



Published in final edited form as:

Nature. ; 474(7351): 372–375. doi:10.1038/nature09995.

CONTROL OF VISUAL CORTICAL SIGNALS BY PREFRONTAL DOPAMINE

Behrad Noudoost and Tirin Moore

Howard Hughes Medical Institute and Department of Neurobiology, Stanford University School of Medicine, Stanford, CA 94305

Abstract

The prefrontal cortex (PFC) is thought to modulate sensory signals in posterior cortices during top-down attention^{1,2}, yet little is known about the underlying neural circuitry. Experimental and clinical evidence suggest that prefrontal dopamine plays an important role in cognitive functions³, acting predominantly through D1 receptors (D1Rs). Here we show that dopamine D1Rs mediate prefrontal control of signals within visual cortex. We pharmacologically altered D1R-mediated activity within the frontal eye field (FEF) of the PFC and measured its effects on the responses of neurons within visual cortex. This manipulation was sufficient to enhance the response magnitude, orientation selectivity and response reliability of neurons in area V4 to an extent comparable with the known effects of top-down attention. The observed enhancement in V4 signals was restricted to neurons with response fields (RFs) overlapping the part of visual space affected by the D1R manipulation. Altering D1R or D2R-mediated FEF activity increased saccadic target selection, but the D2R manipulation did not enhance V4 signals. Our results identify a role of D1Rs in mediating the control of visual cortical signals by the PFC and demonstrate how processing within sensory areas can be altered in mental disorders involving prefrontal dopamine.

Within the PFC, dopamine D1Rs are expressed by about one fourth of all neurons and are localized primarily in superficial and deep layers^{4–6}. Microiontophoretic application of the selective D1R antagonist, SCH23390⁷, at certain doses can increase the persistent, working memory related, component of single-neuron activity within dorsolateral PFC^{3,8,9}. Given the PFC's role in visual attention^{1,2}, we hypothesized that D1Rs might also mediate the PFC's top-down control of visual signals. If true, then changes in D1R-mediated PFC activity might be sufficient to modulate responses within posterior visual cortex, similar to what is observed during selective attention¹⁰. The PFC's influence on visual cortex is achieved in part by the FEF^{1,11,12}, an oculomotor area within posterior PFC. The FEF has a well-established role in saccadic target selection¹³, but recent evidence also implicates this area in

Users may view, print, copy, download and text and data-mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use: http://www.nature.com/authors/editorial_policies/license.html#terms

Correspondence to: Behrad Noudoost, Department of Neurobiology, Stanford University School of Medicine, Fairchild Bldg, 299 Campus Drive West, Stanford, CA 94305, Phone: 650.387.6739, FAX: 650.725.3958, behrad@stanford.edu.

Contributions:

B.N. designed and performed experiments, analysed data and wrote the paper; T.M. designed and performed experiments and wrote the paper.

Competing financial interests:

The authors declare no competing financial interests.

the control of spatial attention^{2,14,15}. To test our hypothesis, we locally infused¹⁶ small volumes (0.5–1 μL) of SCH23390 into sites within the FEF of monkeys performing fixation and eye movement tasks (Fig. 1 and Supplementary Fig. 1). We measured the effects of the FEF infusion on target selection using a free-choice, saccade task¹⁷. In this task, monkeys were rewarded for choosing between two saccadic targets, one located within the FEF_{RF} and one in the opposite hemifield. In the same experiment, we recorded the visual responses of single neurons within extrastriate area V4 during fixation. In particular, we recorded neurons with RFs that overlapped the FEF_{RF}. Thus, we tested the effects of the D1R manipulation both on visual cortical signals and on saccadic target selection.

We found that altering D1R-mediated activity at FEF sites increased the tendency of monkeys to choose targets appearing within the FEF_{RF} (Fig. 1B). In the free choice task, the temporal onset of the two targets was systematically varied such that the FEF_{RF} stimulus could appear earlier or later than the opposite stimulus. The monkey's tendency to select the FEF_{RF} target could then be measured as the temporal onset asynchrony required for equal probability of selecting either stimulus; we termed this the point of equal selection (PES). In the example experiment shown, the monkey chose the FEF_{RF} target as often as the opposite target when the former appeared 76 ms earlier (PES=76). However, infusion of SCH23390 (0.85 μL) into the FEF reduced the PES by 23 ms (binary logistic regression, $p=0.007$), thereby increasing the proportion of FEF_{RF} target choices.

