From preliminary to definitive plans: two classes of neurons in frontal eye field

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Abstract:

Prior to selecting an action, we often consider other possibilities. How does the brain represent these preliminary plans prior to action selection? Here, we investigated this question in the oculomotor system during self-guided search of natural scenes. We found two classes of neurons in the frontal eye field (FEF): 1) "late selection neurons" that represented the selected action plan not long before the upcoming saccade, and 2) "early selection neurons" that became predictive of the upcoming saccade much earlier, often before the previous saccade had even ended. Crucially, these early selection neurons did not only predict the upcoming saccade direction; they also reflected the probabilities of possible upcoming saccades, even when they did not end up being selected. Our results demonstrate that during naturalistic eye movements, separate populations of neurons code for preliminary and definitive plans.

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 limited computational resources on seemingly good options. 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.

Several previous studies have shown that oculomotor structures in the brain utilize prior information for planning saccades [1-6]. In macaque superior colliculus (SC), burst neurons show increased pre-target activity [1,2] when there is an increased probability that a target will be placed in the neurons' receptive fields. The same effect was found in corticotectal neurons in the frontal eye field (FEF) [3]. In both SC and FEF, the neurons with pre-target activity also responded after target onset, with greater activity when the target actually appeared in their receptive fields. That is, the same population of neurons appeared to be involved in the preliminary (pre-target) planning and final (post-target) action selection. However, it remains unclear how the oculomotor system accomplishes various stages of planning and execution, in particular in more naturalistic settings where targets are typically not flashed on and off.

Unlike unconstrained, natural eye movement behavior, the tasks used in previous studies imposed substantial limitations on the prior information available for making preliminary plans. 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 [7,8]. These tasks also removed the possibility of ruling out saccade targets based on previous saccades [4]. Moreover, the oculomotor system is modulated by eye position in a manner that favors movement towards the center of the oculomotor range [9]. By removing starting eye positions as a variable, these previous studies also removed a significant source of prior information for constraining the range of potential eye movements. In naturalistic settings, much remains unknown about how the oculomotor system represents preliminary plans, and how they evolve into definitive plans.

Here, to explore how the oculomotor system represents preliminary and definitive plans during naturalistic saccades, we recorded from macaque FEF during a natural scene search task. Rather than finding that the same neurons represented preliminary and definitive plans, we found two separate classes of neurons. "Early selection neurons" became predictive of the upcoming saccade prior to the current fixation, before they could have received new visual information. "Late selection neurons", on the other hand, coded for the selected action plan shortly before the upcoming saccade. Importantly, the activity of early selection neurons related not only to the upcoming saccade; early selection neurons also reflected the probabilities of upcoming eye movements based on the current eye position, regardless of the actual selected saccade direction. We find that in naturalistic settings, two separate classes of neurons code for preliminary and definitive saccade plans.

Results:

Behavior

To investigate how preliminary and definitive plans are represented during self-guided eye movements, we recorded single units from the frontal eye field (FEF) while head-fixed monkeys freely searched for a target embedded in natural scenes (Fig. 1A) [10,11]. 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 make preliminary plans for saccades before they have new detailed visual information at each upcoming fixation location.

One easily quantifiable factor that could contribute to preliminary saccade plans is the eye position 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 eye position vector (relative to the center) and the upcoming saccade vector (Fig. 1C). When going back towards the center, $\Phi = 180°$, and when going away from the center, $\Phi = 0°$. We found that monkeys are more likely to look approximately opposite of their current position (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 [12-14]. Interestingly, the peak of Φ is not at exactly 180° (when going back towards the center). In both monkeys, there is a higher probability of $\Phi = 135°$ or $\Phi = 225°$ than $\Phi = 180°$. This is because these statistics not only reflect the possible on-screen saccades (which would be centered on 180°); they also reflect any other strategies and biases of the monkeys, which could be involved in preliminary planning.

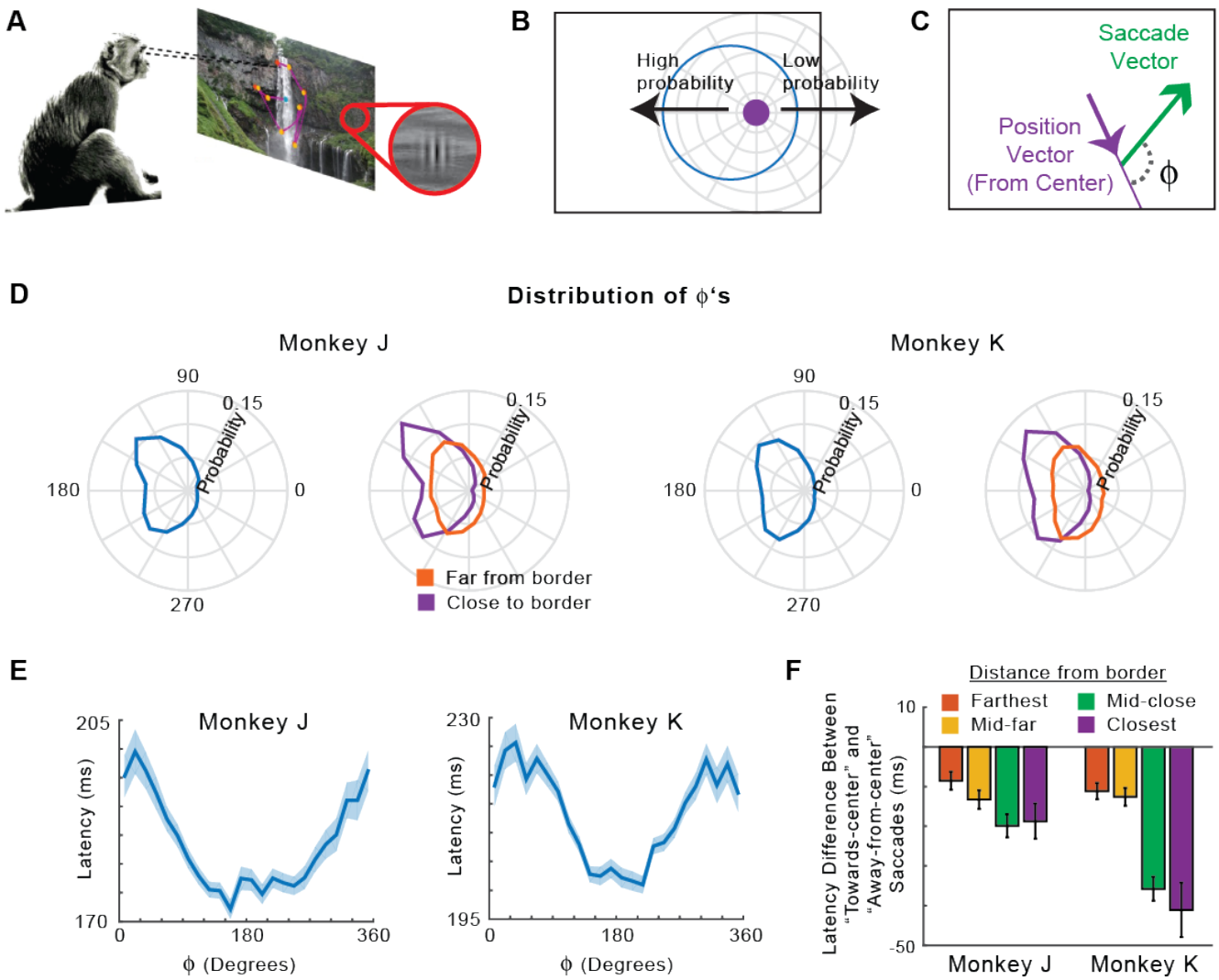

Figure 1: Experiment and behavior

(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 eye position on the screen. This is an example where the eye position is to the right of the screen. **(C)** We quantify the relationship between the upcoming saccade direction and position using Φ, the angle between the position 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 eye position 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. **(F)** The latency difference between saccades towards the center (|Φ-180°|<60°) and saccades away from the center (|Φ-180°|>120°), as a function of the starting eye position's distance from a border. The distance from the border was divided into quartiles.

In addition to saccade directions, preliminary saccade planning may also be reflected in saccade latencies. Indeed, latencies were shorter for saccades made approximately opposite of the eye position, (at Φ close to 180°; both monkeys, $p < 1e\text{-}10$; Fig. 1E), and the effect was stronger for eye positions closer to the border (Monkey J, p=4.9e-4; Monkey K, p=7.9e-10; Fig. 1F). These findings are consistent with several previous studies showing that saccades back towards the center have shorter latencies [9,15,16]. Interestingly, latencies were actually slightly less for saccades at Φ's slightly offset from 180° (Fig. 1E). This is similar to the above finding that the distribution of Φ was peaked at angles slightly offset from 180°. 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.

Saccade-related neural activity

To investigate the neural basis of preliminary and definitive saccade planning, we first looked at the time at which neurons' activities became predictive of the upcoming saccades. We focused on a subset of neurons (86/226, 38% of recorded neurons) whose activity we found to be modulated by the upcoming saccade direction (see *Methods*). Among this subset, we categorized these neurons as Early Selection (E-Sel) or Late Selection (L-Sel) depending on the time that their activity predicted the upcoming saccade direction. More specifically, we found the time that activity distinguished between upcoming saccades into neurons' preferred directions (PDs) versus opposite their PDs (Fig. 2; see *Methods*). L-Sel neurons (48/226, 21% of recorded neurons) became responsive to the upcoming movement direction following fixation (Figs. 2A and S1A, rows 1,2). E-Sel neurons (38/226, 17% of recorded neurons), however, became responsive to the upcoming saccade prior to fixation, i.e., during the previous saccade (Figs. 2A and S1A, rows 3,4). This agrees with the findings of Phillips and Segraves [7], who showed that during self-guided search, a subpopulation of FEF neurons became selective for the upcoming saccade prior to fixation. As E-Sel neurons demonstrated predictive activity that preceded detailed visual information (available only after fixation), these neurons seemed to represent preliminary planning of saccades.

