Suppression of frontal eye field neuronal responses with maintained fixation

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Abstract

The decision of where to make an eye movement is thought to be driven primarily by responses to stimuli in neurons' receptive fields (RFs) in oculomotor areas, including the frontal eye field (FEF) of prefrontal cortex. It is also thought that a saccade may be generated when the accumulation of this activity in favor of one location or another reaches a threshold. However in the reading and scene perception fields, it is well known that the properties of the stimulus at the fovea often affect when the eyes leave that stimulus. We propose that if FEF plays a role in generating eye movements, then the identity of the stimulus at fixation should affect the FEF responses so as to reduce the probability of making a saccade when fixating an item of interest. Using a visual foraging task, in which animals could make multiple eye movements within a single trial, we found that responses were strongly modulated by the identity of the stimulus at the fovea. Specifically, responses to the stimulus in the RF were suppressed when the animal maintained fixation for longer durations on a stimulus that could be associated with a reward. We suggest that this suppression, which was predicted by models of eye movement behavior, could be a mechanism by which FEF can modulate the temporal flow of saccades based on the importance of the stimulus at the fovea.

Significance

In natural viewing, such as reading or scene perception, fixation can be extended temporally when subjects look at a word or object that is important or requires more processing. Numerous models have suggested that this could occur by a suppressive mechanism. Here we show that responses in the frontal eye field are suppressed when animals maintain fixation on a stimulus that may give them a reward. This suggests that the frontal eye field may be able to modulate the temporal flow of eye movements in natural viewing using enhanced activity to generate eye movements and suppression to maintain fixation.

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Introduction

In natural viewing, each saccade is part of a stream of consecutive eye movements and for each our brain has to decide the goal, rapidly and accurately. Making a decision about where to go in the context of visual search is a complex process that is thought to rely on a combination of factors such as a representation of salience (1), the task relevance of visual objects (2) and expectations or predictions based on past experience (3). Neuronal correlates of such factors have been examined in multiple areas of the brain, including the frontal eye field (FEF) of prefrontal cortex (4), the superior colliculus (5) and the lateral intraparietal area (6). In all cases, studies have focused on the properties of the stimulus within each neuron's response field (RF), which is ubiquitously thought of as the main factor in the neuronal response. In natural visual foraging behavior, however, the properties of the object at the center of gaze and deciding when to leave it are of critical importance. The physical shape, complexity or familiarity of an object (7-10) and how it's related to the task (11) significantly influence the amount of time we spend gazing at it. Indeed, a fundamental aspect of models of eye movements in visual search (12, 13), scene perception (14, 15) and reading (9, 16) is the inclusion of an inhibitory action that keeps the eye from moving if the object being foveated is important for the task.

We hypothesize that if activity in FEF plays a role in when and where a saccade is to be made, then it should incorporate the sort of suppression that these models include to accurately mimic human behavior. In particular, we predict that the response to a stimulus in the RF should be reduced when the animal is looking at an object that it should continue to fixate.

Results

To test the hypothesis that properties of the stimulus at the fovea affect the responses of neurons in FEF, we trained two monkeys (Maccaca Mulatta) to forage for a target, by freely moving their eyes among 10 objects (Fig 1A). While monkeys were performing the foraging task, we recorded the activity from single FEF neurons using extracellular electrodes. Five potential targets (T shape) and five distractors (+ shape) were arranged on the screen in a way that when the animal was looking at one of the objects, no more than one other object could be in the RF (large circle in Fig 1A). One T (the target) was loaded with a reward, which the animals received if they fixated it for 500 ms. Since distractors never delivered any reward, the animals tended to forage among the Ts, fixating each for about 600 ms until they found the target and received the reward (17). Fixations of distractors were rare (less than 5% of fixations) and were significantly ($p=8.70x10^{-158}$, paired t-test, n=231) and substantially shorter (237.6±50.5 ms; mean±SD) than fixations of potential targets (613.7±48.9 ms).

Previous studies have shown that, shortly after array onset, FEF neuronal responses differentiate between a target and distractor in the RF in standard visual search tasks (18, 19). We found a similar result in our population when the array appeared: the response to a potential target in the RF (dark trace, Fig 1B) was consistently higher than the response to a distractor in the RF (light trace, Fig 1B). This difference began to become consistently significant approximately 180 ms after array onset (black bar on x-axis of Fig 1B, $p<0.01$, paired t-test every ms on the spike density function). Using trials in which the fixation point was replaced by a stimulus and another stimulus appeared in the RF, the mean response in a 150 ms window starting 150 after array onset was significantly greater when a T was in the RF than when a distractor was in the RF (18.95±1.47 vs 17.26±1.35 sp/s, $p=2.01x10^{-9}$, Wilcoxon Sign Rank test, n=195 neurons; Fig 1C). At the single neuron level, 40 neurons responded significantly more to a T in the RF than to a distractor in the RF ($p<0.05$, t-test), whereas only 4 had a significantly greater response to the distractor, a number that is within the false positive rate.

A similar effect was seen when we sorted data based on what was in the RF and at the fovea. Figure 2A shows the mean normalized response of 193 FEF neurons aligned by array onset as a function of both stimulus identity in the RF and stimulus identity at the fovea for fixations that lasted at least 300 ms (vertical dashed line). Although the difference between the response to a T in the RF and the response to a distractor in the RF is visible (compare dark to light traces, particularly the dark and light blue traces), the more obvious result is the much higher activity when a distractor was at the fovea (blue traces) than when a T was at the fovea (green traces), which was similar to the baseline response (horizontal dashed line).

When we compared the responses based on what was at the fovea, 107/204 neurons showed significantly higher responses when a distractor was at the fovea than when a T was at the fovea ($p<0.05$, t-tests), whereas only 24 responded more when a target was at the fovea. Across the population of 204 neurons, the mean response when a distractor was at the fovea (22.13±1.76 sp/s; 150 ms window starting 150 ms after array onset) was significantly greater than when a T was at the fovea (15.30±1.21 sp/s; $p=1.64x10^{-15}$; Wilcoxon Sign Rank test; Fig 2B) and the response when a T was at the fovea was not significantly different to the baseline activity seen in the 100 ms before array onset (14.25±1.11 sp/s; $p=0.269$). The effect of stimulus identity at the fovea was significant both when a T was in the RF ($p=8.18x10^{-15}$; Fig 2C) and when a distractor was in the RF ($p=1.41x10^{-9}$; Fig 2D). It is worth noting that both the response difference and the number of neurons showing a significant difference were substantially greater when comparing the identity of the stimulus at the fovea (Fig 2B) than when comparing the identity of the stimulus in the RF (Fig 1C). Thus, the effect of the identity of the stimulus at the fovea is far greater than the effect of the identity of the stimulus in the RF.

