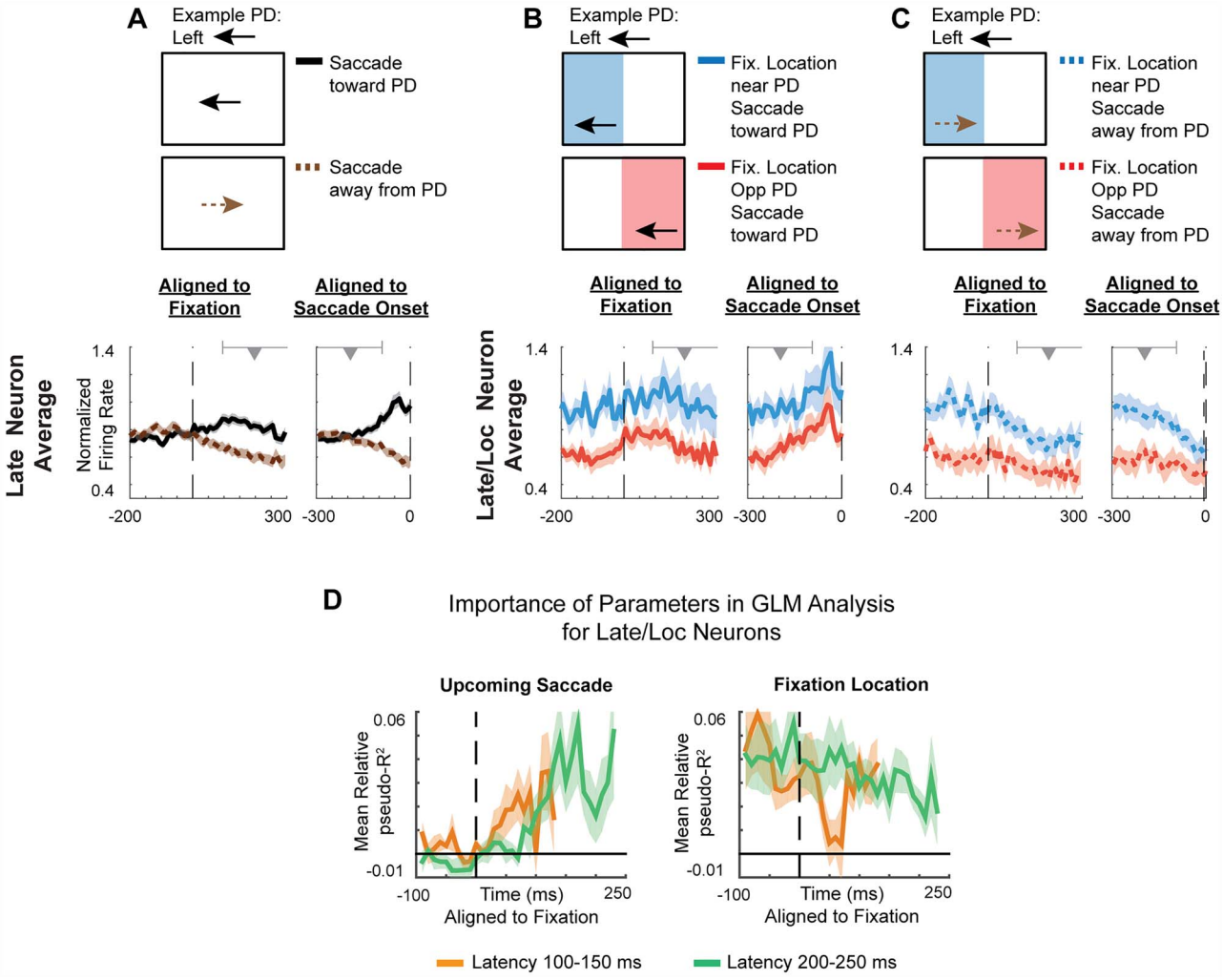

Figure 7. Late Neurons. (*A–C*) PETHs, aligned both to fixation (left part of each column) and the upcoming saccade onset (right part of each column). Ranges of saccade/fixation onset times are shown above the PETHs as in Fig. 2. (*A*) PETHs of saccades toward the PD (black) versus away from the PD (brown, dashed). PETHs are averaged across Late neurons. (*B*) PETHs of saccades toward the PD, with a starting angular fixation location near the PD (unlikely that upcoming saccade will be toward PD; blue) versus an angular location opposite the PD (likely that upcoming saccade will be toward PD; red). For example, if the PD is to the left, angular locations near the PD will be on the left side of the screen (see Methods for details). PETHs are averaged across Late/Loc neurons (Late neurons that are also significant for fixation location). (*C*) PETHs of saccades away from the PD, with a starting angular fixation location near the PD (blue, dashed) versus an angular location opposite the PD (red, dashed). PETHs are averaged across Late/Loc neurons. (*D*) Importance of parameters in the generalized linear model, across time, aligned to fixation. The mean relative pseudo-R^2 (across Late/Loc neurons) of the upcoming saccade (left) and fixation location (right) covariates are shown. We separately determine parameter importance for saccades with latencies of 100–150 ms (orange) and 200–250 ms (green). Shaded areas represent SEMs.