If the 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 [17-20]. We found that this is the case for both E-Sel and L-Sel neurons. For saccades into neurons' PDs, shorter saccade latencies were associated with greater neural activity (Figs. 2B and S1B). This provides additional evidence that both E-Sel and L-Sel neurons are involved in planning upcoming saccades, but at different times.

Preliminary planning based on eye position

In the preceding section, we showed that E-Sel neurons became predictive of the upcoming saccade during early stages, which suggested preliminary planning. These preliminary plans could be related to the monkey's eye position on the screen. 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 involved in preliminary planning, we would expect this neuron to have greater activity when the monkey's eye position was on the left side of the screen. Generalizing this example, we would expect neurons involved in preliminary planning to have greater activity when the monkey's eye positions are such that the next saccade is likely to be into the neurons' PDs. This occurs when the eye positions are approximately opposite of the neurons' PDs. Importantly, we should be able to see evidence of this preliminary planning based on position, regardless of the direction of the actual saccade.

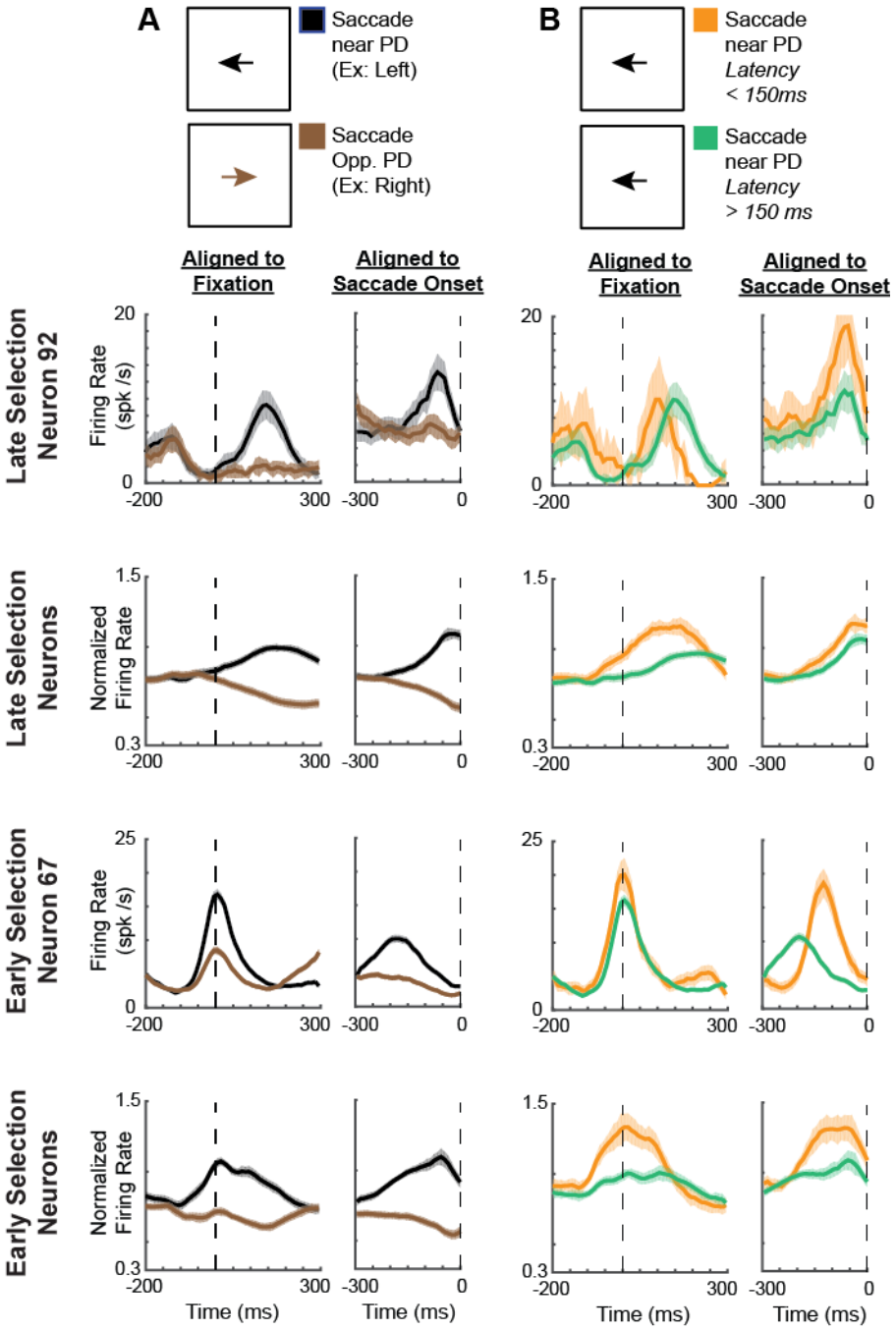

Figure 2: Different times of saccade selectivity for E-Sel and L-Sel neurons, and neural differences related to saccade latencies

Peri-event time histograms (PETHs), aligned both to fixation (left part of each column) and the upcoming saccade onset (right part of each column). **First Row of PETHs**: An example late selection neuron. **Second Row**: Normalized averages of late selection neurons. **Third Row**: An example early selection neuron. **Bottom Row**: Normalized averages of early selection neurons. **(A)** PETHs of saccades near the preferred direction (PD; black) versus opposite the PD (brown). **(B)** PETHs of saccades near the PD, for saccade latencies less than 150 ms (orange) versus latencies greater than 150 ms (green).

We investigated whether the time course of neural activity (as shown by peri-event time histograms, PETHs) of E-Sel neurons depended on the initial eye position. Indeed, we found that these neurons did have greater activity when the eye position at fixation was opposite of the neurons' PDs (Figs. 3 and S2, PETH rows 3,4; red trace higher than blue trace), i.e. when the upcoming saccade is likely to go into the neurons' PDs. This differentiation of activity based on the initial eye position began prior to fixation, long before the upcoming saccade. This is around the same time these neurons became selective for the upcoming saccade (Figs. 2 and S1). Importantly, even when controlling for the direction of the upcoming saccade, E-Sel neurons still had greater activity when the eye position was opposite the PD (Figs. 3 and S2). Moreover, this activity difference was not due to latency differences (Fig. S3). In other words, neurons had higher activity when the eye was in a position that made a saccade into the PD likely, even if the saccade didn't actually end up going into the PD (Figs. 3B and S2B). This finding, along with the early timing of these neurons' responses, supports the idea that E-Sel neurons are involved in preliminary planning.

Do L-Sel neurons also represent this information about preliminary plans? The PETHs reveal that these neurons did not have higher activity when the initial eye position was opposite the PD (Figs. 3 and S2, PETH rows 1,2; red trace does not rise above the blue trace). In fact, on average, activity was higher for positions near neurons' PDs, likely due to persisting activity from the previous saccade. In other words, when the previous saccade was into the PD of a L-Sel neuron, at which point the eye position was often near the PD (blue trace), L-Sel neurons were still firing from the previous saccade into the PD. This finding, along with the late timing of these neurons' responses, supports the idea that L-Sel neurons are not involved in preliminary planning.

Model-based analysis

The previous PETH-based analyses contained several confounding factors. For instance, activity around the time of fixation could have been related to the previous saccade. Plus, there were correlations between eye position and upcoming saccades that were not fully disentangled. To more rigorously determine how much of the observed neural activity related to the actual upcoming saccades versus the eye position (which can be used in preliminary planning), we used a generalized linear model (GLM) analysis. As input variables to the model, we included the eye position, upcoming saccade vector, upcoming saccade velocity, and previous saccade vector (see *Methods*). This model-based analysis allowed us to estimate the importance of saccade and position variables.

For E-Sel neurons, the upcoming saccade covariate's importance began to increase approximately 100 ms before fixation, and ramped up for about 200 ms (Figs. 4B and S4B). The position covariate's importance was also high at this time, and showed a similar increase in importance over time. This analysis supports that early activity was indeed predictive of the actual saccade that would occur, but the activity was also independently influenced in a similar manner by eye position.

For L-Sel neurons, the saccade covariate's importance began to increase after fixation (Figs. 4A and S4A). While the position covariate had some importance on average, its importance across time was static, rather than ramping up. Additionally, the importance of the saccade parameter was much greater than that of the position parameter. This confirms that this later activity was primarily related to the actual saccade that would occur.

