LETTER

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Control of visual cortical signals by prefrontal dopamine

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The prefrontal cortex is thought to modulate sensory signals in posterior cortices during top-down attention[1,2], but little is known about the underlying neural circuitry. Experimental and clinical evidence indicate that prefrontal dopamine has an important role in cognitive functions[3], acting predominantly through D1 receptors. Here we show that dopamine D1 receptors mediate prefrontal control of signals in the visual cortex of macaques (*Macaca mulatta*). We pharmacologically altered D1-receptor-mediated activity in the frontal eye field of the prefrontal cortex and measured the effect on the responses of neurons in area V4 of the visual cortex. This manipulation was sufficient to enhance the magnitude, the orientation selectivity and the reliability of V4 visual responses to an extent comparable with the known effects of top-down attention. The enhancement of V4 signals was restricted to neurons with response fields overlapping the part of visual space affected by the D1 receptor manipulation. Altering either D1- or D2-receptor-mediated frontal eye field activity increased saccadic target selection but the D2 receptor manipulation did not enhance V4 signals. Our results identify a role for D1 receptors in mediating the control of visual cortical signals by the prefrontal cortex and suggest how processing in sensory areas could be altered in mental disorders involving prefrontal dopamine.

Dopamine D1 receptors (D1Rs) are expressed by about one-quarter of all neurons in the prefrontal cortex and are localized primarily in superficial and deep layers[4–6]. Microiontophoretic application of the selective D1R antagonist SCH23390[7] at certain doses can increase the persistent, working-memory-related component of single-neuron activity in the dorsolateral prefrontal cortex[3,8,9]. Given the role of the prefrontal cortex in visual attention[1,2], we hypothesized that D1Rs might also mediate the top-down control of visual cortical signals by the prefrontal cortex. If so, then changes in D1R-mediated prefrontal cortex activity might be sufficient to modulate signals in the posterior visual cortex, similar to the modulation observed during selective attention[10]. The prefrontal cortex's influence on the visual cortex is achieved in part by the frontal eye field (FEF)[1,11,12], an oculomotor area within the posterior prefrontal cortex. The FEF has a well-established role in saccadic target selection[13], but recent evidence also implicates this area in the control of spatial attention[2,14,15]. To test our hypothesis, we locally infused[16] small volumes (0.5–1 μl) of SCH23390 into sites in the FEF of macaques performing fixation and eye movement tasks (Fig. 1a, b and Supplementary Fig. 1). We measured the effects of the FEF infusion on target selection using a free-choice saccade task[17]. In this task, monkeys were rewarded for choosing between two saccadic targets, one located within the FEF response field and one in the opposite hemifield. In the same experiment, we recorded the visual responses of single neurons in area V4 during fixation. In particular, we recorded neurons with response fields that overlapped the FEF response field. Thus, we tested the effects of the D1R manipulation on both visual cortical signals and 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 response field (Fig. 1b). In the free-choice task, the temporal onset of the two targets was systematically varied such that the FEF response field stimulus could appear earlier or later than the opposite stimulus. A monkey's tendency to select the FEF response field target could then

