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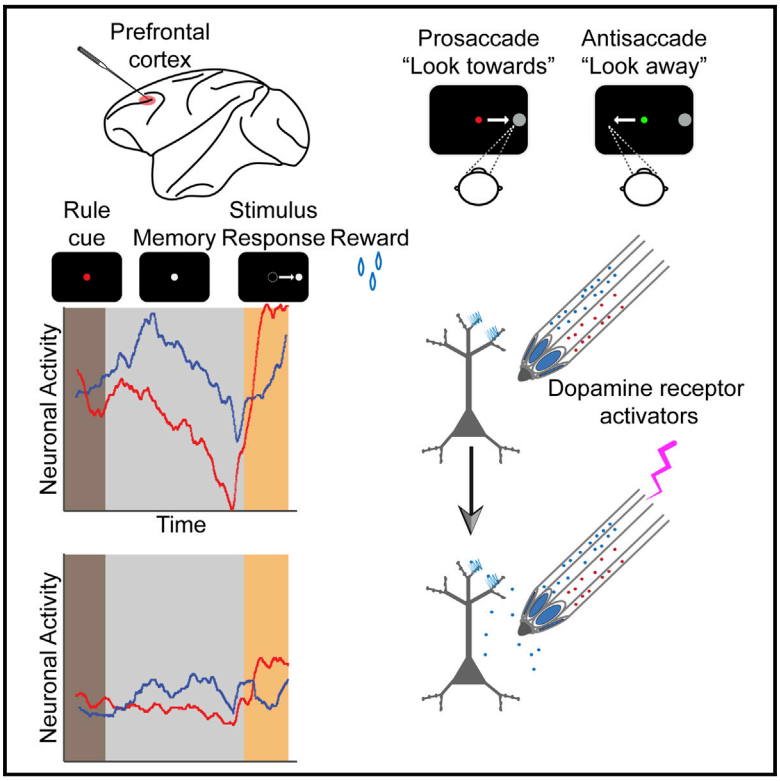
Dopamine D1 and D2 Receptors Make Dissociable Contributions to Dorsolateral Prefrontal Cortical Regulation of Rule-Guided Oculomotor Behavior

Graphical Abstract



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In Brief

Prefrontal cortical activity controls rule-guided flexible behavior. Vijayraghavan et al. examined the effects of dopamine receptor stimulation on working memory activity for rules guiding eye movements. D1 receptor stimulation deteriorates rule maintenance and increases impulsive responding, whereas D2 receptor stimulation selectively enhances movement-related activity depending on the rule context.

Highlights

- Dopamine receptor stimulation affects rule maintenance in monkey prefrontal cortex
- D1 receptor stimulation deteriorates working memory for rules to guide eye movements
- D2 receptor stimulation enhances saccade activity for prosaccades but not antisaccades
- Only D1 receptor stimulation increases impulsive responding and antisaccade errors

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Dopamine D1 and D2 Receptors Make Dissociable Contributions to Dorsolateral Prefrontal Cortical Regulation of Rule-Guided Oculomotor Behavior

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SUMMARY

Studies of neuromodulation of spatial short-term memory have shown that dopamine D1 receptor (D1R) stimulation in dorsolateral prefrontal cortex (DLPFC) dose-dependently modulates memory activity, whereas D2 receptors (D2Rs) selectively modulate activity related to eye movements hypothesized to encode movement feedback. We examined localized stimulation of D1Rs and D2Rs on DLPFC neurons engaged in a task involving rule representation in memory to guide appropriate eye movements toward or away from a visual stimulus. We found dissociable effects of D1R and D2R on DLPFC physiology. D1R stimulation degrades memory activity for the task rule and increases stimulus-related selectivity. In contrast, D2R stimulation affects motor activity tuning only when eye movements are made to the stimulus. Only D1R stimulation degrades task performance and increases impulsive responding. Our results suggest that D1Rs regulate rule representation and impulse control, whereas D2Rs selectively modulate eye-movement-related dynamics and not rule representation in the DLPFC.