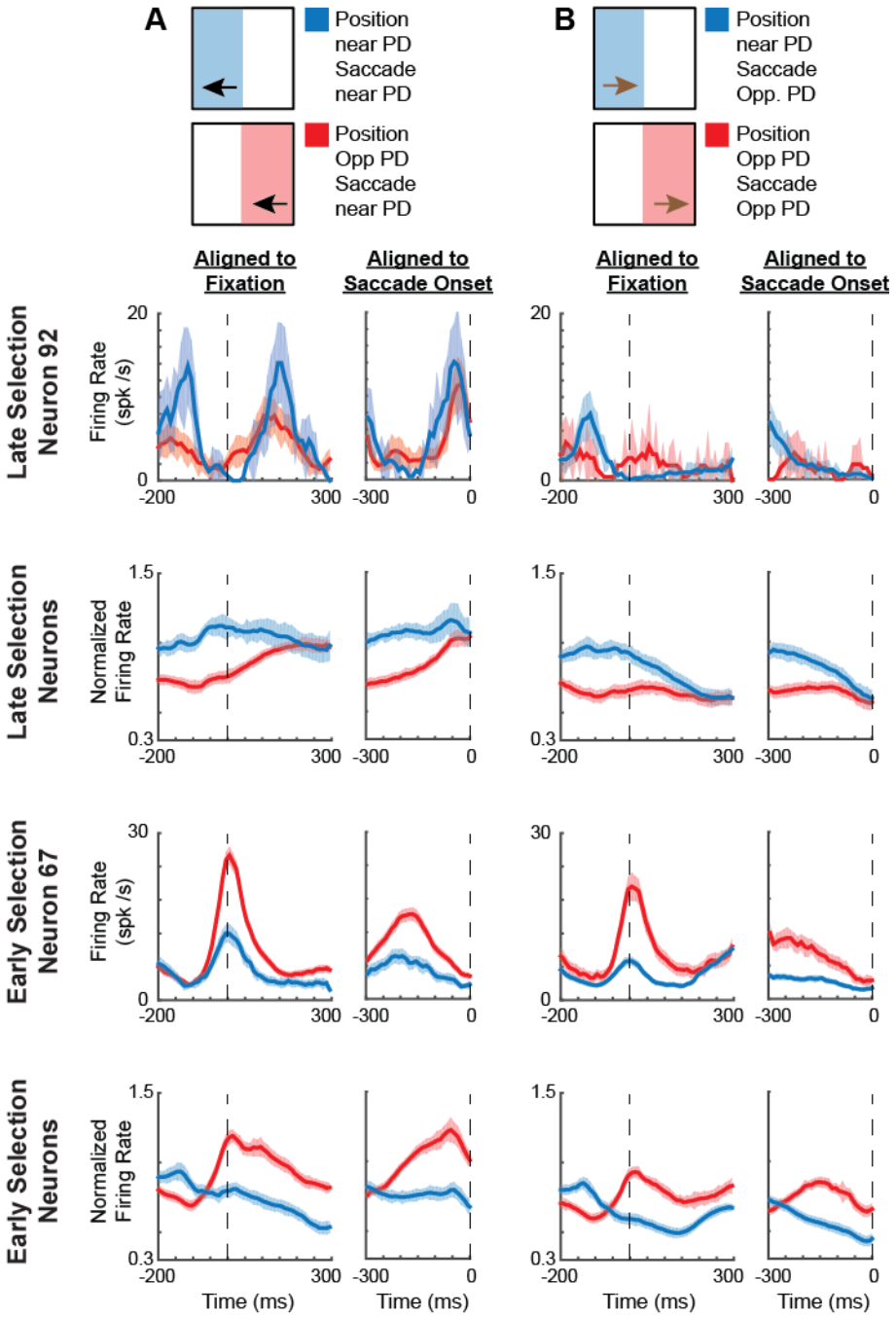

Figure 3: E-Sel, but not L-Sel, neurons have higher activity in positions that are more likely to result in saccades near the PD

Peri-event time histograms (PETHs), aligned both to fixation (left part of each column) and the upcoming saccade onset (right part of each column). **First Row of PETHs**: An example late selection neuron. **Second Row**: Normalized averages of late selection neurons. **Third Row**: An example early selection neuron. **Bottom Row**: Normalized averages of early selection neurons. **(A)** PETHs of saccades near the PD, with a starting position near the PD (unlikely that upcoming saccade will be near PD; blue) versus a position opposite the PD (likely that upcoming saccade will be near PD; red). **(B)** PETHs of saccades opposite the PD, with a starting position near the PD (blue) versus a position opposite the PD (red).

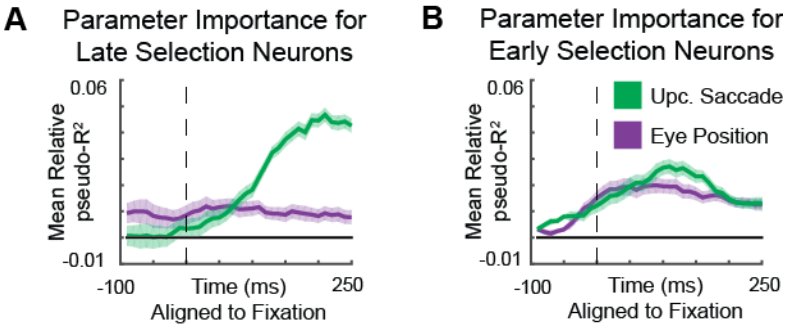

Figure 4: GLM results – importance of upcoming saccade and eye position parameters
Importance of parameters in the generalized linear model, across time, aligned to fixation. **(A)** The mean relative pseudo-R^2 of the upcoming saccade (green) and eye position (purple) covariates for late selection neurons. **(B)** Same plot for early selection neurons. Shaded areas represent SEMs.

Early activity reflects probabilities of upcoming saccades

Above, we observed that E-Sel neurons had greater activity when the eye position made it more likely that the upcoming saccade would be toward neurons' PDs. But does this activity more precisely relate to the task behavior? That is, does the early neural activity reflect the probability distribution of upcoming saccades (Fig. 1d)?

To understand how E-Sel activity relates to the distribution of upcoming saccades, for each neuron we calculated the average activity as a function of the "relative position angle". The relative position angle is the position relative to the PD of the neuron (Fig. 5a), and is an analog to the behavioral measure Φ (Fig. 1c, Fig. 5b). We averaged across all neurons and tracked this distribution over the course of saccade planning. Importantly, we only included fixation periods preceding saccades that were made opposite of the neurons' PDs in order to minimize contamination by neural activity that was related to definitive saccade plans or execution.

In the resulting plot, we observed greater activity when the eye position was approximately opposite the neurons' PDs (Figs. 5c and S5a). This relation was not due to activity from the previous saccade (Fig. S5c). Looking more closely at the 100 ms around fixation, we can see that the greatest neural activity occurred when the eye position was not exactly opposite the PD. It was greatest at a relative position angle of about 135°, similar to the saccade statistics in the task. In fact, the circular means of the neural activity distribution and behavioral distribution were not statistically different ($p > 0.05$ via bootstrapping; Fig. 5d). Thus, the neural population activity reflected the probability distribution of upcoming saccades in the task.

We also examined whether there were differences in FEF activity when the eye position was close versus far from the border. Like before, we only included fixation periods preceding saccades that were made opposite of the neurons' PDs. We found that for eye positions opposite to the PD, there was greater activity when close to the border (Figs. 5e and S5b). This relates to the behavior, in that the probability of saccades opposite the current position is greater when closer to the border (Fig. 5f). For eye positions in the same direction as the PD, there was lower activity when close to the border (Figs. 5e and S5b). This relates to the behavior, in that the probability of saccades in the same direction as the current position is smaller when closer to the border (Fig. 5f). Thus, the early activity of the population of E-Sel neurons closely relates to the probabilities of saccades that will later occur.

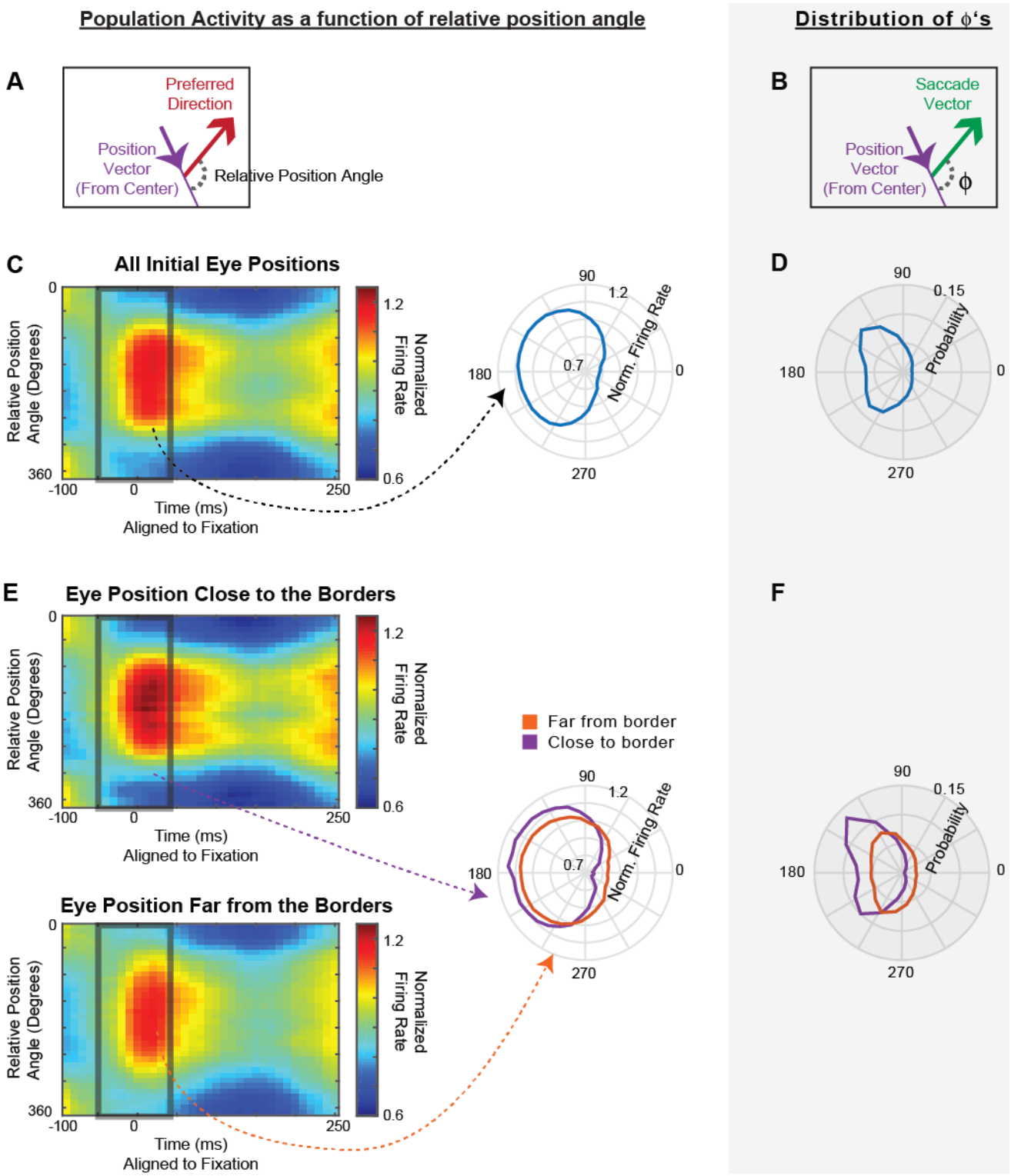

Figure 5: E-Sel population activity reflects the probabilities of upcoming saccades
On the left, we plot the population activity of E-Sel neurons as a function of the relative position angle. On the right, with a gray background, we show how this relates to the behavioral distribution of Φ's. **(A)** The relative position angle is the difference between a neuron's preferred direction and the eye position vector (from the center). **(B)** Copied from Fig. 1c, Φ is the difference between the upcoming saccade and the eye position vector. **(C)** On the left, a heat map of normalized activity over time, as a function of relative position angle, averaged across neurons. On the right, the normalized average activity in the 100 ms

surrounding fixation, plotted as a function of the relative position angle. 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 eye positions close to the borders (top left, right in purple) and far from the borders (bottom left, right in orange). **(F)** Same as panel D, but now separated for initial eye positions close to the borders (purple) and far from the borders (orange).