In the same experiment, we also measured the responses of V4 neurons to oriented bars during fixation in a separate task (Fig. 1C, Supplementary methods). We found that the increase in target selection following the SCH23390 infusion was accompanied by an enhanced V4 neuronal response to oriented bars appearing within the overlapping V4_{RF} and FEF_{RF}. The example neuron shown was selective for orientation; it responded more to the 45° than to the 135° bar stimulus ($p<10^{-3}$). Following the infusion of SCH23390, there was not only a significant increase in the overall visual response of this neuron, but also a significant increase in the differential response to the two orientations (Two-way ANOVA, SCH23390 effect, $p<10^{-3}$; SCH23390-orientation interaction, $p<10^{-3}$). Thus, the local perturbation of D1R-mediated FEF activity not only caused the monkey to select FEF_{RF} stimuli as saccade targets more frequently, but it also led to enhanced and more selective visual responses of a V4 neuron representing the same part of space.

We studied the visual responses of 37 V4 neurons with RFs that overlapped the RFs of FEF infusion sites. The average (mean \pm SEM) distance between V4_{RF} and FEF_{RF} centers was 0.71 ± 0.07 degrees of visual angle (Fig. 2A). As with the example neuron, we measured the responses of all neurons to oriented bars appearing in their RF during a 1-second fixation period (Fig. 2B). Prior to onset of the visual stimulus, there was a significant elevation in baseline activity following the D1R manipulation (baseline= 0.077 ± 0.186 , $p=0.030$). In addition to the baseline increase, the visually driven response of V4 neurons was enhanced by 17% above the control response (response= 0.121 ± 0.054 , $p=0.018$). We confirmed that the enhancement in the visual response was not due to systematic changes in eye position during stimulus presentation (Supplementary Fig. 2). The enhancement of the visual response was independently significant for both preferred (preferred= 0.264 ± 0.087 ; $p=0.004$) and for non-preferred stimuli (non-preferred= 0.132 ± 0.062 ; $p=0.032$). In addition,

there was an increase in the response difference between the preferred and non-preferred orientations (response difference=0.132±0.041; p=0.004) (Supplementary Fig. 3), suggesting an increase in orientation selectivity. To measure selectivity more quantitatively, we used a receiver-operating characteristic (ROC) analysis to quantify the degree to which each neuron's responses could be used to judge stimulus orientation (Fig. 2C). This analysis confirmed that V4 neurons were more orientation selective following changes in D1R-mediated FEF activity (ROC area=0.035±0.009, p<10⁻³). The enhancement in V4 response magnitude and selectivity was accompanied by a decrease in the trial-to-trial variability of visual responses. We measured the variability of V4 responses across trials by computing the Fano factor (FF), which is the variance in the spike count divided by its mean. We found that the FF of V4 responses was reduced after the D1R manipulation (FF=-0.105±0.045; p<10⁻³)(Fig. 2D)(Supplementary Fig. 4). All three V4 effects were comparable in magnitude to the known effects of top-down attention, and consistent with a multiplicative increase in the gain of visual signals^{18,19} (Fig. 2E).

The effect of the D1R manipulation on saccadic target selection was highly consistent across the two monkeys tested. Of 21 double-target experiments, the PES was reduced in every case (Fig. 3A). The mean PES shifted in favor of the FEF_{RF} stimulus by an average of 27 ms (PES=-26.934±3.086, p<10⁻³), significantly increasing the overall proportion of FEF_{RF} choices (Chi-square=80.60, p<10⁻³), thus indicating that the D1R manipulation increased the monkeys' tendency to target FEF_{RF} stimuli. The increase in target selection was apparent across a range of drug dosages (Supplementary Fig. 5). In addition to the D1R manipulation, we tested the effects of the D2R-agonist quinpirole. Previous studies using this drug found that it does not affect persistent activity, but rather increases saccade-related activity within dorsolateral PFC²⁰. We found that, like the D1R effect, local manipulation of D2R-mediated FEF activity increased the selection of FEF_{RF} targets (Fig. 3A). The PES shifted an average of 22 ms (PES=-21.993±6.758, p=0.010), increasing the proportion of FEF_{RF} choices (Chi-square= 13.86, p<10⁻³). Thus, the D1R and D2R-mediated manipulations of FEF activity resulted in equivalent increases in saccadic target selection.