fixation location, a much lower percentage than for Early neurons. Moreover, when we further investigate these "Late/Loc" neurons, it is clear that they are not representing prior information about the upcoming saccade in the manner of Early/Loc neurons. For instance, the importance of the location parameter stays relatively constant over time (Fig. 7*D*; note that the transient decrease in the orange trace is primarily driven by outliers). More importantly, PETHs show that average activity is actually higher when the angular location is near neurons' PDs (blue trace), which is when the upcoming saccade is less likely to be in the PD (Fig. 7*B*,*C*). Thus, separate from Early neurons, there is another subset of neurons that only represents saccades after fixation onset and doesn't represent prior information based on fixation location.

Discussion

Here, during a self-guided search task, we found a subset of ("Early") neurons that represented prior information about the upcoming saccade, often before the onset of fixation. This early neural activity related to prior information was predictive of the final selected saccade in a Bayesian manner. As time elapsed toward the upcoming saccade, prior information continued to have an influence on these neurons' activities, but the activities evolved so that activity became more related to the final saccade selection. In a separate subset of ("Late") neurons, activity only related to the final selected saccade and not prior information. Our findings demonstrate how prior information influences and evolves into definitive saccade plans.

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Our findings have some overlap with the results of Phillips and Segraves (Phillips and Segraves 2010), who also studied FEF during a natural scene search task. Like us, they found early saccade predictive activity in many neurons, sometimes prior to fixation. In their study, they also found that many neurons' activities were predictive of future saccades (not just the upcoming saccade), which they called "advanced predictive activity." When they split neurons into two subsets depending whether the neurons had advanced predictive activity or not, they found that neurons with advanced predictive activity also became selective for the upcoming saccade significantly earlier. Their separation based on whether neurons had advanced predictive activity (i.e., whether their activity predicted future saccades) may thus overlap with our separation into Early and Late neurons.

Our findings suggest a link between previous studies showing pretarget preparatory activity in constrained tasks and studies showing advanced saccade planning during self-guided saccades. Past studies have shown that superior colliculus neurons had higher activity prior to target onset when there was a higher probability the target would be shown in the neurons' PDs (Basso and Wurtz 1998; Dorris and Munoz 1998). This parallels our finding that Early/Loc neurons had higher activity when there was a greater probability of the upcoming saccade being in their PDs. Additionally, during self-guided search, researchers have provided evidence for FEF planning more than one saccade in advance (Phillips and Segraves 2010; Zhou and Desimone 2011). These advanced plans could be reflected by Early neurons, which are predictive of the upcoming saccade before gathering new information. Thus, there may be a common mechanism, where Early neurons are involved in preliminary planning, whether based on saccade probabilities or some saccade sequence planned in advance.

Source of the Prior Information

How does the FEF have access to information about its fixation location to use for saccade planning? The simplest explanation would be that it is an eye position signal, as FEF neurons are known to be modulated by eye position (described in the next subsection). As Early/Loc neurons are modulated by the fixation location prior to the start of fixation, these neurons could not be receiving an eye position signal from area 3a of somatosensory cortex, which occurs ~60 ms after fixation (Xu et al. 2011). However, as the neural activity is modulated by the upcoming fixation location throughout the previous saccade (Supplementary Fig. 11), it could be possible that it is a proprioceptive signal that tracks the eye movement. In opposition to this view, previous researchers have argued against eye position signals in the FEF being proprioceptive in origin (Bizzi 1968; Bizzi and Schiller 1970; Cassanello and Ferrera 2007). This is because FEF neurons that were modulated by eye position during saccades were not modulated by eye position during other nonballistic eye movements (Bizzi 1968; Bizzi and Schiller 1970).