The strong modulation of the neuronal response by the identity of the object at the fovea was also observed during ongoing visual search. Figure 3A shows the mean normalized response to the population

of all 231 neurons during ongoing search from fixations of at least 150 ms (vertical dashed line) and in which there was a stimulus at the fovea and a stimulus in the RF. For this and the following analyses, we have pooled the responses to Ts and distractors in the RF, but the results are qualitatively similar if we restrict the analyses to only one of the two stimulus categories, as illustrated in Figs 2B, C & D. The response when a distractor was at the fovea (blue trace, Fig 3A) was substantially and significantly ($p=2.34x10^{-21}$, n=231 neurons, Wilcoxon Sign-Rank test; Fig 3B) higher than when a T was at the fovea (green trace, Fig 3A). Interestingly, this difference started approximately 140 ms before the fixation onset (see black bar on x-axis of Fig 3A; $p<0.01$ paired t-test at each ms) and, in the 100 ms window before the fixation onset, was significant in 100/231 neurons ($p<0.05$, t-tests) and in the population as a whole ($p=8.17x10^{-7}$, Wilcoxon sign-rank test; Fig 3C). This is a greater proportion of neurons than show traditional RF remapping in FEF (20) and suggests that knowledge about the identity of the stimulus that is about to be fixated affects a large proportion of the neurons in FEF and may be independent of previously documented RF remapping.

The modulation of the neuronal response by the stimulus at the fovea was seen in all classes of neurons as categorized in the memory-guided saccade (see Supplemental Information Methods for class definitions). Supplemental Figure S2 plots the data from Fig 3B for the 157 neurons that had sufficient memory-guided saccade mapping data to characterize the neurons as visual (Fig S2A), visuomovement (Fig S2B) or movement (Fig S2C) neurons. For each class of neuron, we found that the response to a stimulus in the RF was significantly greater when a distractor was at the fovea than when a T was at the fovea (all $ps<6x10^{-4}$, Wilcoxon Sign-Rank tests). In addition, the percentage of neurons that responded significantly more when a distractor was at the fovea than when a target was at the fovea were not statistically different across each population (17/37: 45.9%; 54/91: 59.3% and 14/29: 48.3% for visual, visuomovement and movement respectively; $ps>0.170$, chi-squared tests).

To quantify the magnitude of the effect of each factor on the response of all 231 neurons, we ran an ANOVA model on the neuronal responses from a 150 ms window starting at fixation onset using the identity of the object at the fovea and the identity of the object in the RF as fixed variables and neuron identity as a random variable. Neuron identity is an identifier associated with each neuron. We included this as a random variable to take into account the overall responsiveness of the neuron, this way the ANOVA can deal with non-normalized responses across neurons with different response gains and variations. The only significant fixed factor was the identity of the object at the fovea ($p = 0.00054$). The magnitude of this factor was about 30 times stronger than the factor representing the identity of the object in the RF (3.413 compared to 0.113) and there was no significant linear interaction between the fixed factors ($p=0.97$). Note that the effect of the stimulus identity in the RF is considerably weaker in ongoing visual search compared to array onset. This is due to some heterogeneity in the responses to the stimulus in the RF in ongoing search. At the single neuron level, 110 (51%) neurons showed a significant effect of object identity at the fovea, compared to only 38 (18%) of neurons with receptive field effect. Only a few neurons (25, 12%) showed any interaction between the fixed variables (average absolute value of the ANOVA coefficients for all neurons = 1.339).

To test whether the large effect of object identity at the fovea may represent a change in response gain, we looked at two pairs of conditions in which we compared the response to an object in the RF (Fig 3D) or the activity when nothing was in the RF (Fig 3E) as a function of the identity of the object at the fovea. If the increase in activity is due to a consistent gain increase, then the activity should be correlated, with a slope that is significantly different from 1 and with slopes that are the same whether a stimulus was in the RF or not. We found that whether a stimulus was in the RF or not, the activity when a distractor was at the fovea was a little more than 1.2 times greater than when a T was at the fovea, with best fit slopes of 1.23 ± 0.079 ($p=8.1\times10^{-82}$; $R^2=0.81$) with an object in the RF (Fig 3D) and 1.26 ± 0.081 ($p=4.9\times10^{-}$

[90]; R^2=0.84) with nothing in the RF (Fig 3E). Intercepts of the fits were close to the origin (3.57±2.26 sp/s with an object in the RF and 1.17±1.88 sp/s with nothing in the RF), showing that the difference in activity could easily be due to a gain change. To confirm that this was not due entirely to the overall responsiveness of individual neurons, we plotted the ratio of the activity with a distractor at the fovea divided by the activity with a T at the fovea for conditions in which an object was in the RF or nothing was in the RF (Fig 3F). The ratios in the two conditions were correlated (p=0.0081), but more importantly, the majority of the cells (66.2%; 145/219) lay in a cluster in the top right quadrant, meaning they have a positive gain in both conditions. If we only look at neurons that showed a significant effect of object identity at the fovea from the ANOVA analysis described in the previous paragraph then 75.2% (82/109) lie in the top right quadrant and the correlation is much stronger ($p=2.35x10^{-6}$; R^2=0.189), with a slope of 1.03±0.41 and an intercept of 0.73±0.81. Thus, the data are consistent with the hypothesis that the identity of the stimulus at the fovea changes the gain of the neuronal response and that this gain change is relatively consistent across neurons and sessions and is independent of the overall responsiveness of each neuron.

We propose that the reduced response seen when a T is at the fovea is due to a mechanism that suppresses responses throughout the peripheral representation in FEF, thereby minimizing the chance that a saccade will be generated when fixation should be maintained. We have previously shown that animals rarely fixate previously examined Ts (less than 5% of fixations), which will not give them a reward (17). Because fixation durations of previously fixated Ts are bimodal (Fig. 4A), we can test our hypothesis by examining the responses during the two types of fixations. If the reduced response seen when the animal fixates a T is due to a suppressive input aimed at keeping the animal from moving on, then we should see suppression when the animal foveates a previously fixated T for a long duration (>350 ms; see vertical dashed line in Fig 4A), even though it should know that it won't get a reward from the stimulus. Likewise, we should see a strong response, similar to that when the distractor is at the fovea, if the animal only

foveates the previously fixated T for a short duration (<350 ms). Alternatively, if the response modulation is purely due to the identity of the stimulus at the fovea, then we would predict that fixation duration should not affect the response when a previously seen T is being fixated.

Figure 4B shows the response of the neurons to a previously fixated T at the fovea for long and short fixation durations as well as the mean response to a distractor and unseen T at the fovea (lines without error bars). All data are from trials with fixations that lasted for more than 150 ms (vertical dashed line in Fig 4B). In fixations in which the animals foveated the previously fixated T for more than 350 ms, the response was suppressed to a level that was not significantly different from the response when an unseen T was at the fovea ($p=0.406$, Wilcoxon Sign Rank Test, $n=207$, 100 ms window starting 50 ms after fixation onset, Fig 4C). For short duration fixations, the response was significantly higher than for longer durations ($p=8.32 \times 10^{-19}$) and was statistically indistinguishable from the response when a distractor was at the fovea ($p=0.165$, Wilcoxon Sign Rank Test, Fig 4D). This is consistent with our hypothesis that responses in FEF are suppressed when the animal maintains fixation for longer durations.

All the analyses presented so far utilized the responses aligned by the start of fixation when the animals made a saccade away from the receptive field of the neuron. Consistent with previous studies, when the animals made a saccade to the receptive field, the response of the population ramped up to the highest response levels we measured (Fig 5A). Notably, starting approximately 180 ms before the saccade was made, this movement-related activity was not affected by the identity of the stimulus at the fovea (see thick black line on x-axis; $p<0.01$, paired t-tests each ms). Looking at the activity in the 100 ms window leading up to the saccade, there was no significant difference in response as a function of what was currently at the fovea ($p=0.978$, $n=138$, Wilcoxon Sign Rank test; Fig 5B) and this was true even in the subset of neurons that showed a significant effect of object identity at the fovea in the ANOVA analysis described above ($p=0.801$, $n=71$). In addition, the saccade metrics were similar in both cases (see

Supplemental Information Results section for details). Thus, in the time leading up to the saccade, the identity of the stimulus at the fovea no longer affects the movement-related activity nor the movement itself and, in other locations away from the saccade goal, the identity of the stimulus that will end up at the fovea starts to have an effect on responses (as shown in Fig 3A).