In spite of the increase in target selection, manipulation of D2R-mediated activity in FEF failed to enhance the responses of V4 neurons. We found no significant effect on the visual response magnitude, orientation selectivity or response variability of V4 neurons following the D2R manipulation (response=0.001±0.048, p=0.999; ROC area=-0.007±0.010, p=0.426; FF=0.037±0.052, p=0.338; n=15) (Fig. 3B). Moreover, the changes in these measures were all significantly different from the changes we observed with the D1R manipulation (response_{D2R}< response_{D1R}, p=0.045; selectivity_{D2R}< selectivity_{D1R}, p=0.011; FF_{D2R}> FF_{D1R}, p=0.019). Thus, the equivalent effects of D1R and D2R on saccadic target selection were accompanied by contrasting effects in V4, in which the enhancement of visual signals was specific to D1R-mediated activity.

We also found that the enhancement of visual signals following the D1R manipulation was confined to V4 neurons with RFs that overlapped the FEF_{RF}. For V4 neurons with RFs that did not overlap the FEF_{RF} (mean distance between V4_{RF} and FEF_{RF}=9.00±0.86 d.v.a.; n=15), we found no significant effect of the D1R manipulation on response magnitude (response=-0.028±0.087, p=0.9780), orientation selectivity (ROCarea=-0.017±0.010,

$p=0.187$) or the FF ($FF=0.010\pm 0.043$, $p=.688$). Importantly, the changes in these measures were all significantly different from the changes observed in neurons with overlapping RFs ($\text{response}_{\text{non-overlap}} < \text{response}_{\text{overlap}}$, $p=0.044$; $\text{selectivity}_{\text{non-overlap}} < \text{selectivity}_{\text{overlap}}$, $p=0.007$; $FF_{\text{non-overlap}} > FF_{\text{overlap}}$, $p=0.034$) (Fig. 3B). Thus, the enhancement in visual cortical signaling produced by the manipulation of D1R-mediated FEF activity was spatially specific.

We also tested the effects of complete inactivation of FEF sites on the responses of V4 neurons with overlapping RFs. Previous studies have shown that local inactivation of the FEF disrupts saccadic target selection and impairs attention^{17,21}. We therefore wondered if inactivation could reduce the components of V4 responses that were enhanced by the D1R manipulation. We locally inactivated FEF sites with the GABA_A agonist muscimol. Unlike the sparsely localized D1Rs, GABA_A receptors are widely expressed by all neurons in all cortical layers²². As in previous studies, local inactivation of FEF sites with muscimol decreased the targeting of FEF_{RF} stimuli. FEF inactivation also significantly reduced V4 orientation selectivity ($\text{ROC area} = -0.030 \pm 0.011$, $p=0.003$; $n=33$). However, the inactivation did not change the response magnitude or variability of V4 neurons ($\text{response} = 0.016 \pm 0.061$, $p=0.809$; $FF = -0.002 \pm 0.023$, $p=0.921$) (Fig. 3B). Thus, in contrast to the D1R manipulation, which altered all 3 components of V4 activity, complete inactivation altered only one. All 3 inactivation effects were significantly different from the D1R effects ($\text{response}_{\text{muscimol}} < \text{response}_{\text{D1R}}$, $p=0.024$;

$\text{selectivity}_{\text{muscimol}} < \text{selectivity}_{\text{D1R}}$, $p < 10^{-3}$; $FF_{\text{muscimol}} > FF_{\text{D1R}}$, $p=0.007$). Although the reduction in orientation selectivity is consistent with previous electrical microstimulation studies¹², and with the effects of inactivation on orientation discrimination²¹, the lack of a reduction in response magnitude may seem less congruent. However, we suggest that this difference is due to variation between experimental paradigms (Supplemental discussion). Finally, we tested for any effects of vehicle (saline) infusions into the FEF. The infusion of saline failed to change the response magnitude, selectivity or variability of V4 neurons ($\text{response} = 0.018 \pm 0.048$, $p=0.380$; $\text{ROC area} = -0.010 \pm 0.013$, $p=0.569$; $FF = -0.035 \pm 0.061$, $p=0.179$; $n=12$) (Fig. 3B). All 3 measures were significantly different from the D1R effects ($\text{response}_{\text{saline}} < \text{response}_{\text{D1R}}$, $p=0.045$; $\text{selectivity}_{\text{saline}} < \text{selectivity}_{\text{D1R}}$, $p=0.013$; $FF_{\text{saline}} > FF_{\text{D1R}}$, $p=0.009$).