While the PETH results suggested that L-Sel neurons are not involved in preliminary planning, we still analyzed L-Sel neurons' activity as a function of eye position to check whether they represent the probabilities of upcoming saccades (Fig. 6). Early on, around the time of fixation, there was the greatest activity when the eye position was in the same direction as the preferred direction. This was due to activity related to the previous saccade, which was more likely to be into the PD when the current eye position was in the direction of the PD. Later during the fixation period (150-250 ms from fixation onset), activity as a function of relative position angle matched the statistics of saccades (Fig. 6a). However, this was only because we included all saccades, and the saccade-related activity captured the correlations with eye positions. When we only included saccades away from the PD (as in Fig. 5), almost all of the activity disappeared (Fig. 6b). Another way we tested whether the apparent position-related activity was actually due to the correlation between position and upcoming saccades was to resample saccades to get a different correlation structure between eye positions and saccades (i.e., we resampled to get a different distribution of Φ's). When we did this, L-Sel neurons' activity no longer matched the true distribution of Φ's (Fig. 6c). On the other hand, for E-Sel neurons, this resampling still yielded activity that was close to the true distribution of Φ's (Fig. 6c). This demonstrated that the activity of L-Sel neurons related to the actual saccades themselves, while E-Sel neurons' activities related to the probabilities that saccades would occur.

Comparison to classical cell types

Classically, researchers have used a memory-guided saccade task to categorize FEF neurons as having visual, delay, and/or movement activity [21,22] (although see [23] for recent work revisiting these classifications). As past work has shown sensory to motor transformations from visual to movement cells [24], it is interesting to consider how our neuron classes map onto classical cell types. Since both E-Sel and L-Sel neurons are selective for the upcoming movement, one would initially assume that they would both have classical movement activity. However, during movements in natural scenes, neurons with classical visual activity have also been shown to be selective for the upcoming saccade [25,26]. While we did not conduct a memory-guided saccade task here, we can still look at whether neurons had "visual" activity based on whether there was a significant increase in activity when the visual scene first appeared (see *Methods*). We found that 87% (33/38) of E-Sel neurons and 71% (34/48) of L-Sel neurons had visual activity. This agrees with the findings of Phillips and Segraves [7], who found that neurons with classical visual activity can be selective for the upcoming saccade at widely varying times (both early and late). Thus, it does not appear that E-Sel and L-Sel neurons cleanly map onto classical FEF cell types.

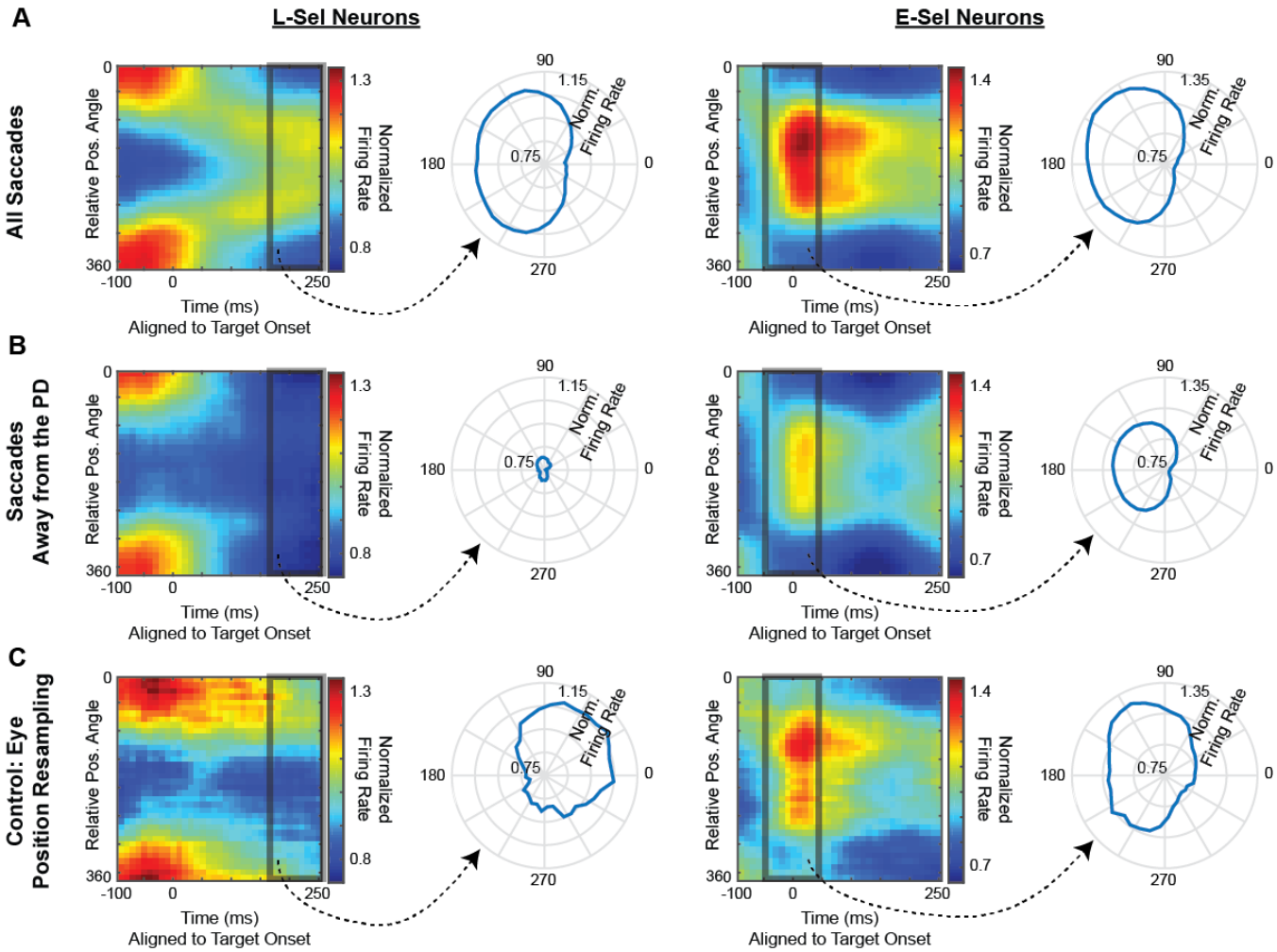

Figure 6: L-Sel population activity does not reflect the probabilities of upcoming saccades
We plot the population activity of L-Sel neurons (left) and E-Sel neurons (right) as a function of the relative position angle, as in Figs. 5 and S4. For the polar plots on the right, we use activity in the 100 ms around fixation for E-Sel neurons, as in Fig. 5. For L-Sel neurons, we use activity from 150-250 ms following fixation. Note that the color bars for E-Sel neurons differ from those in Fig. 5. **(A)** All saccades are included. **(B)** Only saccades away from the PD are included. **(C)** We control for the correlation between the eye position and upcoming saccade direction. We resampled saccades to create a distribution of saccade directions relative to position angles that were centered on 45°. This plot ensures that our main results are not simply caused by a correlation with the true upcoming saccade (in which case the activity after resampling would become peaked closer to 45°), but rather reflect the distribution of upcoming saccades (in which case the activity after resampling would remain peaked at ~135°).

Discussion:

Here, during a self-guided search task we found separate functional classes of neurons within the frontal eye field (FEF). Early selection (E-Sel) neurons became predictive of the upcoming saccade direction prior to fixation, before new visual information could be processed, while late selection (L-Sel) neurons became predictive of the upcoming saccade direction following fixation. Along with being predictive of the actual upcoming saccade, E-Sel neurons activity reflected the probability distribution of upcoming saccades, regardless of the actual upcoming saccade direction. This was not the case for L-Sel neurons, whose activity primarily related to the saccade

itself. This suggests E-Sel neurons are involved in preliminary planning of possible movements that may or may not be selected, while L-Sel neurons are involved in definitive planning.

Our findings have some overlap with the results of Phillips and Segraves [7], 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 subpopulations 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 classification based on whether neurons had advanced predictive activity (i.e. whether their activity predicted future saccades), may thus overlap with our classification into E-Sel and L-Sel neurons. Importantly, our study goes beyond confirming their finding that neurons have predictive activity for the upcoming saccade at widely varying times (some early and some late). Here, we have shown that E-Sel neurons don't only have activity related to the actual upcoming saccade, but they (unlike L-Sel neurons) have activity related to the probability of the upcoming saccade (based on eye position), regardless of the actual direction of the saccade that is made. This allowed us to more generally suggest a role for E-Sel neurons in preliminary plans, which may or may not be executed.