INTRODUCTION

The dorsolateral prefrontal cortex (DLPFC) is an essential node in the execution of complex cognitive tasks (Goldman-Rakic, 1995; Miller and Cohen, 2001). DLPFC neurons encode multiple facets of activity in cognitive tasks, including persistent post-visual activity encoding the location of visual stimuli in short-term memory, or spatial working memory (WM; Funahashi et al., 1989; Fuster and Alexander, 1971). DLPFC neuronal activity also encodes WM for task rules used to guide motor responses to sensory stimuli (Wallis et al., 2001), spatial attention (Lebedev et al., 2004), visual responses (Takeda and Funahashi, 2002), and rapid-eye-movement (saccade)-related responses (Boch and Goldberg, 1989; Takeda and Funahashi, 2002; Wang et al., 2004). The DLPFC in monkeys and humans is subject to substantial neuromodulation (Arnsten et al., 2012; Robbins, 2005), receiving ascending projections from all major neuromodulatory systems, including dopamine (Björklund and Dunnett, 2007; Goldman-Rakic et al., 1992; Williams and Goldman-Rakic, 1998). Dopamine modulation of DLPFC function has been extensively studied, since dopaminergic denervation of DLPFC was found to disrupt WM function (Brozoski et al., 1979) comparably to lesions or inactivation of DLPFC (Buckley et al., 2009; Funahashi et al., 1993; Goldman and Rosvold, 1970).

Dopamine D1 receptors (D1Rs), densely expressed in DLPFC layers II and III (Paspalas and Goldman-Rakic, 2005), and D2 receptors (D2Rs), expressed in layer V projection neurons (Lidow et al., 1998), influence DLPFC function in diverse contexts. D1R blockade disrupts DLPFC spatial WM activity (Sawaguchi and Goldman-Rakic, 1991, 1994; Williams and Goldman-Rakic, 1995) and task performance in monkeys (Sawaguchi and Goldman-Rakic, 1994). D1R blockade also disrupts prefrontal cognitive rule-related selectivity (Ott et al., 2014) and enhances saccade target selection (Noudoost and Moore, 2011) in the frontal eye field (FEF). D1R stimulation has complex dose-dependent effects, with low doses enhancing spatial WM activity tuning and differential rule activity (Ott et al., 2014; Vijayraghavan et al., 2007), while enhancing behavioral performance in rodents (Zahrt et al., 1997) and monkeys (Arnsten et al., 1994). Higher doses suppress monkey DLPFC neurons (Vijayraghavan et al., 2007) and disrupt spatial WM performance (Gamo et al., 2015). Contrastingly, D2R manipulation in monkeys was shown to selectively modulate neurons active during the saccadic eye movement response, while neurons with spatial memory activity were unaffected (Wang et al., 2004). D2R stimulation disrupts and improves monkey WM performance (Arnsten et al., 1995), augments saccade target selection, and increases perseverative behavior (Noudoost and Moore, 2011). In contrast, D2R blockade had no behavioral effect on spatial WM (Sawaguchi and Goldman-Rakic, 1994). Interestingly, while D1R blockade in the FEF affected top-down modulation of activity in sensory area V4, D2R stimulation had no effect on V4 activity (Noudoost and Moore, 2011). This is consistent with anatomical studies suggesting that D2Rs control DLPFC subcortical outputs and that D1Rs are involved in intracortical sensory-visual processing