Given the timing of the prior signal, another possibility is that the prior could arise from a predictive signal based on the saccade that is occurring. That is, the upcoming eye position (or fixation location) could be computed based on a corollary discharge signal of the saccade plan. A strong candidate source for this signal is from the superior colliculus via mediodorsal thalamus (Sommer and Wurtz 2002, 2004). In fact, when the collicular thalamo-cortical pathway is blocked, monkeys are not able to successfully make sequences of saccades (Sommer and Wurtz 2002, 2004). If this is the source of our prior information, we would hypothesize that blocking this corollary discharge pathway would interfere with Early/Loc neurons' representation of prior information.

Another potential explanation for the early activity is visual remapping (Colby and Goldberg 1992; Sommer and Wurtz 2006; Zirnsak et al. 2014). This early activity could be related to the visual scene that is about to be brought into the neurons' receptive fields (RFs). For example, let's say a neuron has a receptive field to the left. When the monkey is looking on the right side of the screen, there may be more interesting features in the neuron's receptive field (to the left), as compared with when the monkey is looking on the left side of the screen, when the receptive field may include some visual space outside (to the left) of the scene. Importantly, this visually remapped information could act as a prior to influence the upcoming saccade before the new visual information has been processed.

However, there are a couple reasons we believe visual remapping is unlikely to explain our results. First, visual remapping typically occurs prior to saccade onset. Thus, if visual remapping was explaining our early activity that is predictive of the upcoming saccade, we would expect this activity to occur prior to the previous saccade onset. However, our "early planning" signal typically happens around the time of the previous saccade onset (Supplementary Fig. 11). Moreover, if the early activity were due to visual remapping, we would expect that there is greater activity when an important/attended visual stimulus is about to be brought into the RF (Gottlieb et al. 1998; Joiner et al. 2011). However, when comparing cases when the target is being brought into the RF versus not (Fig. 6A, right panel, black condition versus brown condition), we see that there is not an activity difference at the time of fixation. This does not support the hypothesis that the early activity is primarily a visual remapping signal.

Finally, rather than being related to visual information that is just being updated, the information could be related to a supraretinal (craniotopic) representation of the visual environment. In human experiments, it has been shown that it takes a few saccades to establish this representation (Poletti et al. 2013).

However, when we analyze only the first three saccades (before the supraretinal representation should have formed), we still find that fixation location affects Early/Loc neurons' activities in the same manner (Supplementary Fig. 12). Ultimately, the biological source of the fixation location-related prior information remains unclear. Future experiments designed to test the above hypotheses would be valuable.

Neural Activity Related to Eye Position

Here, we assumed that the neural activity of Early neurons related to fixation location (equivalent to eye position in our study) was used for preliminary planning. This is in line with previous research showing that a lower stimulation threshold in FEF was required to elicit saccades opposite of the current eye position (Russo and Bruce 1993), which suggested that eye position biases upcoming saccades. However, it is possible that FEF activity related to position was used for computations other than, or in addition to, saccade planning. For instance, Cassanello and Ferrera (2007) found that there was generally greater activity in FEF neurons when the initial eye position was opposite the neurons' PDs. However, they argued that this position-based modulation of activity could allow vector subtraction, with the purpose of keeping a memory of the target

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location across saccades. It is important to note that a position signal could ultimately be used for multiple purposes. For instance, there could be multiple read-outs of this position signal, one that is used for saccade planning, and another that does vector subtraction for the purpose of stability across saccades. Ultimately, given that Early/Loc neurons' activities with respect to position matched the statistics of upcoming saccades and given that FEF has a known role in saccade planning (Bichot and Schall 1999; Gold and Shadlen 2000; Ding and Gold 2011), it is improbable that these neurons were representing position solely for a purpose other than making saccade decisions.

Previous studies have also suggested that neural activity in SC is modulated by eye position in order to bias upcoming saccades. Pare and Munoz (Paré and Munoz 2001) found that burst neurons in SC had higher firing rates when the eye position was opposite the neurons' PDs, as we found here for FEF. However, other studies in SC (Van Opstal et al. 1995; Campos et al. 2006) found the reverse result (although in different tasks)—that firing rates were generally higher when the eye position was in the same direction as the neurons' PDs. It is thus possible that a subset of SC neurons use position for preliminary planning. Given the effect of eye position (fixation location) on saccade latencies (Fig. 1), it makes sense that it would affect neural activity related to saccade planning throughout the oculomotor system.

Cell Types

While we split neurons into Early and Late neurons, these neurons may lie along a spectrum rather than being discrete classes. While the majority of Early neurons had activity predictive of the upcoming saccade both near the time of fixation and near the time of the saccade (e.g., top row of Fig. 2; see Supplementary Fig. 4 for more), a small number of Early neurons did not have much saccade-predictive activity near the time of the upcoming saccade (e.g., third row of Fig. 2). Late neurons only had saccade-predictive activity near the time of the upcoming saccade. Thus, it could be the case that neurons lie on a spectrum from having saccade-predictive activity only around fixation to only around the upcoming saccade, with many neurons having a mixture (Supplementary Fig. 13).