A general question in neuroscience is whether neurons belong to distinct cell types or are part of a spectrum. Here, while we have split neurons into two separate classes (E-Sel and L-Sel), it is possible that they lie along a spectrum. We did a preliminary analysis that suggested that the data is better explained by two classes of neurons (Fig. S6). To do this, we approximated a spectrum by subdividing the E-Sel and L-Sel neurons into finer groups (8 total instead of 2) by when they became selective for upcoming saccades. All subgroups of the E-Sel neurons represented preliminary plans similarly, and all subgroups of L-Sel neurons did not represent preliminary plans (Fig. S6). Thus, we believe that placing the neurons on a spectrum did not add explanatory power above and beyond two groups. However, it is difficult to differentiate between separate classes and a spectrum with a limited number of intermediate types. Future work that records from more neurons, and examined these neurons across multiple tasks could help to resolve this distinct-classes versus spectrum question.

While we aimed to record from neurons within FEF, it is possible that some of the recorded neurons were from nearby areas within prefrontal cortex (see *Methods*). Thus, it is possible that both E-Sel and L-Sel may not both have been in FEF; one class may have been in a nearby area. However, we believe this is unlikely as there were many instances in which both E-Sel and L-Sel neurons were recorded from the same electrodes at the same depths. Moreover, in M16, we recorded both E-Sel and L-Sel neurons from electrodes that were confirmed to be in FEF. Thus, while some of the neurons may have been in nearby prefrontal oculomotor structures, at least a portion of both E-Sel and L-Sel neurons were from FEF proper.

Here, we assumed that the neural activity of E-Sel neurons related to eye position 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 [27], 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 [28] 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 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 E-Sel neurons' activities with respect to position matched the statistics of upcoming saccades, and given that FEF has a known role in saccade planning [5,29,30], it is improbable that E-Sel neurons were representing position solely for a purpose other than making saccade decisions.

Previous studies have also suggested that neural activity in superior colliculus (SC) is modulated by eye position in order to bias upcoming saccades. Pare and Munoz [9] 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 [31,32] found the opposite 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 on saccade latencies (Fig. 1), it makes sense that it would affect neural activity related to saccade planning throughout the oculomotor system.

How does the FEF have access to eye position information to use for saccade planning? Given that E-Sel neurons are modulated by the fixation position prior to the start of fixation, these neurons cannot be using a sensory eye position signal. Rather, we suspect that this information is computed based on a corollary discharge signal of the saccade plan coming from superior colliculus (via mediodorsal thalamus) [33,34]. In fact, when this corollary discharge pathway is blocked, monkeys are not able to successfully make sequences of saccades [33,34]. Thus, we would hypothesize that blocking this corollary discharge pathway would interfere with E-Sel neurons' preliminary planning.

When averaging activity across saccades, the activity of E-Sel neurons reflected the full continuous probability distribution of upcoming saccades. This 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 [1-3,35,36]. 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 beneficial to simultaneously record many FEF neurons and perform a single-trial decoding analysis (as in [37]) to determine whether probability distributions are represented prior to single saccades.

Our findings suggest a link between previous studies showing pre-target preparatory activity in constrained tasks and studies showing advanced saccade planning during self-guided saccades. Everling and Munoz [3] showed that FEF neurons had higher activity prior to target onset when there was a higher probability the target would be shown in the neurons' PDs. This parallels our finding that E-Sel 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 [7,8]. These advanced plans could be reflected by E-Sel neurons, which are predictive of the upcoming saccade before gathering new information. Thus, there may be a common mechanism, where E-Sel neurons are

involved in preliminary planning, whether based on saccade probabilities or some saccade sequence planned in advance.

Previous studies have shown that burst neurons in SC and corticotectal neurons in FEF have activity related to the probabilities of upcoming targets prior to target onset [1-3]. After target onset, the activity of these neurons relates to where the target (and saccade) actually are. In the framing of this paper, the same neurons would be involved in both preliminary planning (prior to target onset) and definitive planning (after target onset). Interestingly, our finding of two separate classes is unique from these past studies.

One possible reason for this difference is that we have simply recorded different neurons than in these previous studies, possibly because we used chronic arrays rather than targeting neurons with single electrodes. For instance, the layer 5 corticotectal neurons recorded by Everling and Munoz [3] may be more motor-related since they are the output cells of FEF, while we did not focus on this neuron type. Alternatively, it could be due to differences in the experiments, as the previous experiments involved trials with single saccades to displayed targets, while our trials had multiple saccades and no target onset. In previous experiments, the activity after the target was displayed could have specifically been a visually-evoked response, which we did not see because we did not flash a target onscreen. Additionally, it is possible that E-Sel neurons' activity is specific to our continuous and self-guided saccades. For instance, the activity could be triggered by the end of the previous saccade, or based on planning multiple saccades in advance, both of which would not happen in an experiment with a single saccade. In the future, in order to better understand the differences in our findings, it would be useful to conduct both a classical task with targets and a self-guided search task, while recording from the same neurons.

While we have shown separate neurons related to preliminary (E-Sel) and definitive (L-Sel) planning, the neural circuits involved in transforming preliminary to definitive plans remain unclear. One possibility is that E-Sel neurons project to L-Sel neurons within FEF to influence the saccade plan. Another possibility is that E-Sel neurons project to neurons in SC, which then go on to influence the saccade plan. Both possibilities could also happen simultaneously. Our work clearly could be explained by a large number of different circuit models. Future work should aim to elucidate the circuit mechanisms behind the transformation from preliminary to definitive saccade plans.

Methods:

Many of the methods here, especially for neural data analysis, are the same as in our other recent manuscripts [10,37], 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 [10,11]) freely searched for an embedded Gabor target in a natural scene background, as in [10,11]. They were rewarded for fixating near the target for 200 ms. If they did not find the target within 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, Bozeman, MT, USA) over the frontal eye field (FEF). The depth of each individual tungsten electrode (Alpha-Omega, Alpharetta, GA) could be independently adjusted over a range of 20 mm.

Automatic spike sorting with some manual correction was performed offline using the Plexon Offline Sorter (Plexon, Inc., Dallas, TX, USA). 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.

As stimulation quickly degrades the recording fidelity of the tungsten electrodes in the array, we were unable to stimulate during recording to verify FEF location. Thus (in addition to having the array stereotaxically above FEF), we used functional measures to include neurons that were likely in FEF. We only included neurons that either had visual onset activity or presaccadic 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, to see whether there was a significant difference. To determine whether there was presaccadic activity, we looked at peri-saccadic time histograms aligned to the start of the upcoming saccade, binned into 8 angular directions (according to saccade direction), with each bin subtending 45 degrees. In any bin, if there was a significant difference between a firing rate and baseline, and the rise started before the saccade onset, then there was presaccadic activity. More details about recording locations and

electrical stimulation results can be found in [10]. In sum, while most of the neurons were likely in FEF, it is possible that some neurons were in nearby areas.

We also only included neurons with average firing rates of at least 2 spikes / second in either the early or late period. For the eye movement experiment, the early/late periods were defined as -50 to 100 ms from the start of fixation, and -100 to 0 from saccade onset, respectively. This left us with 104 neurons from Monkey J and 122 neurons from Monkey K.

Behavioral Analysis

We excluded saccades that started or ended off of the screen. Behavioral data was combined across all sessions.

Statistics of movement

We defined the position angle, ϕ_P, as the initial fixation location (prior to saccades) 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 position angle (Fig. 1). That is, $\phi = \phi_S - \phi_P$.

Latency effects

Latency was defined as the time from 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 eye position (when ϕ is near 180°), we did the following test: We calculated the Pearson's correlation between latency and $|\phi - 180°|$. 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 towards the center (|Φ-180°|<60°) and saccades away from the center (|Φ-180°|>120°), based on the distance of the eye position from the borders of the screen. To test whether the latency difference between towards-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 towards-center saccades compared to away-from-center saccades.

Neural Data Analysis

As in our behavioral analyses, we only included saccades that remained on the screen.

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 (position, previous movement, or the upcoming movement). For instance, we created a map of how neural activity varied over all positions on the screen, 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 proportional 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 data points 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 GLM analysis. For all other times, k = the smaller of 30% of the 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. position) we can get the associated estimated firing rate, θ_P, by looking up the firing rate for that position on the smoothed map. If, for instance, we want to get the estimated firing rates due to position 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 rate due to the upcoming saccade, $\boldsymbol{\theta_{US}}$, or previous saccades, $\boldsymbol{\theta_{PS}}$.

Determining Preferred Directions of Neurons

When determining the PD, we used the 100 ms preceding saccade initiation. Let $\boldsymbol{Y}$ be the vector of firing rates in that interval for every saccade. It is possible that some of the neural activity during these time periods is related to the eye position and/or previous saccade, rather than the upcoming saccade. Thus, we first aimed to remove the effect of these variables that might bias the calculated PD. To do so, we created a smoothed map of how position and previous saccades were related to neural activity, and then subtracted the activity related to these variables from the total activity (leaving activity due to upcoming saccades). That is, if $\boldsymbol{\theta_P}$ is the vector of expected firing rates at given positions and $\boldsymbol{\theta_{PS}}$ is the vector of expected firing rates with given previous saccades, then we fit the tuning curves to $\boldsymbol{Y} - \boldsymbol{\theta_P} - \boldsymbol{\theta_{PS}}$. More specifically, we fit a von Mises function to relate the movement directions to the firing rate due to movement:

$$\boldsymbol{Y} - \boldsymbol{\theta_P} - \boldsymbol{\theta_{PS}} = \alpha \exp\left[\beta \cos(\boldsymbol{\phi_S} - \phi_S{}^*)\right]$$

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.

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. All traces are smoothed using a 50 ms sliding window.

PETHs were made for different categories of movements. For the PETHs, saccades near the PD were defined as those that were within 60° of the PD. Saccades opposite the PD were defined as those greater than 120° from the PD. Positions opposite the PD were defined as position angles greater than 120° away from the PD. Positions near the PD were defined as position angles less than 60° away from the PD.