Discussion

Here we showed that the response to a stimulus in the RF was greatly affected by the properties of the stimulus at the fovea: when the animal maintained fixation on a stimulus that could be related to a reward for at least 350 ms, the response was strongly suppressed. This surprisingly strong effect appeared to be implemented by a gain control mechanism. This resulted in a robust response to a stimulus in the RF, but only when the animal was fixating a stimulus it would quickly move away from. These results fit with the idea of FEF as an oculomotor area that identifies not only where the next saccade should go, but that can also affect the flow of saccadic behavior.

Within the eye movement literature, the mechanisms thought to be important in driving the temporal flow of saccades are quite different depending upon the field of research. Within the field of reaction time analyses, particularly in decision making and visual search, and within the neurophysiology community, studies have primarily focused on models in which evidence is accumulated before an eye movement is triggered (21-23), including recent work in FEF (24, 25). However, these studies almost all involve eye movements that are punished or rewarded based on whether the eyes go to the correct stimulus. Given that this does not generally occur in natural behavior, it is unclear whether such mechanisms are involved in generating eye movements in unrestrained conditions – indeed, when animals were allowed to move their eyes freely, we previously found that a saccade was generated approximately 50 ms after a peak of activity emerged in LIP (26) rather than when the activity reached a threshold response (27).

On the other hand, within the reading (9, 16) and scene perception (14, 28) communities, it has long been thought that at least part of the intersaccadic interval is due to a suppressive mechanism that keeps the eyes from moving away from items of interest. Models of these eye movements usually include a mechanism in addition to the suppressive mechanism to affect fixation duration, which can include an adaptive timer (13) or an accumulator mechanism (15). Our data bridge the divide between these two communities of oculomotor research by clearly showing that activity in FEF can be suppressed in a way consistent with these models and indicate that this mechanism, which is necessary to describe fixation durations in natural behavior, is present in the brain. In doing so, we validate these models at the neural level, while showing the neurophysiological field that understanding when a saccade will occur depends on more than accumulators alone. Indeed, whether the suppression mechanism in natural viewing works in concert with accumulator mechanisms, as suggested by Tatler et al. (15), or whether there is an alternative mechanism that allows saccades to go to locations of high priority after a timer expires (13) or a peak emerges (26) is yet to be determined.

Although it is not possible to pinpoint the exact origins of this modulatory signal in such a free parameter task, it doesn't change the phenomenological value of this observation. Considering that most of the neurons showed no interaction between the modulation of the receptive field and fovea, this gain based mechanism can easily represent both inside and outside receptive field parameters, such as salience (29) or task relevance (30), although it is unlikely that reward modulation itself causes this effect, since reward modulation is FEF has been reported to be spatially selective and non-significant outside the receptive field (31, 32). The fact that both signals are evident in the response suggests that the activity represents the integration of eye movement priority signals, such as shown in LIP (17, 33), with ongoing cognitive control to fine tune the flow of eye movements.

It may be noted that the difference in response between a T and a distractor in the RF (Fig. 1B) occurs later and is not quite as strong as shown in some previous studies (18, 34, 35). This is due to our choice of comparing the responses on trials in which a saccade was not made to the T in the RF. A similarly small difference can be seen when comparing across conditions in FEF (4) and has been shown in LIP when comparing the responses of targets and distractors when a saccade is made outside of the RF (36) compared to when it is made toward the RF (26).

Our results can also be seen as a multiplexing scheme that integrates multiple factors into a neural code that controls eye movement patterns. In this scheme, the priority of the motor movement is defined by the final readout, but the parameters of the decision are also decodable. Although the task we presented here was relatively simple, with two categories of objects and one level of reward, we hypothesize that the results may be extended to more complex situations. Therefore, a contingency of multiple layers of stimulus identity and reward value related to eye movements could be multiplexed with a gain change mechanism as suggested in other brain areas (37). This kind of coding scheme would not only make the cortical representations more efficient and condensed, but could also be beneficial in solving the dynamic relationship between the current task state in general and a focal object as the goal of the eye movement during strategic planning. In addition, having different levels of gain can be used as the source of diverse top-down modulations on other cortical areas independent of eye movements execution.

Methods

Details can be found in the Supplementary Methods. All experiments were approved by the Chancellor's Animal Research Committee at University of California, Los Angeles as complying with the guidelines established in the Public Health Service Guide for the Care and Use of Laboratory Animals. Electrophysiological recordings were made from two rhesus monkeys, which were trained on a standard memory-guided saccade task and the visual foraging search task (Fig. 1A). Single-unit activity was analyzed during fixations in which there was a single object inside the receptive field and the animal was foveating an object.

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Figure Legends:

Fig. 1. Behavioral task and response of FEF neurons. (A) Example stimulus arrangement in the foraging task, in which five potential targets (T) and five distracters (+) were presented. One T (the target) had a fluid reward linked to it, such that when the monkey looked at it for 500 ms, he obtained the reward. The stimuli were arranged so that when looking at one stimulus (small circle) another stimulus was centered in the FEF neuron's RF (large circle). (B) Normalized population spike density functions in which a T (dark gray trace) or distractor (light gray trace) was in the neuron's RF and the animal made a saccade away from the RF. Thickness of the traces represent the standard error of the mean, with N being the number of neurons in the population. The thick black trace on the x-axis represents times at which the two traces were significantly different ($p<0.01$, paired t-test every ms). (C) The mean responses of the 195 FEF neurons averaged during a 150-ms window starting 150 ms after array onset. Each point represents the activity of a single cell in which a T was in the RF compared to fixations in which a distractor was in the RF. Activity in the scatter is plotted as the square root of spike rate for better visualization.

Fig. 2. (A) Mean normalized responses of 193 FEF neurons aligned by array onset as a function of both stimulus identity in the RF and stimulus identity at the fovea for fixations that lasted at least 300 ms (vertical dashed line) and for which the following saccade was made away from the RF. Blue traces: distractor at the fovea, green traces: T at the fovea, dark traces: T in the RF, light traces: distractor in the RF. The horizontal dashed line indicates the mean response before array onset and the thickness of the traces represent the standard error of the mean, with N being the number of neurons in the population. (B, C, D) the mean responses of FEF neurons during a 150-ms window starting 150 ms after array onset. Each point represents the activity of a single cell when a distractor was at the fovea plotted against the activity

when a T was at the fovea under conditions in which (B) any stimulus was in the RF, (C) a T was in the RF and (D) a distractor was in the RF.