Our results identify prefrontal D1Rs as a component of the neural circuitry controlling signals within visual cortex. Manipulation of D1R-mediated FEF activity was sufficient to enhance the magnitude, reliability and visual selectivity of neuronal responses within area V4, three known effects of visual attention. The observed enhancement might account for the benefits in visually guided behavior that accompany attentional deployment (Supplementary Fig. 6), though a causal link between attentional modulation of visual cortical signals and visual perception remains to be established. Our results demonstrate how visual representations within posterior areas can be altered merely by changes in dopamine tone within the PFC. Given the complex effects of dopamine through D1Rs, one might predict that at “optimum” dopamine levels⁹, optimal effects of top-down control of visual cortical signals, would be achieved.

The circuitry underlying top-down control of visual cortex likely involves a number of different neuromodulators e.g. 23 and an array of different brain structures e.g. 24. Our results show that this circuitry involves prefrontal dopamine acting via D1Rs. Within dorsolateral PFC, dopamine D1Rs are thought to modulate recurrent glutamatergic connections, thereby influencing working memory related activity in this area^{25,26}. The present results suggest that D1Rs contribute to the FEF's control of visual signals by an analogous mechanism, namely by modulating (long-range) recurrent connections between the FEF and visual cortex (Supplementary Fig. 7). Since superficial layer FEF neurons are reciprocally connected with neurons in V4^{2,27}, dopaminergic modulation of these connections via superficial layer D1Rs would be expected to mediate the FEF's control of V4 signals. The specificity of V4 effects to D1Rs, rather than D2Rs, might be explained by the relative absence of D2Rs in superficial layers of prefrontal cortex⁴⁻⁶. The equivalent target selection effects of D1R and D2R manipulations might be explained by the presence of both receptor subtypes within infragranular layers of cortex⁴⁻⁶, where layer V FEF neurons project to the superior colliculus²⁷. Importantly, impairments in saccadic control are prominent among the set of impairments exhibited in attention deficit/hyperactivity disorder (ADHD)²⁸. The observed influence of prefrontal D1Rs on saccadic target selection and visual cortical signals, combined with their known influence on persistent activity, may explain the behavioral links between saccadic control, attention and working memory²⁹, and the coincidence of their corresponding impairments in ADHD³⁰.

Methods

The effects of pharmacologic perturbations of FEF activity on target selection and the visual responses of V4 neurons was studied in three macaque monkeys performing fixation and eye movement tasks (supplementary information). All experimental procedures were in accordance with National Institutes of Health Guide for the Care and Use of Laboratory Animals, the Society for Neuroscience Guidelines and Policies, and approved by the Stanford University Animal Care and Use Committee. Eye position was monitored with a scleral search coil. In each experiment, we infused small volumes of drug into sites within the FEF through a surgically implanted titanium chamber overlaying the arcuate sulcus using a custom-made recording microinjector. We identified FEF sites by eliciting short-latency, fixed-vector saccadic eye movements with trains (50 – 100 ms) of biphasic current pulses (50 μ A; 250 Hz; 0.25 ms duration). In the same experiment, recordings from V4 neurons were made through a chamber overlaying the prelunate gyrus. Response fields (RF) of V4 neurons were all located in the lower quadrant of the contralateral hemifield (<12° eccentricity). The position of the FEF microinjector was adjusted so that the saccade elicited by FEF microstimulation either shifted the monkey's gaze to within the V4 RF (overlapping) or far outside of it (non-overlapping).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank Doug S. Aldrich for technical assistance, N. Steinmetz for help with the Fano factor analysis, and W.T. Newsome, E.I. Knudsen, K. M. Armstrong, and R.F. Squire for valuable comments on the manuscript. This work was supported by NIH EY014924, NSF IOB-0546891, The McKnight Foundation, and an IBRO Fellowship to B.N.