Classically, researchers have used a memory-guided saccade task to categorize FEF neurons as having visual, delay, and/or movement activity (Bruce and Goldberg 1985; Sommer and Wurtz 2000) (although see [Lowe and Schall 2017] for recent work revisiting these classifications). As past work has shown sensory to motor transformations from visual to movement cells (Sajad et al. 2016), it is interesting to speculate how Early and Late neurons relate to these classical cell types. One simple explanation could be that these neurons lie on the classical visual to movement spectrum depending on how much of their saccade-predictive activity is near the time of fixation versus near the time of saccade. However, it is probably not that simple. Phillips and Segraves (Phillips and Segraves 2010) found that similar proportions of (classically defined) visual and visuo-movement cells had advanced predictive activity. Moreover, the majority of our Late neurons had activity modulated by visual scene onset (Supplementary Fig. 14), suggesting that Late neurons are not purely movement related. Thus, it does not appear that Early and Late neurons cleanly map onto classical FEF cell types.

Probability Distributions

When averaging activity across saccades, the activity of Early/Loc neurons was similar to the full continuous probability distribution of upcoming saccades (Fig. 4C,D). However, it did not match exactly. The distribution of neural activity did not have the peaks at around 135° and 225° like the behavioral distribution. This could be because the activity of these FEF neurons only serves as general prior information to direct saccades toward the center. In this scenario, other oculomotor structures could relate to other aspects of the prior. Alternatively, we only recorded a limited number (28) of Early/Loc neurons, and it is possible that recording a large number would reveal a distribution that more precisely matches behavior. Further experiments while recording even more neurons will be necessary to differentiate these possibilities.

Demonstrating that neural activity relates to a full, continuous probability distribution of saccade directions extends previous work showing that neural activity in the oculomotor system reflects the probabilities of upcoming saccades when deciding between a small number of discrete targets (Basso and Wurtz 1997, 1998; Dorris and Munoz 1998; Everling and Munoz 2000; Yang and Shadlen 2007). Importantly, because our results were based on averaging across saccades, we do not know whether the FEF population, prior to single saccades, reflects the probability distribution of the upcoming saccade. An alternative explanation is that the population always makes preliminary plans for a single saccade, and when averaged across saccades, these individual plans create a distribution. In the future, it would be beneficial to simultaneously record many FEF neurons and perform a single-trial decoding analysis (as in [Glaser et al. 2017]) to determine whether probability distributions or individual plans are represented prior to single saccades.

Bayesian Decision-Making

There is a large literature demonstrating that decision-making for movement is approximately Bayesian (Körding and Wolpert 2004; Jazayeri and Shadlen 2010). Moreover, it was recently shown that the smooth pursuit region of FEF (FEF_{SEM}) has activity that maps onto approximately Bayesian behavior (Darlington et al. 2018). Here, we showed that neural activity relates to aspects of this Bayesian decision-making process during self-guided saccades. The early activity of Early/Loc neurons (which reflected prior information) was less predictive of the final saccade decision when there was stronger visual ("likelihood") information (when the next saccade was to a target). Moreover, it is not only the early activity (around the time of fixation) that may relate to Bayesian decision-making; we can also view the evolution of Early/Loc neurons' activities through a Bayesian framework. Given that the activity of Early/Loc neurons is continuously related to prior information, and increasingly related to the final decision over time, the activity may represent a posterior distribution. That is, it could represent the current beliefs about the upcoming saccade, based on the prior information and visual likelihood information. It would be valuable to do future experiments with more controlled visual information, to further understand FEF's role in Bayesian computations for saccade decisions.

Additionally, it would be interesting to understand how this posterior gets transformed into a selected plan, which is reflected in the activity of Late neurons. From a computational perspective, Kim and Basso (Kim and Basso 2010) showed that

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in SC, a Bayesian maximum a posteriori model better predicted selected saccades than winner-take-all or population vector average models. From a neurobiological perspective, the neural circuits involved in transforming prior information to selected saccades remain unclear. One possibility is that Early neurons project to Late neurons within FEF to influence the saccade plan. Another possibility is that Early neurons project to neurons in SC, which then go on to influence the saccade plan. Both possibilities could also happen simultaneously. Clearly, our work could be explained by a large number of different circuit models. Future work should aim to elucidate the circuit mechanisms behind the transformation from prior information to definitive saccade plans.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

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