Fig. 3. (A) Mean normalized responses of 221 neurons during ongoing search from fixations of at least 150 ms (vertical dashed line) when a distractor (blue) or a potential target (green) was at the fovea and in which the following saccade would go away from the RF. The horizontal dashed line indicates the mean response before array onset and the thickness of the traces represent the standard error of the mean, with N being the number of neurons in the population. The thick black trace on the x-axis represents times at which the two traces were significantly different ($p<0.01$, paired t-test every ms). For a non-normalized population response, see Supplementary Figure S1. (B, C) Mean responses of single FEF neurons to a distractor at the fovea compared to a T at the fovea during a 100-ms window starting 50 ms after fixation onset (B) or 100 ms before fixation onset (C). To see the data plotted as a function of neuronal class, see Supplementary Figure S2. (D, E) Mean activity of single FEF neurons to a distractor at the fovea compared to a T at the fovea during a 100-ms window starting 50 ms after fixation onset with an object in the RF (D) or with nothing in the RF (E). To see these data plotted in [sqrt(sp/s)] units, see Supplementary Figure S3. (F) The ratio of the activity with a distractor at the fovea divided by the response with a T at the fovea for conditions in which an object was in the RF or nothing was in the RF.

Fig. 4. (A) Distribution of fixation durations when a previously fixated T (seen T) was at the fovea. (B) Mean normalized responses of 224 neurons during ongoing search from fixations of at least 150 ms (vertical dashed line) when a previously fixated T was at the fovea for <350 ms or ≥350 ms or an unfixated target or a distractor was at the fovea. Thickness of the traces represent the standard error of the mean, with N being the number of neurons in the population. The thick black trace on the x-axis represents times

at which the two seen T traces were significantly different ($p<0.01$, paired t-test every ms). (C) Mean responses of single FEF neurons to a distractor at the fovea compared to a previously fixated T (fixation ≥350 ms) during a 100-ms window starting 50 ms after fixation onset with an object in the RF. (D) Mean responses of single FEF neurons to a unseen T at the fovea compared to a previously fixated T (fixation <350 ms) during a 100-ms window starting 50 ms after fixation onset with an object in the RF.

Fig. 5. (A) Mean normalized responses of 221 neurons during ongoing search aligned by saccade onset when the animal made a saccade toward the RF. Thickness of the traces represent the standard error of the mean, with N being the number of neurons in the population. The thick black trace on the x-axis represents times at which the two traces were significantly different ($p<0.01$, paired t-test every ms). (B) The mean responses of single FEF neurons to a distractor at the fovea compared to a T at the fovea during a 100-ms window starting 100 ms before saccade onset.

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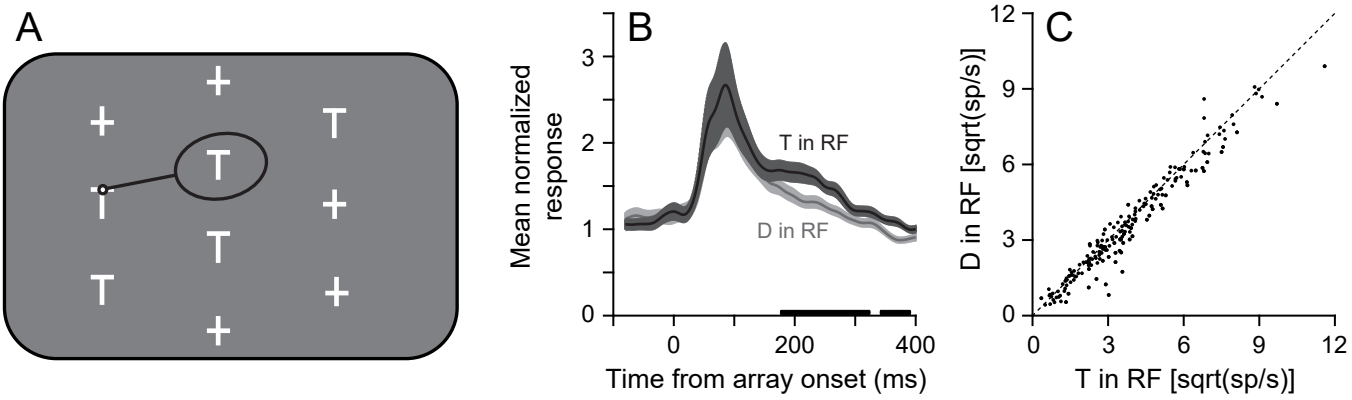
A
B
C
T in RF
D in RF
Mean normalized response
Time from array onset (ms)
D in RF [sqrt(sp/s)]
T in RF [sqrt(sp/s)]

Figure 1

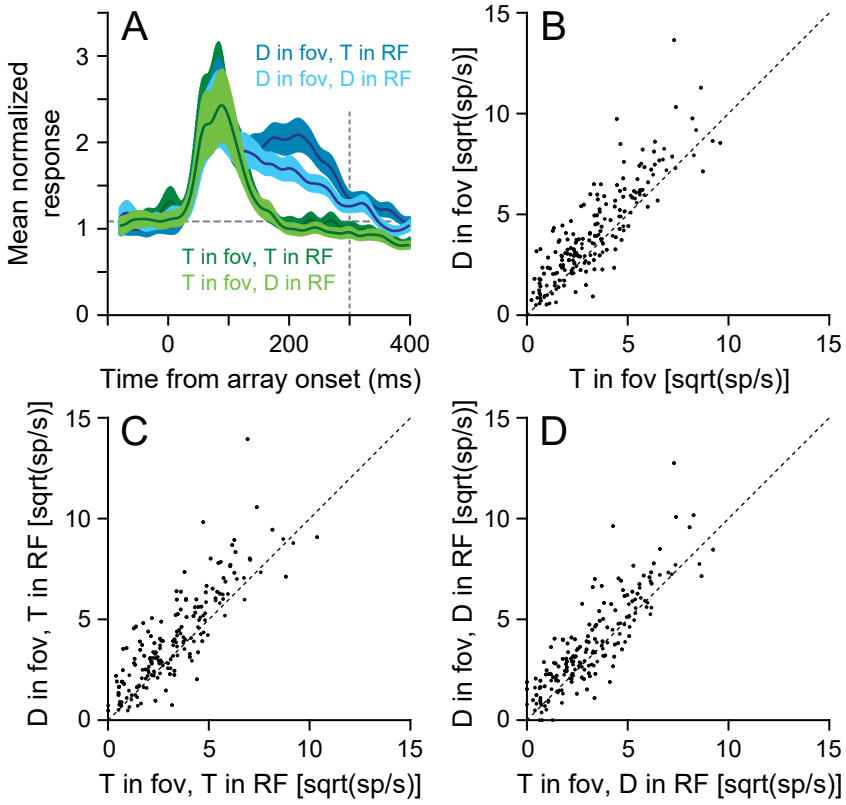
A
D in fov, T in RF
D in fov, D in RF
T in fov, T in RF
T in fov, D in RF
Mean normalized response
Time from array onset (ms)
B
D in fov [sqrt(sp/s)]
T in fov [sqrt(sp/s)]
C
D in fov, T in RF [sqrt(sp/s)]
T in fov, T in RF [sqrt(sp/s)]
D
D in fov, D in RF [sqrt(sp/s)]
T in fov, D in RF [sqrt(sp/s)]