References

1. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* 2001; 24:167–202. [PubMed: 11283309]
2. Noudoost B, Chang MH, Steinmetz NA, Moore T. Top-down control of visual attention. *Curr. Opin. Neurobiol.* 2010; 20:183–190. [PubMed: 20303256]
3. Robbins TW, Arnsten AF. The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. *Annu. Rev. Neurosci.* 2009; 32:267–287. [PubMed: 19555290]
4. Lidow MS, Goldman-Rakic PS, Gallager DW, Rakic P. Distribution of dopaminergic receptors in the primate cerebral cortex: quantitative autoradiographic analysis using [3H]raclopride, [3H]spiperone and [3H]SCH23390. *Neuroscience.* 1991; 40:657–671. [PubMed: 2062437]
5. Lidow MS, Wang F, Cao Y, Goldman-Rakic PS. Layer V neurons bear the majority of mRNAs encoding the five distinct dopamine receptor subtypes in the primate prefrontal cortex. *Synapse.* 1998; 28:10–20. [PubMed: 9414013]
6. Santana N, Mengod G, Artigas F. Quantitative analysis of the expression of dopamine D1 and D2 receptors in pyramidal and GABAergic neurons of the rat prefrontal cortex. *Cereb. Cortex.* 2009; 19:849–860. [PubMed: 18689859]
7. Bourne JA. SCH 23390: the first selective dopamine D1-like receptor antagonist. *CNS. Drug Rev.* 2001; 7:399–414. [PubMed: 11830757]
8. Williams GV, Goldman-Rakic PS. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature.* 1995; 376:572–575. [PubMed: 7637804]
9. Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nat. Neurosci.* 2007; 10:376–384. [PubMed: 17277774]
10. Reynolds JH, Chelazzi L. Attentional modulation of visual processing. *Annu. Rev. Neurosci.* 2004; 27:611–647. [PubMed: 15217345]
11. Gregoriou GG, Gotts SJ, Zhou H, Desimone R. High-frequency, long-range coupling between prefrontal and visual cortex during attention. *Science.* 2009; 324:1207–1210. [PubMed: 19478185]
12. Moore T, Armstrong KM. Selective gating of visual signals by microstimulation of frontal cortex. *Nature.* 2003; 421:370–373. [PubMed: 12540901]
13. Schall JD, Hanes DP. Neural basis of saccade target selection in frontal eye field during visual search. *Nature.* 1993; 366:467–469. [PubMed: 8247155]
14. Thompson KG, Biscoe KL, Sato TR. Neuronal basis of covert spatial attention in the frontal eye field. *J. Neurosci.* 2005; 25:9479–9487. [PubMed: 16221858]
15. Armstrong KM, Chang MH, Moore T. Selection and maintenance of spatial information by frontal eye field neurons. *J. Neurosci.* 2009; 29:15621–15629. [PubMed: 20016076]
16. Noudoost B, Moore T. A reliable microinjectrode system for use in behaving monkeys. *J. Neurosci. Methods.* 2011; 194:218–223. [PubMed: 20951736]
17. Schiller PH, Tehovnik EJ. Cortical inhibitory circuits in eye-movement generation. *Eur. J. Neurosci.* 2003; 18:3127–3133. [PubMed: 14656309]
18. Mitchell JF, Sundberg KA, Reynolds JH. Differential attention-dependent response modulation across cell classes in macaque visual area V4. *Neuron.* 2007; 55:131–141. [PubMed: 17610822]
19. McAdams CJ, Maunsell JH. Effects of attention on orientation-tuning functions of single neurons in macaque cortical area V4. *J. Neurosci.* 1999; 19:431–441. [PubMed: 9870971]
20. Wang M, Vijayraghavan S, Goldman-Rakic PS. Selective D2 receptor actions on the functional circuitry of working memory. *Science.* 2004; 303:853–856. [PubMed: 14764884]

21. Monosov IE, Thompson KG. Frontal eye field activity enhances object identification during covert visual search. *J. Neurophysiol.* 2009; 102:3656–3672. [PubMed: 19828723]
22. Huntsman MM, Isackson PJ, Jones EG. Lamina-specific expression and activity-dependent regulation of seven GABAA receptor subunit mRNAs in monkey visual cortex. *J. Neurosci.* 1994; 14:2236–2259. [PubMed: 8158267]
23. Herrero JL, et al. Acetylcholine contributes through muscarinic receptors to attentional modulation in V1. *Nature.* 2008; 454:1110–1114. [PubMed: 18633352]
24. McAlonan K, Cavanaugh J, Wurtz RH. Guarding the gateway to cortex with attention in visual thalamus. *Nature.* 2008; 456:391–394. [PubMed: 18849967]
25. Goldman-Rakic PS. Cellular basis of working memory. *Neuron.* 1995; 14:477–485. [PubMed: 7695894]
26. Durstewitz D, Seamans JK, Sejnowski TJ. Neurocomputational models of working memory. *Nat. Neurosci.* 2000; (3 Suppl):1184–1191. [PubMed: 11127836]
27. Pouget P, et al. Visual and motor connectivity and the distribution of calcium-binding proteins in macaque frontal eye field: implications for saccade target selection. *Front Neuroanat.* 2009; 3:2. [PubMed: 19506705]
28. Munoz DP, Armstrong IT, Hampton KA, Moore KD. Altered control of visual fixation and saccadic eye movements in attention-deficit hyperactivity disorder. *J. Neurophysiol.* 2003; 90:503–514. [PubMed: 12672781]
29. Awh E, Armstrong KM, Moore T. Visual and oculomotor selection: links, causes and implications for spatial attention. *Trends Cogn Sci.* 2006; 10:124–130. [PubMed: 16469523]
30. Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat. Rev. Neurosci.* 2002; 3:617–628. [PubMed: 12154363]