Generalized Linear Model

To determine which variables were reflected in the neural activity, we used a Poisson Generalized Linear model (GLM). Let $\boldsymbol{Y}$ be a vector containing the number of spikes in the time interval we are considering, for every saccade. It has size $m\ x\ 1$. We aimed to predict $\boldsymbol{Y}$ based on several factors. We used the eye position, the previous saccade vector, the upcoming saccade vector, the peak velocity of the upcoming saccade, and a baseline term. More specifically, the covariate matrix $\boldsymbol{X}$ was:

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

where $\boldsymbol{\theta_P}, \boldsymbol{\theta_{US}}$, and, $\boldsymbol{\theta_{PS}}$ are generated from the smoothed maps (see *Smoothed maps of neural activity* above). Essentially, these covariates are the expected firing rates from position, upcoming saccade, and previous saccade (respectively) by themselves. $\mathbf{v_{max}}$ is the vector of peak velocities of movements. The peak velocity was relative to the main sequence [38], to control for the changes of velocity with saccade amplitude (as in [10]). Note that when we run GLMs during different time intervals, we make separate smoothed maps for these time intervals.

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

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

where $\boldsymbol{\beta}$ is a vector of the weights for each covariate that we fit, and $\boldsymbol{X}$ is the matrix of covariates, which is z-scored before fitting. If there are j covariates, then $\boldsymbol{\beta}$ has size $j\ x\ 1$. $\boldsymbol{X}$ has size $m\ x\ j$. Note the use of an exponential nonlinearity to ensure that firing rates are positive. The model assumes that the number of spikes, $\boldsymbol{Y}$, 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 position (described in *Smoothed maps of neural activity*), we only used k-nearest neighbors from the training set, to avoid overfitting.

To test whether an individual covariate significantly influenced neural activity, we first made sure that a simplified model with only that individual covariate had significant predictive power. To determine the value of a model fit, we used pseudo-R^2 [26,39], a generalization of R^2 for non-Gaussian variables, which is defined as:

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

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 $L(\bar{n})$ is the log likelihood of a model that uses only the average firing rate.

Then, in order to determine the importance of that covariate to the full model, we tested whether the full model predicts neural activity significantly better than a model where that covariate is left out (reduced model). To compare the fits between the reduced model (model 1) and full model (model 2), we used relative pseudo-R^2, which is defined as:

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

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.

Neuron types

The activities of both Early Selection and Late Selection neurons were significantly modulated by movement in the GLM analysis (in the early and/or late period). Because many neurons were significantly modulated by movement in both the early and late period, we could not split them into Early and Late Selection neurons based on the GLM results. Rather, we compared the PETHs for saccades near the PD and opposite the PD. To determine the time when a neuron became selective for movement, we found the time when the difference between the "near PD" and "opposite PD" PETHs was growing the most (constrained to be between -150 and 200 ms relative to fixation). This metric essentially found the time when neural activity was separating most between saccades near and opposite the PD. Neurons with a selection time before/after fixation were categorized as Early/Late Selection, respectively.

To compare our classifications with classical cell types, we determined "visual" cells based on the response after the visual scene was initially displayed. For this analysis, for each neuron, we only included trials in which the first saccade after scene onset was opposite 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 50-150 ms after scene onset had to be significantly different ($p < .05$ 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 40-90 ms after scene onset, or 50-100 ms).

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 position angle (Figs. 5,6). We defined the relative position angle as the difference between a neuron's PD and the eye position (the PD minus the eye position angle). 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.

We also made several variants of the above plot (Figs. 5 & 6, Fig. S5). We made plots in which only saccades near or far from the border (split based 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°. To show that the apparent position-related activity was not just due to the correlation with the actual upcoming saccades, we made a plot in which the saccades were resampled, so that the distribution of ϕ's was peaked at 45°, rather than being peaked at ~135°. More specifically, we resampled saccades so that the resampled ϕ's came from a von Mises distribution: $g(\phi) \propto \exp\left[\cos(\phi - 45°)\right]$.

To determine the relative angular position resulting in peak activity (in the 100 ms before target onset), we calculated the activity at 20 relative angular positions (evenly spaced from 0 to 360°), and calculated the circular means of the angles weighted by their activities. We created a 95% confidence interval of peak relative position angles by bootstrapping over the set of neurons, and checked whether this overlapped with the circular mean of the behavioral distribution of ϕ's .

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Supplementary Figures

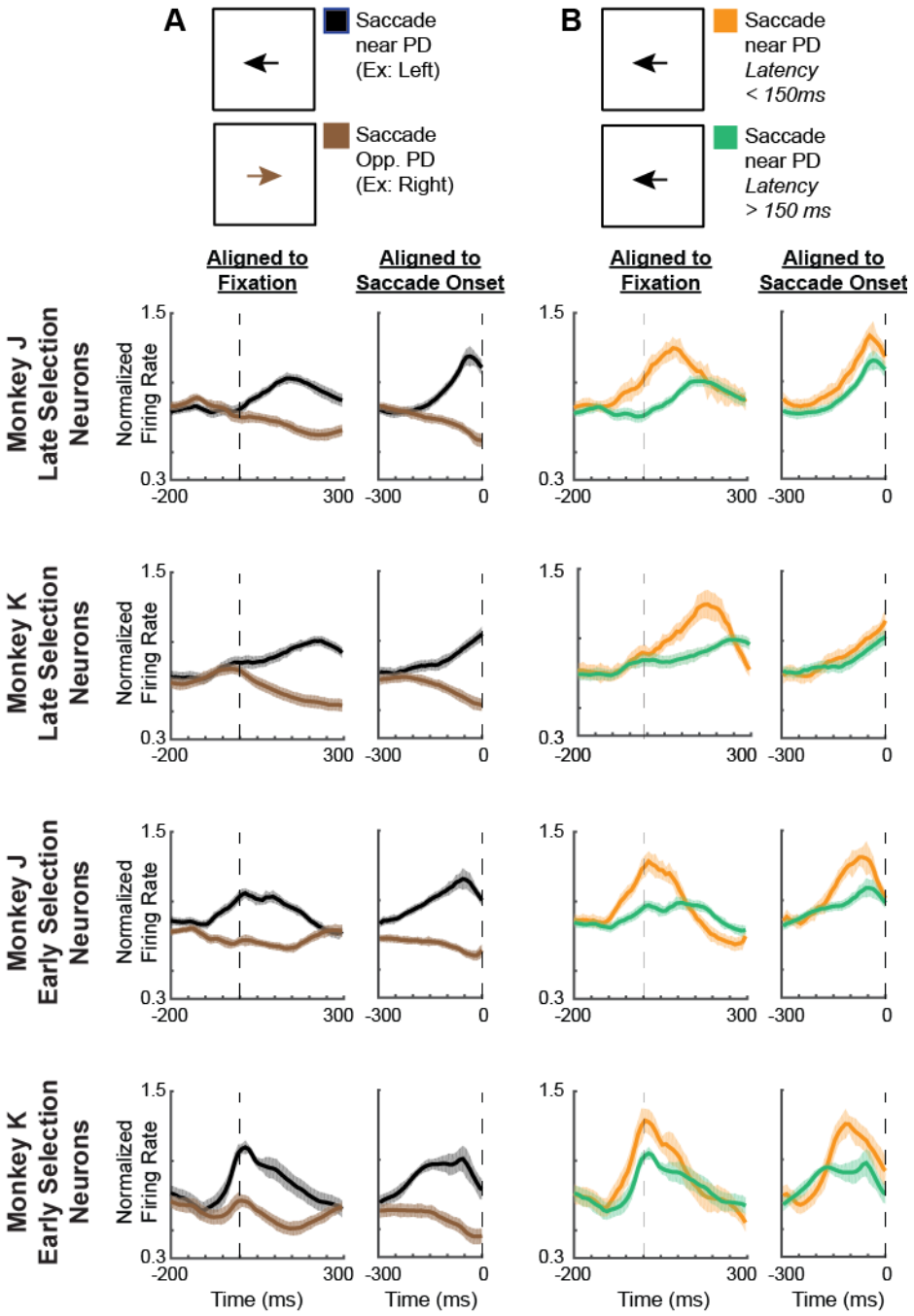

Figure S1: PETHs based on saccade direction and latency, for individual monkeys
Peri-event time histograms (PETHs), aligned both to fixation (left part of each column) and the upcoming saccade onset (right part of each column). **First Row of PETHs**: Normalized averages of late selection neurons from Monkey J. **Second Row**: Normalized averages of late selection neurons from Monkey K. **Third Row**: Normalized averages of early selection neurons from Monkey J. **Bottom Row**: Normalized averages of early selection neurons from Monkey K. **(A)** PETHs of saccades near the preferred direction (PD; black) versus opposite the PD (brown). **(B)** PETHs of saccades near the PD, for saccade latencies less than 150 ms (orange) versus latencies greater than 150 ms (green).