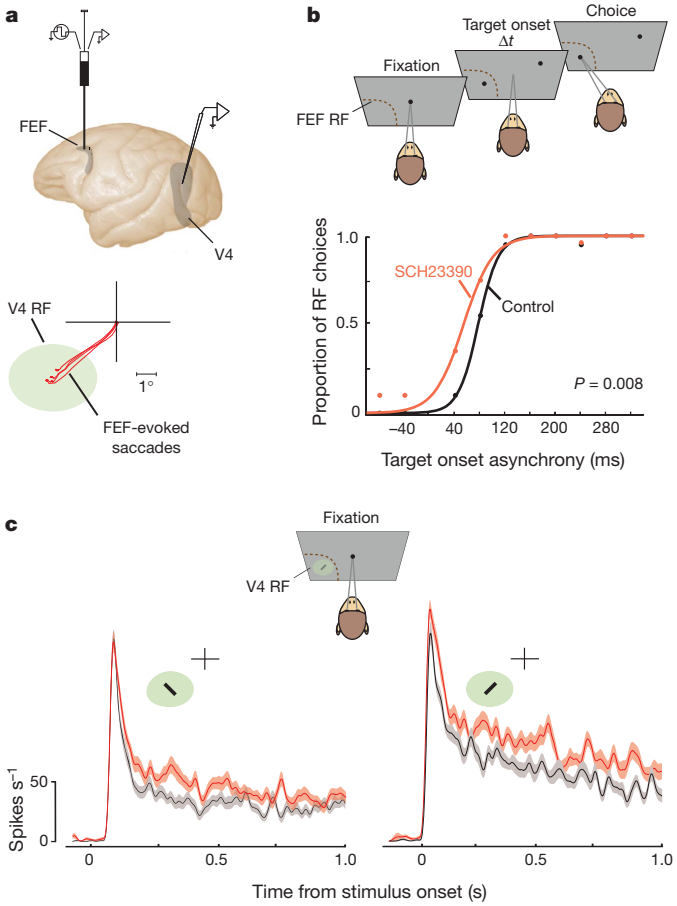

Figure 1 | Local manipulation of D1R-mediated activity in the FEF during single-neuron electrophysiology in area V4. a, Lateral view of the macaque brain depicting the location of a recording microsyringe in the FEF and of recording sites in area V4. Bottom diagram shows saccades evoked via electrical microstimulation at the infusion site (red traces) and the response field (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 response field versus one at an opposite location across varying temporal onset asynchronies. Positive asynchrony values denote earlier onset of FEF response field targets. Bottom plot shows the leftward shift in the PES, indicating more FEF response field choices, after infusion of SCH23390 into an FEF site. **c**, Visual responses of a V4 neuron with a response field that overlapped the FEF response field, measured during passive fixation. The plot shows mean ± s.e.m of visual responses to a bar stimulus presented at orthogonal orientations before (grey) and after (red) the infusion of SCH23390 at the FEF site.

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be measured as the temporal onset asynchrony required for an 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 response field 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 response field 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 and Supplementary Methods). We found that the increase in target selection after the SCH23390 infusion was accompanied by an enhanced V4 neuronal response to oriented bars appearing within the overlapping V4 and FEF response fields. The example neuron shown was selective for orientation: it responded more to the 45° than to the 135° bar stimulus ($P < 10^{-3}$). After the infusion of SCH23390, there was a significant increase in the overall visual response of this neuron as well as a significant increase in the differential response to the two orientations (two-way analysis of variance, 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 response field stimuli as saccade targets more frequently, 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 response fields that overlapped the response fields of FEF infusion sites. The average (mean ± s.e.m.) distance between V4 response field and FEF response field centres was 0.71 ± 0.07 degrees of visual angle (d.v.a.) (Fig. 2a). As with the example neuron, we measured the responses of all neurons to oriented bars appearing in their response field during a 1 s fixation period (Fig. 2b). Before the onset of the visual stimulus, there was a significant elevation in baseline activity after the D1R manipulation (Δ 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 (Δ 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 (Δ preferred = 0.264 ± 0.087; $P = 0.004$) and non-preferred stimuli (Δ non-preferred = 0.132 ± 0.062; $P = 0.032$). There was also an increase in the response difference between the preferred and non-preferred orientations (Δ response difference = 0.132 ± 0.041; $P = 0.004$) (Supplementary Fig. 3), indicating 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 after changes in D1R-mediated FEF activity (Δ ROC area = 0.035 ± 0.009, $P < 10^{-3}$). The enhancement in the magnitude and selectivity of the V4 response 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, which is the variance in the spike count divided by its mean. We found that the Fano factor of V4 responses was reduced after the D1R manipulation (Δ FF = −0.105 ± 0.045; $P < 10^{-3}$) (Fig. 2d and 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. In 21 double-target experiments, the PES was reduced in every case (Fig. 3a). The mean PES shifted in favour of the FEF response field stimulus by an average of 27 ms (Δ PES = −26.934 ± 3.086, $P < 10^{-3}$), significantly increasing the overall proportion of FEF response field choices