Figure 2

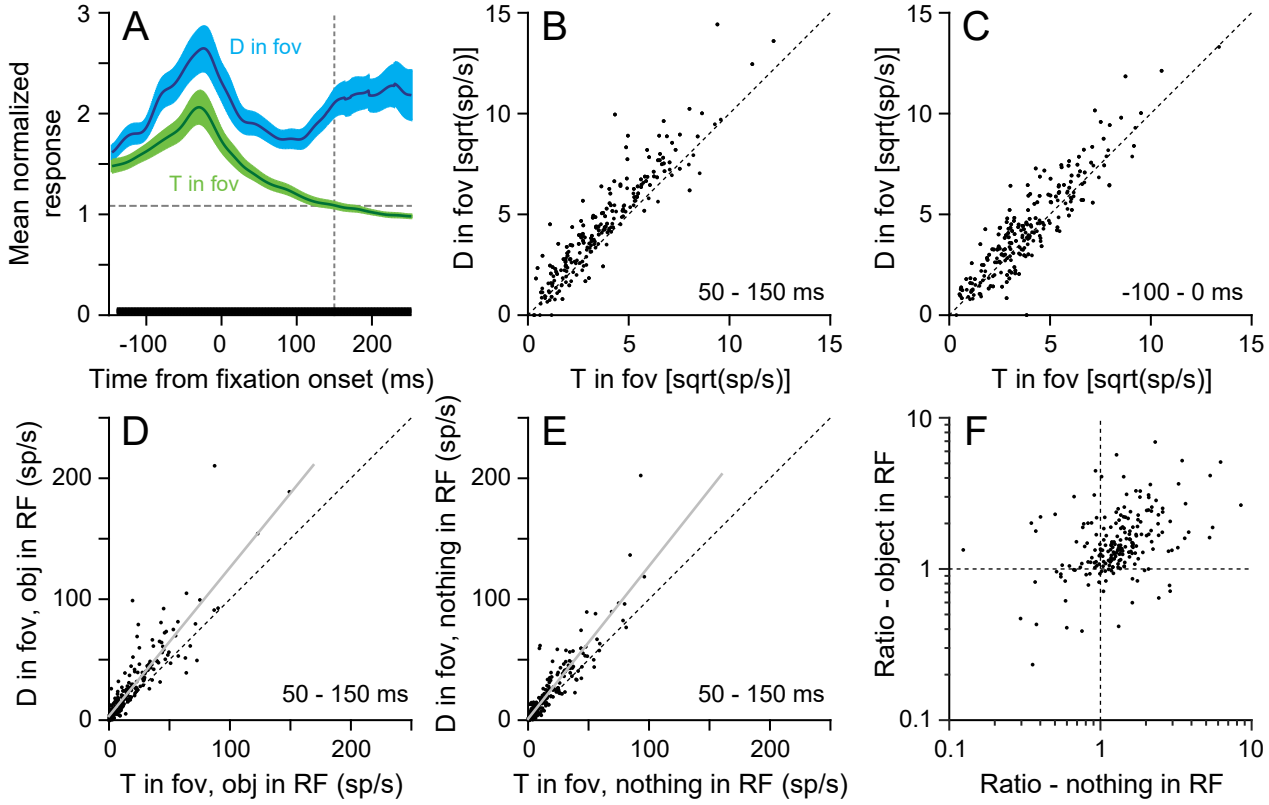
A
D in fov
T in fov
Mean normalized response
Time from fixation onset (ms)
B
D in fov [sqrt(sp/s)]
T in fov [sqrt(sp/s)]
50 - 150 ms
C
-100 - 0 ms
D
D in fov, obj in RF (sp/s)
T in fov, obj in RF (sp/s)
E
D in fov, nothing in RF (sp/s)
T in fov, nothing in RF (sp/s)
F
Ratio - object in RF
Ratio - nothing in RF

Figure 3

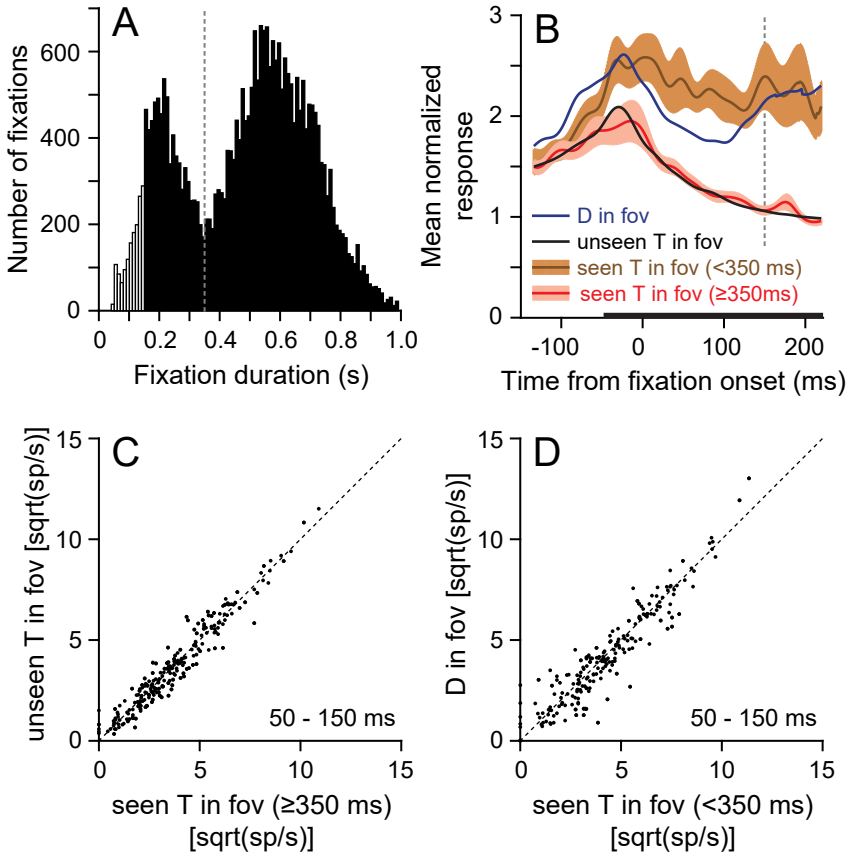
A
Number of fixations
600
400
200
0
0
0.2
0.4
0.6
0.8
1.0
Fixation duration (s)
B
Mean normalized response
3
2
1
0
D in fov
unseen T in fov
seen T in fov (<350 ms)
seen T in fov (≥350ms)
-100
0
100
200
Time from fixation onset (ms)
C
unseen T in fov [sqrt(sp/s)]
15
10
5
0
50 - 150 ms
0
5
10
15
seen T in fov (≥350 ms) [sqrt(sp/s)]
D
D in fov [sqrt(sp/s)]
15
10
5
0
50 - 150 ms
0
5
10
15
seen T in fov (<350 ms) [sqrt(sp/s)]

Figure 4

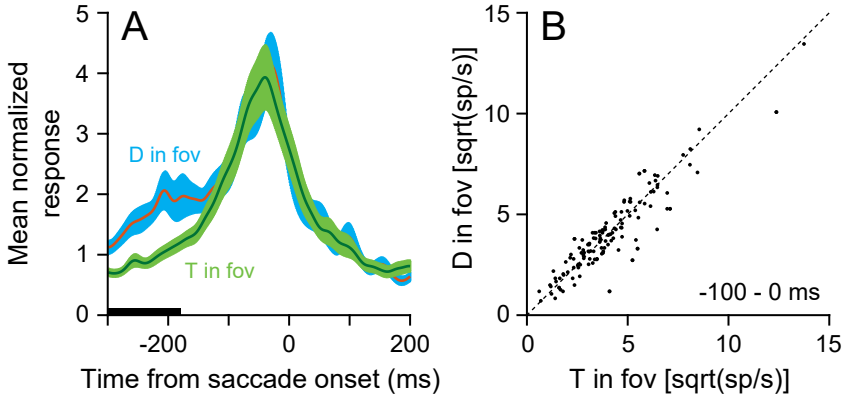
A
B
Mean normalized response
D in fov
T in fov
Time from saccade onset (ms)
D in fov [sqrt(sp/s)]
T in fov [sqrt(sp/s)]
-100 - 0 ms