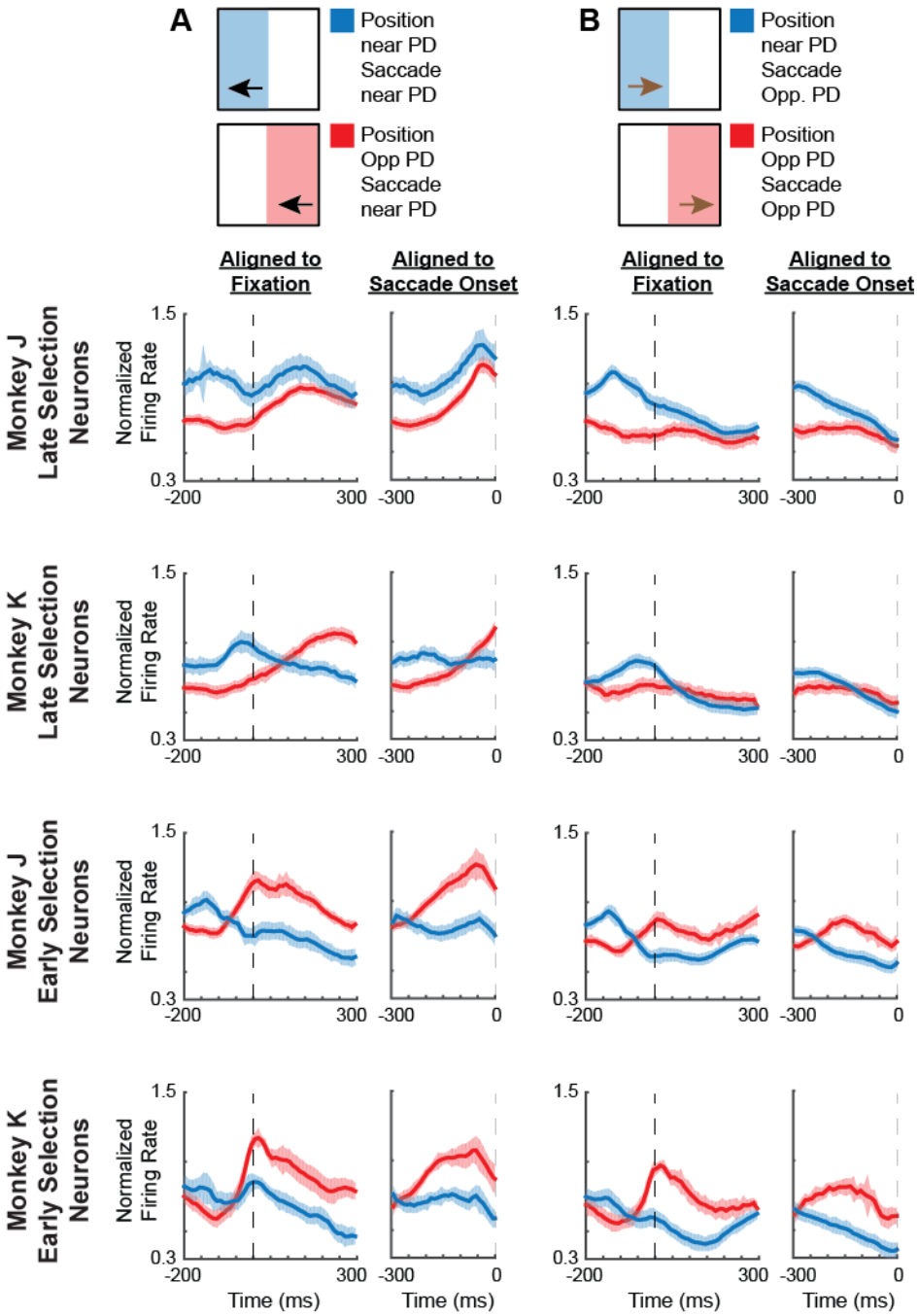

Figure S2: PETHs based on eye position, for individual monkeys
Peri-event time histograms (PETHs), aligned both to fixation (left part of each column) and the upcoming saccade onset (right part of each column). **First Row of PETHs**: Normalized averages of late selection neurons from Monkey J. **Second Row**: Normalized averages of late selection neurons from Monkey K. **Third Row**: Normalized averages of early selection neurons from Monkey J. **Bottom Row**: Normalized averages of early selection neurons from Monkey K. **(A)** PETHs of saccades near the PD, with a starting position near the PD (blue) versus a position opposite the PD (red). **(B)** PETHs of saccades opposite the PD, with a starting position near the PD (blue) versus a position opposite the PD (red).

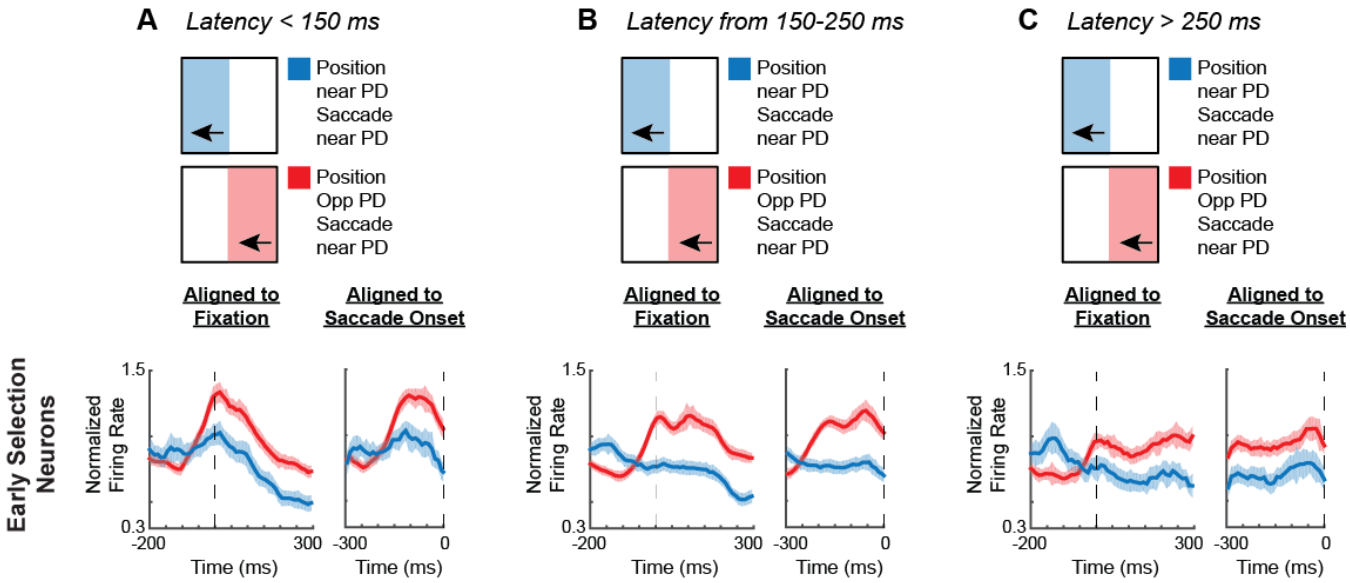

Figure S3: PETHs based on eye position, for different saccade latencies
Peri-event time histograms (PETHs) of E-Sel neuron averages, aligned both to fixation (left part of each column) and the upcoming saccade onset (right part of each column). As in Fig. 3A, we compare PETHs of saccades near the PD, with a starting position near the PD (blue) versus a position opposite the PD (red). Now, we show these plots for **(A)** saccade latencies less than 150 ms, **(B)** saccade latencies from 150-250 ms, and **(C)** saccade latencies greater than 250 ms.

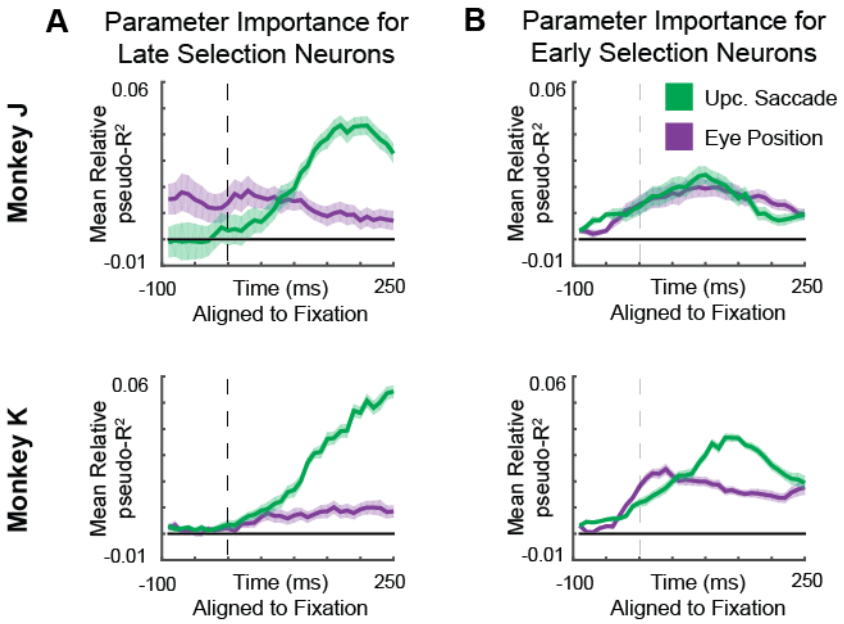

Figure S4: GLM results, for individual monkeys
Importance of parameters in the generalized linear model, across time, aligned to fixation. Results for Monkeys J and K are in the top and bottom rows, respectively. **(A)** The mean relative pseudo-R^2 of the upcoming saccade (green) and eye position (purple) covariates for late selection neurons. **(B)** Same plot for early selection neurons. Shaded areas represent SEMs.