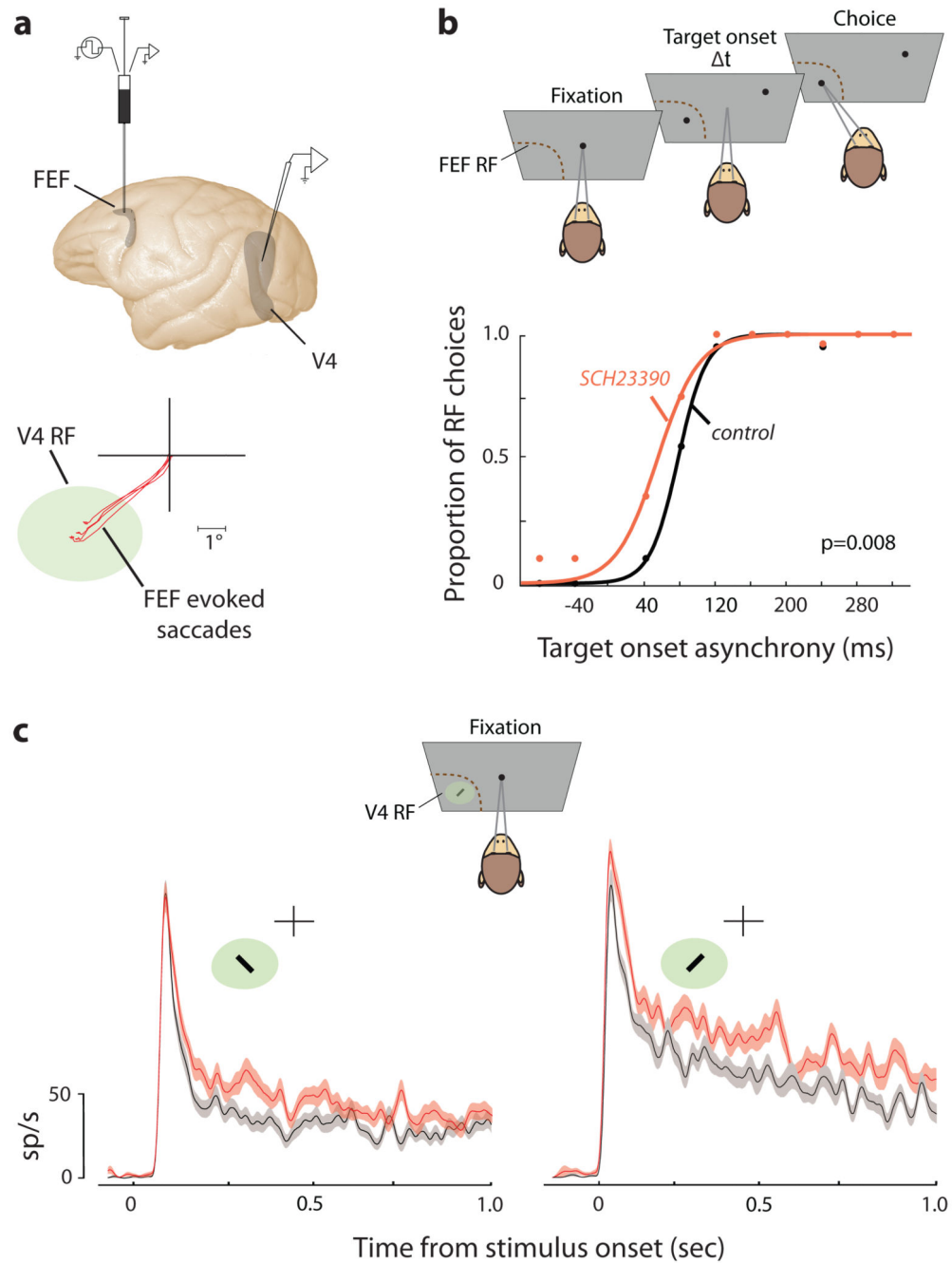


Figure 1. Local manipulation of DIR-mediated activity within the FEF during single neuron electrophysiology in area V4. **a**, Lateral view of the macaque brain depicts the location of a recording microsyringe within the FEF and of recording sites within area V4. Bottom diagram shows saccades evoked via electrical microstimulation at the infusion site (red traces) and the RF (green ellipse) of a recorded V4 neuron in an example experiment. **b**, Double-target, saccade task used to measure the monkey's tendency to make saccades to a target within the FEF_{RF} vs. one at an opposite location across varying temporal onset

asynchronies. Positive asynchrony values denote earlier onset of FEF_{RF} targets. Bottom plot shows the leftward shift in the PES, indicating more FEF_{RF} choices, following infusion of SCH23390 into an FEF site. **c**, Visual responses of a V4 neuron with a RF that overlapped the FEF_{RF} measured during passive fixation. The plot shows mean±S.E.M. visual responses to a bar stimulus presented at orthogonal orientations before (gray) and after (red) the infusion of SCH23390 at the FEF site.