Figure 5

Supplementary Information

for

Suppression of frontal eye field neuronal responses with maintained fixation

by

Koorosh Mirpour, Zeinab Bolandnazar and James W. Bisley

Supplementary Results

Effect of foveated object on metrics of the next saccade. To determine whether the accuracy or peak velocity of a saccade was related to the object being foveated before the saccade, we examined a subset of saccades with similar lengths from each session. Within a session, saccades of many lengths were made (Fig S4A). As in most sessions, there were two modes of saccade lengths, which were a result of the arrangement of the array. To analyze saccade metrics we took two groups of saccades within the session (gray columns in Fig S4A): those that were within 1 deg length of the peak of the highest mode (mode 1) and those that were within 1 deg length of the peak of the second highest mode (mode 2). To avoid analyzing the same data twice when the peaks were close together or a single peak was present, the second peak had to be at least 2 deg in length longer or shorter than the first peak. No saccades shorter than 1.25 deg were analyzed (vertical dashed line in Fig S4A). A session was only included if there were at least 5 saccades in each mode in each condition. On average, mode 1 included 28.9±0.66% (mean±SEM) of all saccades and mode 2 included 18.3±0.60% of all saccades. In the example shown, mode 1 and mode 2 included 33.4% and 22.9% of saccades within the session

We analyzed two metrics for each saccade: peak velocity and accuracy. While peak velocity is a standard metric easy to identify, determining accuracy in ongoing search is less well defined. In this case, we calculated an error distance, which we defined as the distance between the saccade landing point and the center of the closest stimulus. Figure S4B shows the error distance as a function of the saccade length for all saccades in the same session shown in Fig S4A, separated based on whether the saccade started from a target (blue points) or from a distractor (black points). Figure S4C shows the error distances for modes 1 and 2 plotted close to their mean length. For both modes, there was no difference in error distance based on whether a T was at the fovea or whether a distractor was at the fovea ($p=0.794$, mode 1; $p=0.890$, mode 2; Wilcoxon Rank-Sum tests). For mode 1, only 5 sessions showed a significant difference in error

distance ($p<0.01$, Wilcoxon Rank-Sum test): for 2 sessions the error was greater after leaving a target and for the remaining 3 the error was greater after leaving a distractor. And only 4 sessions showed a significant difference in peak velocity, with 3 having a greater peak velocity after leaving a distractor. For mode 2, only 4 sessions showed a significant difference in error distance and all had greater errors after leaving a distractor and four sessions showed a significant difference in peak velocity, with 3 having a greater peak velocity after leaving a target. Thus, at the single session level, there was no evidence that saccade metrics were affected by the stimulus the animal was foveating before the saccade. Consistent with this, we found no clear effect of the identity of the stimulus at the fovea before the saccade on error distance or peak velocity across the population. For this analysis, we calculated the median peak velocity and error distance for each mode and condition for each session. We then plotted the median error distances (Figs S4D, S4E) and peak velocity for each session for both modes and tested whether they were different using Wilcoxon Sign-Rank tests. Neither metric showed a significant difference in the mode 1 data ($p=0.665$, error distance; $p=0.390$, peak velocity) and, while both metrics showed trends in the mode 2 data ($p=0.063$, error distance; $p=0.033$, peak velocity), neither passed a simple Bonferroni correction ($p<0.0125$). Thus, overall we found no clear and consistent effect of the identity of the stimulus at the fovea on either saccadic metric.

Supplementary Methods

Subjects. All experiments were approved by the Chancellor's Animal Research Committee at UCLA as complying with the guidelines established in the Public Health Service Guide for the Care and Use of Laboratory Animals. Using standard techniques (1, 2), two rhesus monkeys (8-12 kg) were implanted with head posts, scleral coils and recording cylinders during sterile surgery under general anesthesia (2); animals were initially anesthetized with ketamine and Xylazine and maintained with isofluorane. Surgery was conducted using aseptic techniques and analgesics and antibiotics were provided during post-operative recovery.

Behavioral tasks. Both animals were trained on a standard memory guided saccade (MGS) and the foraging visual search task (2, 3). To begin a trial of the MGS, the animals had to fixate a central spot for 300-500 ms, after which a peripheral target was flashed for 200 ms. After the target was extinguished, the animal had to remember the location of the target for 600 ms, after which the fixation point was extinguished and the animal had 450 ms to make a saccade to the remembered location of the target. If the animal landed and remained within 2 deg of the target location, the target reappeared, after which the trial ended and the animal was rewarded with a small drop of juice.

To begin a trial of the foraging task (Fig 1A), the monkeys had to fixate on a spot placed to one side of the screen. After a delay of 450-700 ms, an array of five potential targets (T) and five distractors (+) were presented, with one over the fixation spot. One of the Ts had a juice reward associated with it, such that if the monkey looked at it for 500 ms within 8 seconds after start of trial, he would get the reward. As in previous free-viewing visual search studies in LIP (2, 3), the stimuli were arranged in such a fashion that when the monkey looked at one stimulus, the receptive field of an FEF neuron was likely to encompass one other stimulus (large oval in Fig 1A).

Electrophysiological recording. We recorded extracellular single-unit activity from area FEF using tungsten microelectrodes from the anterior bank of the arcuate sulcus guided by coordinates from MRI images. We confirmed that we were in FEF by the ability to evoke saccades with microstimulation using current intensities of up to 50 μA. Microstimulation was done while animals performed a blink task (4), with a 70 ms train of biphasic pulses, negative first, 0.2 ms width/pulse phase, delivered at a frequency of 330 Hz. Recorded neurons were included in the study if they showed increased activity to one of the stages of visual, delayed or motor MGS and it was significantly higher than response during fixation on fixation point. Consequently, fixation neurons (5) were excluded from this study. The size and position of the receptive field of each neuron was mapped using an automated MGS task covering 9 and then 25 locations (for details see 6). Neurons were also excluded from the study if their receptive fields were so large that they would encompass two stimuli in the array. Receptive field centers ranged from 2.8 deg eccentricity to 15 deg eccentricity and receptive field sizes ranged from 1.25 to 6.5 deg radius in the horizontal direction and 1.25 to 4 deg radius in the vertical direction. After mapping, the foraging task was run and neuronal data were recorded.

Data analysis. Neuronal data were recorded from 231 FEF neurons (78 from monkey E and 135 from monkey M). We roughly discriminated action potentials online and then accurately sorted spikes offline using the SortClient software (Plexon Inc., Dallas, TX). The experiments were run using the REX system (7) and data were recorded using the Plexon system (Plexon Inc., Dallas, TX). Data were analyzed using custom code written in Matlab (Mathworks Inc.).