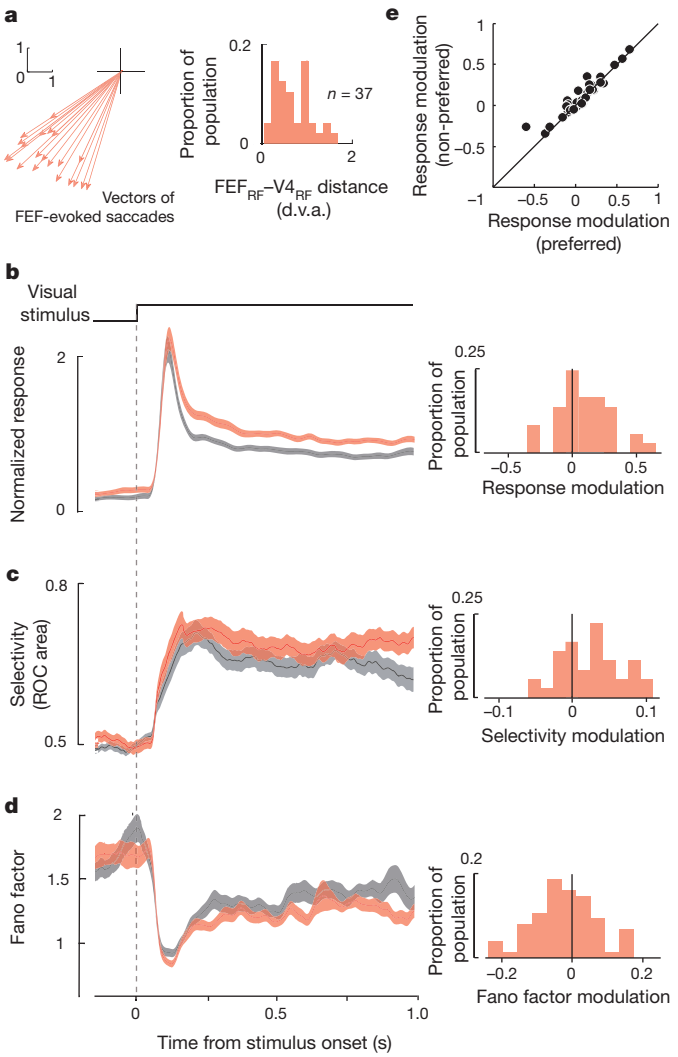

Figure 2 | Manipulation of D1R-mediated activity enhances V4 visual signals. a, Average vectors of saccades evoked at all FEF sites that overlapped V4 response fields (left panel). The distribution of distances between the endpoints of evoked saccades and the centres of overlapping V4 response fields for 37 V4 neurons is shown in the right panel. **b**–**d**, The mean normalized response magnitude (**b**), orientation selectivity (**c**) and response variability (Fano factor) (**d**) of V4 neurons before (grey) and after (red) microinfusion of SCH23390 into the FEF. Means ± s.e.m. are shown within a 100-ms moving window measured during the 1-s response field 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 after the SCH23390 infusion for preferred and non-preferred response field stimuli.

(chi-squared = 80.60, $P < 10^{-3}$) and thus indicating that the D1R manipulation increased the monkeys' tendency to target FEF response field 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 the dorsolateral prefrontal cortex[20]. We found that local manipulation of D2R-mediated FEF activity, like the D1R manipulation, increased the selection of FEF response field targets (Fig. 3a). The PES shifted by an average of 22 ms (Δ PES = −21.993 ± 6.758, $P = 0.010$), increasing the proportion of FEF response field choices (chi-squared = 13.86, $P < 10^{-3}$). Thus, the D1R- and D2R-mediated manipulations of FEF activity resulted in equivalent increases in saccadic target selection.