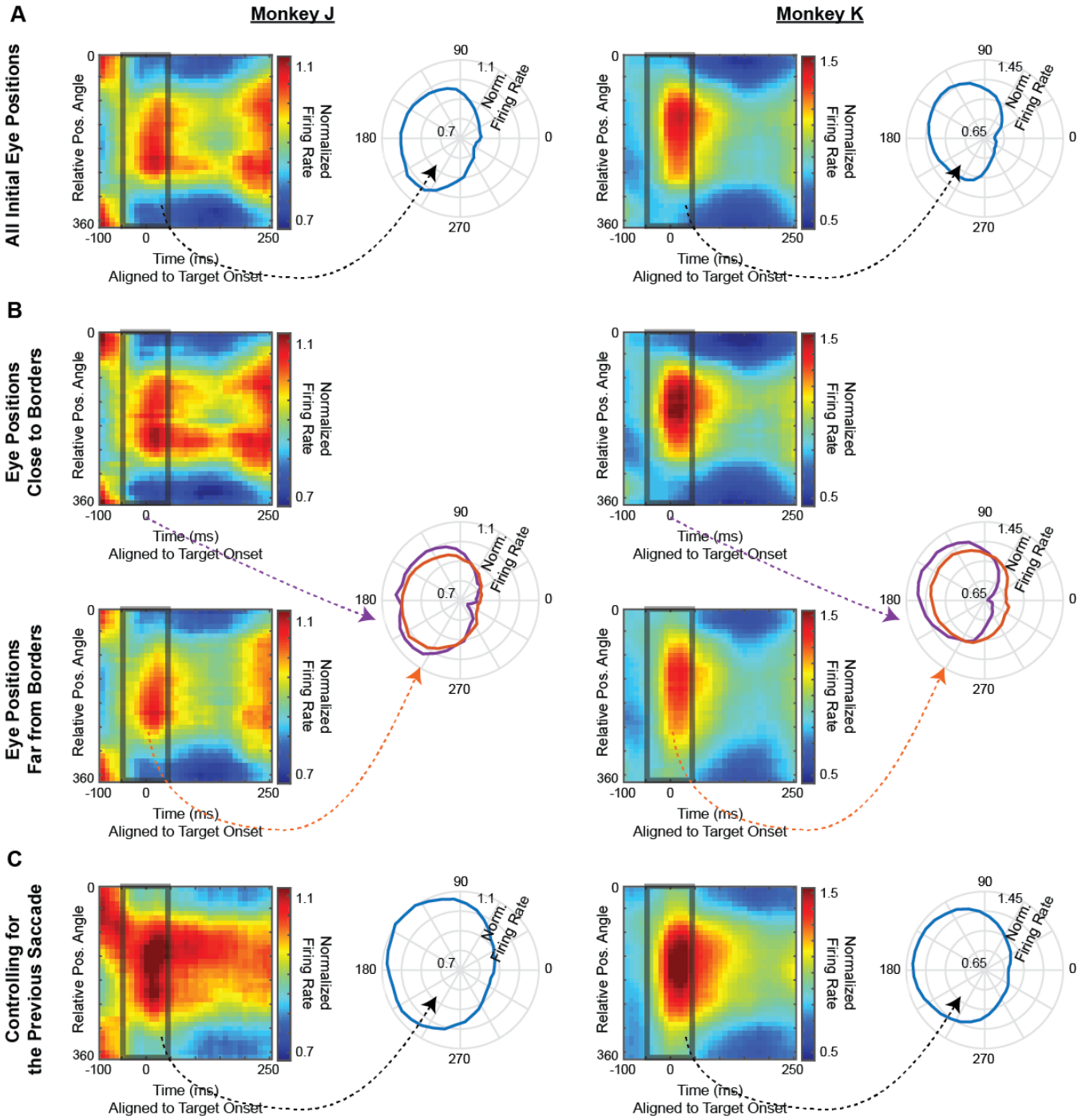

Figure S5: E-Sel population activity reflects the probabilities of upcoming saccades, for individual monkeys

Population activity of E-Sel neurons as a function of relative position angle, for Monkeys J (left) and K (right). **(A)** On the left, a heat map of normalized activity over time, as a function of relative position angle, averaged across neurons. On the right, the normalized average activity in the 100 ms surrounding fixation, as a function of the relative position angle. Only saccades away from the PD are included. **(B)** Same as panel A, but now separated for initial eye positions close to the borders (top left, right in purple) and far from the borders (bottom left, right in orange). **(C)** We control for the correlation between the previous and upcoming saccade directions. We only included saccades in which the previous and upcoming saccade directions were less than 90° apart (while in the actual data, previous and upcoming saccades are more likely to be in opposite directions). Unlike in panels A and B, we do not exclude saccades towards the PD.

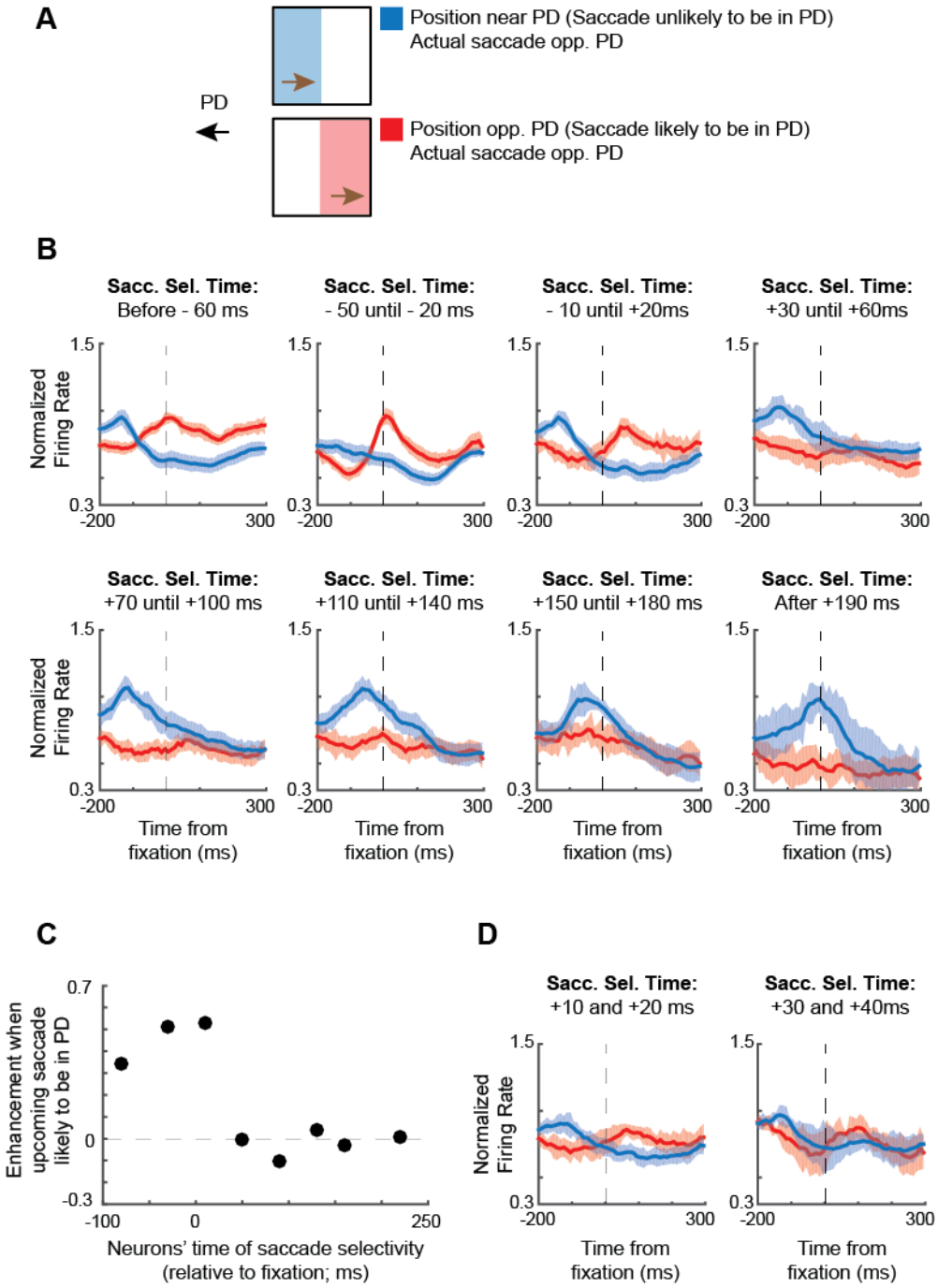

Figure S6: Separate classes of neurons, rather than a spectrum

While we have split neurons into separate classes (E-Sel and L-Sel), they may actually lie along a spectrum. If this were the case, we would expect a gradual transition from strong representation of preliminary plans to no representation. If neurons instead fall into separate classes, we would expect a transition between two response patterns at the class boundary. **(A)** As in Fig. 3b, we show PETHs of saccades opposite the PD, with a starting position near the PD (unlikely that upcoming saccade will be near PD; blue) versus a position opposite the PD (likely that upcoming saccade will be near PD; red). **(B)** PETHs show normalized averages across neurons, and are aligned to fixation onset. Going from left to right, and continuing from the top to bottom row, each panel is for a different set of neurons, with increasing times of saccade selectivity in 40 ms bins. A neuron's time of saccade selectivity is when neural activity was separating most between

saccades near and opposite the neuron's PD (see *Methods*), and were determined at 10 ms resolution. Neurons with early saccade selectivity times (panels 1-3) had greater activity when the upcoming saccade was more likely to be into the PD (red trace greater than the blue trace), an effect not seen for neurons with later selectivity times (panels 4-8). Crucially, there was not a gradual change across the panels, but a stark change between panels 3 and 4. Thus, these PETHs support the hypothesis that the neurons belong to separate classes (although the division appears to be at +20ms rather than at fixation onset; see panel D). **(C)** For each of the PETHs in panel B (the 8 dots shown here), we plot the enhancement of activity (proportion increase) when the upcoming saccade is likely versus unlikely to be in the PD (red trace versus blue trace). For each PETH, we determine the median saccade selectivity time of all the neurons, which is the x-axis value of the dot. For that PETH, we calculate the proportion increase in activity for the red trace 50 ms after the median saccade selectivity time (to allow some time for planning activity to ramp up). This panel more succinctly suggests that the neurons belong to separate classes. **(D)** Evidence that the threshold for saccade selectivity times between the neuron classes is about 20 ms after fixation. On the left, we show neurons with saccade selectivity times of 10 and 20 ms after fixation, and on the right, we show neurons with saccade selectivity times of 30 and 40 ms after fixation. All schematics are the same as in panel B. Note that neurons in the left, but not right, panel have higher activity when it is more likely the upcoming saccade will be near the PD.