When sufficient trials were available from the MGS mapping protocol, we used the definitions from Bruce and Goldberg (8) to categorize neurons as visual, visuomovement and movement neurons.

We compared the visual response (50-150 ms after target onset) and the movement response (in the 50 ms before saccade onset) to a baseline response (100 ms before target onset) from that trial. We used paired t-tests at the $p<0.01$ level to indicate significance. Neurons were categorized as visual neurons if only the visual response was significantly higher than the baseline response. Neurons were categorized as visuomovement neurons if both the visual and movement responses were significantly higher than the baseline response. And neurons were categorized as movement neurons if only the movement response was significantly higher than the baseline response.

To analyze the data in the visual foraging task, we first separated trials down into fixations in which there was a single object inside the receptive field. Data were aligned by the beginning of fixation or by the onset of the saccade, using an eye-velocity detection algorithm to detect the saccades. Data are presented as spike density functions (9) using a sigma of 10 ms. Before averaging across neurons, the spike density functions for each neuron were normalized by dividing the activity by a normalizing factor. The factor was calculated for each neuron from all fixations that occurred after the first saccade, that lasted at least 300 ms and that had a T at the fovea and a distractor in the RF. The window for the calculation was 150 ms long starting 150 after fixation onset. When plotting the spike density functions, we plot the mean and standard error of the mean, where the N is the number of neurons.

Different epochs were used to examine spike rates for population and single neuron statistical tests. During the appearance of the visual array, an epoch of 100 ms starting 100 ms after stimulus onset was used. For these analyses, fixations were only included if the animal maintained fixation for at least 300 ms. After the first saccade and during the search an epoch of 100 ms starting 50 ms after the start of fixation was used and for these analyses, fixations were only included if the animal maintained fixation for at least 150 ms. Population tests were performed on average epochs using paired nonparametric

Wilcoxon sign-rank tests. Student t-tests were used for comparing neural responses in different conditions at the single cell level.

Supplementary Figure 1

Fig S1. Mean responses of 221 neurons during ongoing search from fixations of at least 150 ms (vertical dashed line) when a distractor (blue) or a potential target (green) was at the fovea and the following saccade would go away from the RF. Error bars indicate standard error of the mean across the neurons.

Fig S2. Mean responses of single FEF neurons to a distractor at the fovea compared to a T at the fovea during a 100-ms window starting 50 ms after fixation onset plotted separately based on neuron class. These figures plot the same data as in Fig 3B, except they have been sorted based on the neuronal classification using the memory guided saccade: (A) visual neurons; (B) visuomovement neurons; (C) movement neurons. P-values are from Wilcoxon Sign-Rank tests.

Fig S3. The mean activity of single FEF neurons to a distractor at the fovea compared with a T at the fovea during a 100-ms window starting 50 ms after fixation onset in which an object was in the RF (A) or in which nothing was in the RF (B) are included. These show the same data as in Fig 3D and 3E, but plotted as the square root of spike rates for better visualization. In these panels, the line of best fit does not directly relate the mean activity when a distractor is at the fovea to the mean activity when a T is at the fovea.

Fig S4. Illustration of how we tested whether saccade accuracy was affected by the identity of the stimulus at the fovea. (A) The distribution of saccade lengths from all saccades within a single session. The gray bars show the modes of saccade lengths that were used in the detailed analyses. Saccades shorter than 1.25 deg (vertical dashed line) were not analyzed as these represented saccades within the stimulus. (B) The error distance for each saccade is plotted against the length of that saccade for all saccades within the same

session shown in (A) for fixations with a T in the fovea (blue points) and with a distractor in the fovea (black points). (C) The error distance from all saccades with lengths of 4.25-6.25 deg and with lengths of 10.5-12.5 deg are plotted as a function of the identity of the stimulus at the fovea. The p-value above each pair is from a Wilcoxon Rank-Sum test. (D, E) Median error distance for each session in which there were at least 5 saccades in each mode and condition are compared according to the identity of the stimulus at the fovea. (D) shows the results from mode 1 and (E) shows the results from mode 2. The p-values are from Wilcoxon Sign-Rank tests.

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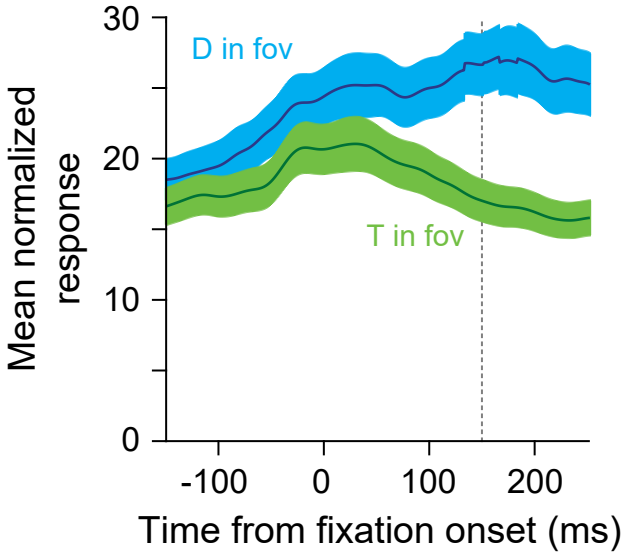

30
20
10
0
D in fov
T in fov
Mean normalized response
-100
0
100
200
Time from fixation onset (ms)

Figure S1

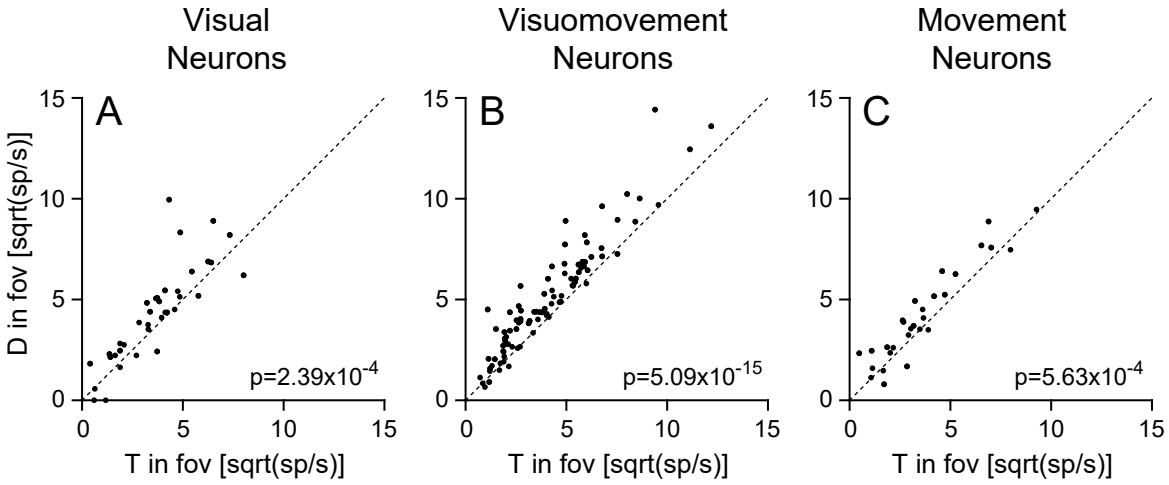
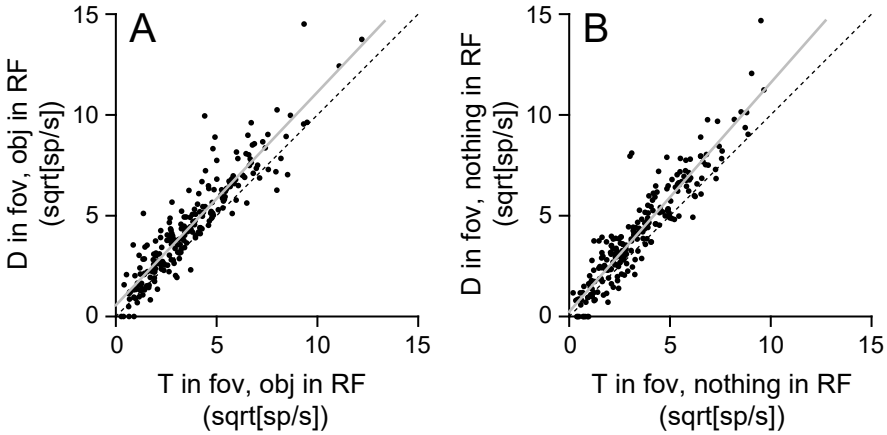