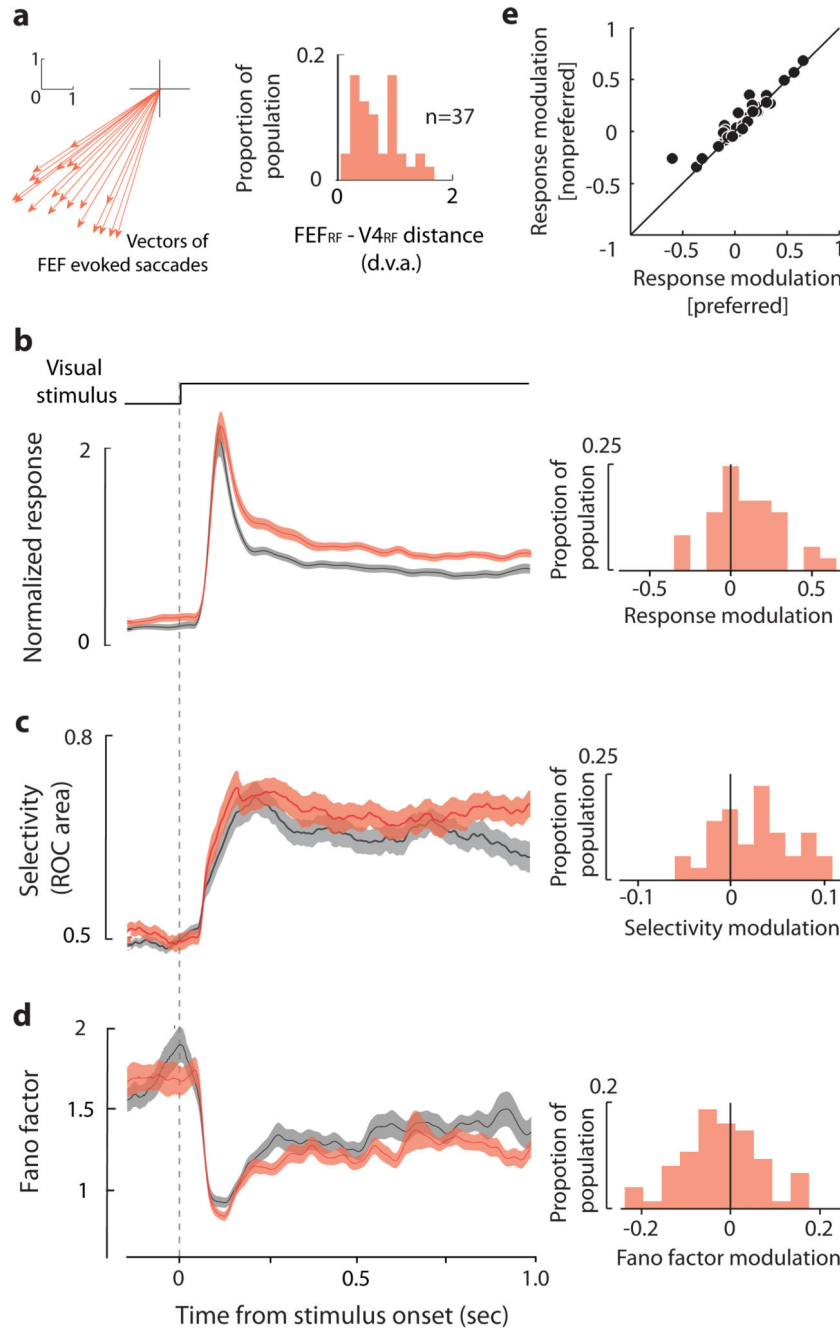


Figure 2. Manipulation of D1R-mediated activity enhances V4 visual signals. **a**, Average vectors of saccades evoked at all FEF sites that overlapped V4 RFs (left). Distribution of distances between the endpoint of evoked saccades and the centers of overlapping V4_{RF}s for 37 V4 neurons. The mean normalized response magnitude (**b**), orientation selectivity (**c**) and response variability (FF) (**d**) of V4 neurons before (gray) and after (red) microinfusion of SCH23390 into the FEF. Shown are means ± S.E.M. within a 100-ms moving window measured during the 1-second RF stimulus presentation (top event plot). Histograms to the

right of each response profile show the distributions of modulation indices for response magnitude (**b**), selectivity (**c**) and variability (**d**) across the population of neurons. **e**, Comparison of V4 response modulation following the SCH23390 infusion for preferred and non-preferred RF stimuli.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