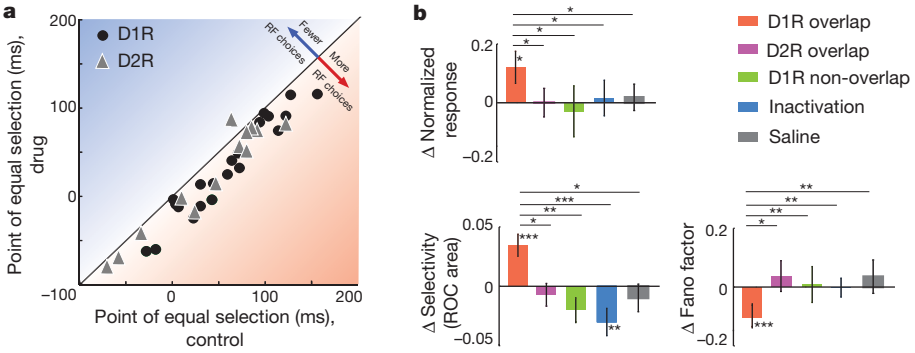

Figure 3 | Changes in saccadic target selection and V4 visual responses. **a**, Scatter plot shows the consistent increase in FEF response field target choices (decrease in PES) after manipulation of both D1R-mediated (circles) and D2R-mediated (triangles) FEF activity. For both drug effects, the increase in FEF response field 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 (Fano factor) after each drug manipulation. Changes shown are mean differences from pre-infusion values. Error bars denote s.e.m.; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

Despite the increase in target selection, manipulation of D2R-mediated activity in the 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 after the D2R manipulation (Δ response $= 0.001 \pm 0.048$, $P = 0.999$; Δ ROC area $= -0.007 \pm 0.010$, $P = 0.426$; Δ FF $= 0.037 \pm 0.052$, $P = 0.338$; $n = 15$) (Fig. 3b). Moreover, the changes in these measures were all significantly different from the changes we observed after the D1R manipulation ($\Delta\,\text{response}_{D2R} < \Delta\,\text{response}_{D1R}$, $P = 0.045$; $\Delta\,\text{selectivity}_{D2R} < \Delta$ selectivity$_{D1R}$, $P = 0.011$; $\Delta\,\text{FF}_{D2R} > \Delta\,\text{FF}_{D1R}$, $P = 0.019$). Thus, the equivalent effects of D1R and D2R manipulations on saccadic target selection were accompanied by contrasting effects in V4, with the enhancement of visual signals being specific to D1R-mediated activity. We also found that this enhancement was confined to V4 neurons with response fields that overlapped the FEF response field. For V4 neurons with response fields that did not overlap the FEF response field (mean distance between V4 response field and FEF response field = 9.00 ± 0.86 d.v.a.; $n = 15$), we found no significant effect of the D1R manipulation on response magnitude (Δ response $= -0.028 \pm 0.087$, $P = 0.9780$), orientation selectivity (Δ ROC area $= -0.017 \pm 0.010$, $P = 0.187$) or the Fano factor (Δ FF $= 0.010 \pm 0.043$, $P = 0.688$). Of note, the changes in these measures were all significantly different from the changes observed in neurons with overlapping response fields ($\Delta\text{response}_{\text{non-overlap}} < \Delta\,\text{response}_{\text{overlap}}$, $P = 0.044$; $\Delta\,\text{selectivity}_{\text{non-overlap}} < \Delta\,\text{selectivity}_{\text{overlap}}$, $P = 0.007$; $\Delta\,\text{FF}_{\text{non-overlap}} > \Delta\,\text{FF}_{\text{overlap}}$, $P = 0.034$) (Fig. 3b). Thus, the enhancement in visual cortical signalling produced by manipulation of D1R-mediated FEF activity was spatially specific.