Visual
Neurons
Visuomovement
Neurons
Movement
Neurons
A
B
C
D in fov [sqrt(sp/s)]
T in fov [sqrt(sp/s)]
T in fov [sqrt(sp/s)]
T in fov [sqrt(sp/s)]
p=2.39x10-4
p=5.09x10-15
p=5.63x10-4
0
5
10
15

Figure S2


A
B
D in fov, obj in RF
(sqrt[sp/s])
T in fov, obj in RF
(sqrt[sp/s])
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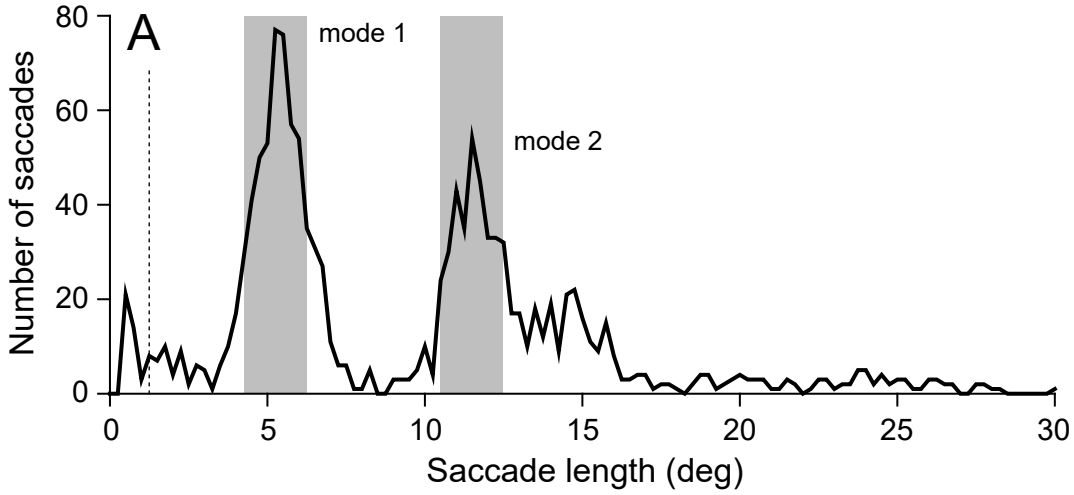
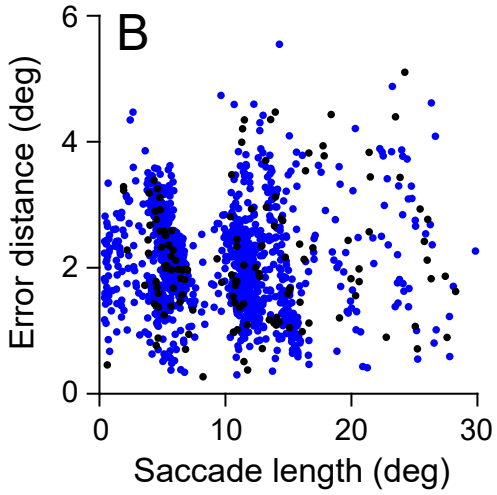
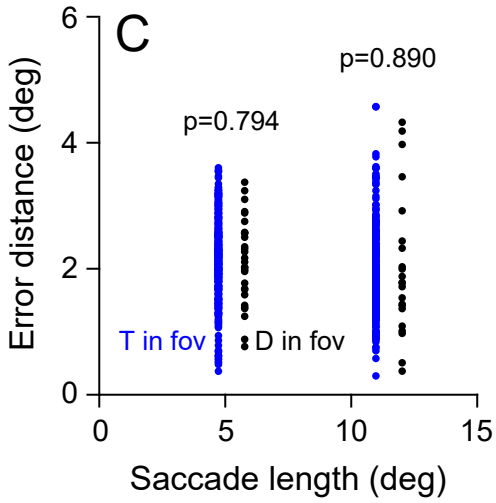
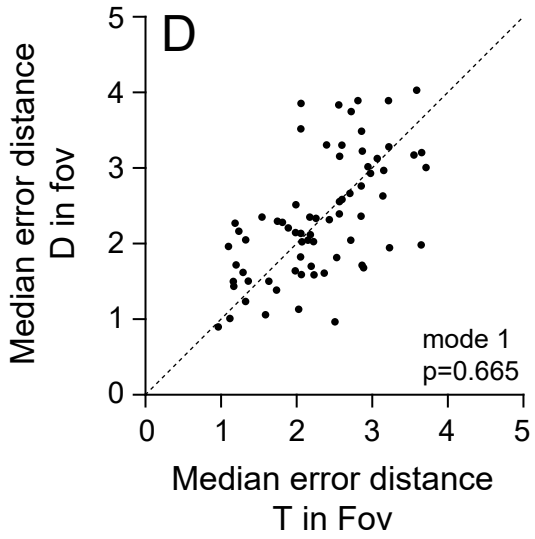
(sqrt[sp/s])
T in fov, nothing in RF
(sqrt[sp/s])
0
5
10
15

Figure S3


A
mode 1
mode 2
Number of saccades
Saccade length (deg)


B
Error distance (deg)
Saccade length (deg)


C
p=0.890
p=0.794
T in fov
D in fov
Error distance (deg)
Saccade length (deg)


D
Median error distance
D in fov
mode 1
p=0.665
Median error distance
T in Fov

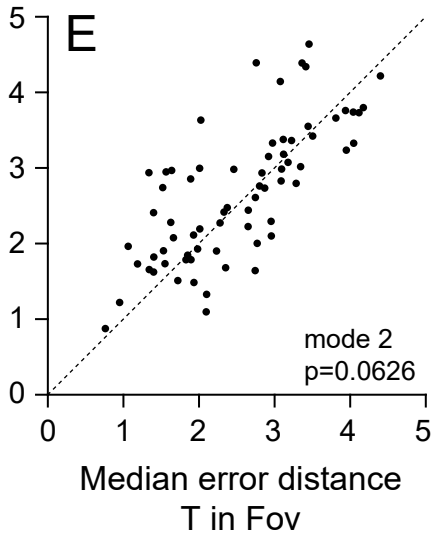

E
mode 2
p=0.0626
Median error distance
T in Fov

Figure S4