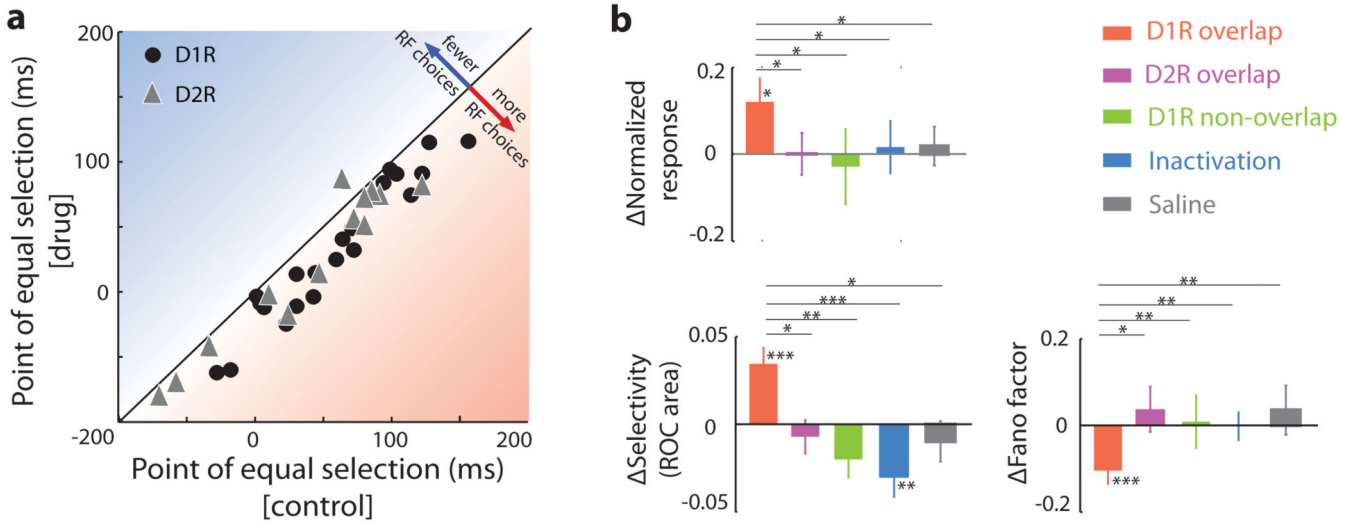


Figure 3. Changes in saccadic target selection and V4 visual responses. **a**, Scatter plot shows the consistent increase in FEF_{RF} target choices (decrease in PES) after manipulation of both D1R (circles) and D2R-mediated (triangles) FEF_{RF} activity. For both drug effects, the increase in FEF_{RF} target selection was constant across a range of control PES values; the slope in the linear fit did not differ significantly from unity in either case (D1R: slope=0.96, $p=0.552$; D2R: slope=0.97, $p=0.502$). **b**, Changes in response magnitude, orientation selectivity and response variability (FF) following each drug manipulation. Changes shown are mean differences from pre-infusion values. Error bars denote S.E.M.. Single, double and triple asterisks denote significance at $p<0.05$, $p<0.01$, and $p<0.001$, respectively.