We also tested the effect of complete inactivation of FEF sites on the responses of V4 neurons with overlapping response fields. 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 using the $GABA_A$ (γ-aminobutyric acid subtype A) receptor agonist muscimol. Unlike the sparsely expressed D1Rs, $GABA_A$ receptors are expressed by all neurons in all cortical layers[22]. As in previous studies, local inactivation of FEF sites with muscimol decreased the targeting of FEF response field stimuli. It also significantly reduced V4 orientation selectivity (Δ 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 (Δ response $= 0.016 \pm 0.061$, $P = 0.809$; Δ FF $= -0.002 \pm 0.023$, $P = 0.921$) (Fig. 3b). Thus, in contrast to the D1R manipulation which altered all three components of V4 activity, complete inactivation altered only one. All three inactivation effects were significantly different from the D1R effects ($\Delta\,\text{response}_{\text{muscimol}} < \Delta\,\text{response}_{D1R}$, $P = 0.024$; $\Delta\,\text{selectivity}_{\text{muscimol}} < \Delta\,\text{selectivity}_{D1R}$, $P < 10^{-3}$; $\Delta\,\text{FF}_{\text{muscimol}} > \Delta\,\text{FF}_{D1R}$, $P = 0.007$). Although the reduction in orientation selectivity is consistent with previous electrical microstimulation studies[12] and with the effects of inactivation on orientation discrimination[21], the lack of a reduction in response magnitude may seem inconsistent. However, we suggest that this difference is due to variation between experimental paradigms (Supplementary Discussion). Finally, we tested for any effect of vehicle (saline) infusion into the FEF. The infusion of saline failed to change the response magnitude, selectivity or variability of V4 neurons (Δ response $= 0.018 \pm 0.048$, $P = 0.380$; Δ ROC area $= -0.010 \pm 0.013$, $P = 0.569$; Δ FF $= -0.035 \pm 0.061$, $P = 0.179$; $n = 12$) (Fig. 3b). All three measures were significantly different from the D1R effects ($\Delta\,\text{response}_{\text{saline}} < \Delta\,\text{response}_{D1R}$, $P = 0.045$; $\Delta\,\text{selectivity}_{\text{saline}} < \Delta\,\text{selectivity}_{D1R}$, $P = 0.013$; $\Delta\,\text{FF}_{\text{saline}} > \Delta\,\text{FF}_{D1R}$, $P = 0.009$).

Our results identify prefrontal D1Rs as a component of the neural circuitry controlling signals in the visual cortex. Manipulation of D1R-mediated FEF activity was sufficient to enhance the magnitude, reliability and visual selectivity of neuronal responses in area V4, three known effects of visual attention. The observed enhancement might account for the benefits in visually guided behaviour that accompany attentional deployment (Supplementary Fig. 6), although a causal link between attentional modulation of visual cortical signals and visual perception remains to be established. We have demonstrated that visual representations in posterior areas can be altered merely by changes in dopamine tone in the prefrontal cortex. Given the complex effects of dopamine through D1Rs, one might predict that at 'optimum' dopamine levels[9], optimal top-down control of visual cortical signals would be achieved.

The circuitry underlying top-down control of the visual cortex probably involves several different neuromodulators[23] and an array of different brain structures[24]. Our results show that this circuitry involves prefrontal dopamine acting via D1Rs. In the dorsolateral prefrontal cortex, dopamine D1Rs are thought to modulate recurrent glutamatergic connections, thereby influencing activity related to working memory in this area[25,26]. This study shows 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 the visual cortex (Supplementary Fig. 7). Because FEF neurons in the superficial layer are reciprocally connected with neurons in V4[2,27], dopaminergic modulation of these connections via D1Rs in the superficial layer 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 the prefrontal cortex[4–6]. The equivalent effects of D1R and D2R

manipulations on target selection might be explained by the presence of both receptor subtypes in infragranular layers of the cortex[4–6], where layer-V FEF neurons project to the superior colliculus[27].

Impairments in saccadic control are prominent among the 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 behavioural links between saccadic control, attention and working memory[29] and the coincidence of their corresponding impairments in ADHD[30].

METHODS SUMMARY

The effects of pharmacological perturbation of FEF activity on target selection and the visual responses of V4 neurons were studied in three macaques (*Macaca mulatta*) performing fixation and eye movement tasks (Supplementary Methods). All experimental procedures were in accordance with the National Institutes of Health guide for the care and use of laboratory animals and with the Society for Neuroscience guidelines and policies. They were also 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 in the FEF through a surgically implanted titanium chamber overlying the arcuate sulcus using a custom-made recording microinjectrode. We identified FEF sites by eliciting short-latency, fixed-vector saccadic eye movements with trains (50–100 ms) of biphasic current pulses ($\leq$50 μA; 250 Hz; 0.25 ms duration). In the same experiment, recordings from V4 neurons were made through a chamber overlying the prelunate gyrus. Response fields of V4 neurons were all located in the lower quadrant of the contralateral hemifield ($<12^{\circ}$ eccentricity). The position of the FEF microinjectrode was adjusted so that the saccade elicited by FEF microstimulation shifted the monkey's gaze either to within the V4 response field (overlapping) or far outside it (non-overlapping).

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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