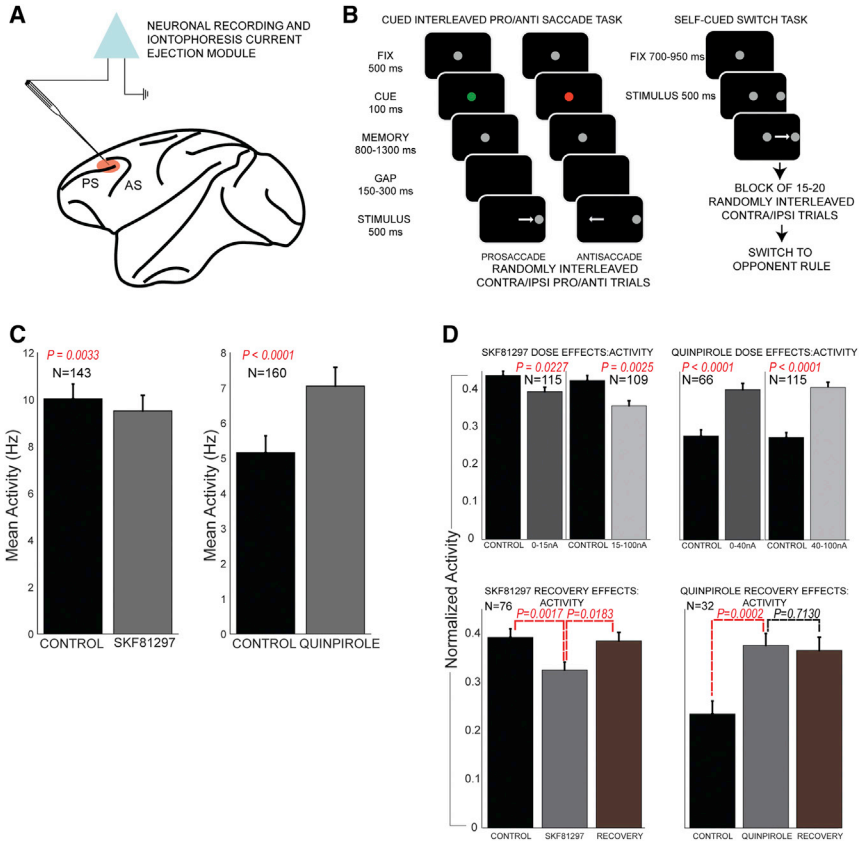

Figure 1. Behavioral Task, Recording Locus, and Overall Physiological Effects of Dopamine Agonists

(A) Recording locus within prefrontal cortex with schematic of a multi-barrel iontophoretic recording electrode. Most recordings' loci were in a patch dorsal to caudal principal sulcus and within the sulcus. PS, principal sulcus; AS, arcuate sulcus.

(B) Behavioral tasks: all variants of the task involved execution of pro- and antisaccades to randomly presented peripheral stimuli contralateral (CONTRA) and ipsilateral (IPSI) to fixation. Task epoch timings are indicated. Two task types were used: pseudorandomly cued (green/red fixation spot) rule (left) and the switch task (right).

(C) SKF81297 (left) significantly reduced, while quinpirole (right) increased, population raw activity.

(D) Dose response and recovery (left, SKF81297; right, quinpirole): population normalized activity for control (black), low-dose (dark gray), and high-dose (light gray) ranges of agonists shown (top). Bottom panels show activity changes in populations tested for drug application and recovery (black bars, control; gray bars, drug; brown bars, recovery). Red dashed lines and p values indicate significant comparison, and black dashed lines indicate nonsignificant p values indicate WSR-HB. Error bars indicate ±SEM.

(Jacob et al., 2013) and memory maintenance within the DLPFC (Arnsten et al., 2015). D1Rs and D2Rs also influence prefrontal contributions to visuomotor learning, with stronger D1R- and weaker D2R-mediated impairment in learning new associations (Puig et al., 2014; Puig and Miller, 2012).

Dysfunctional dopamine modulation is widely implicated in many psychiatric and neurological disorders, including schizophrenia and Parkinson's disease (Arnsten et al., 2015). Antipsychotic efficacy in treating positive symptoms of schizophrenia is correlated with cortical/striatal D2R affinity (Kapur et al., 2000), and D1Rs are being actively investigated in treatment of WM deficits and other cognitive symptoms of schizophrenia (Robbins and Arnsten, 2009).

Recently, D1R and D2R stimulation were shown to augment WM for rules specifying non-saccade responses in the prefrontal cortex (PFC) of monkeys in a numerical comparison task (Ott et al., 2014), in contrast with reported dissociation of D1R and D2R effects on spatial WM physiology and performance (Wang et al., 2004). This leaves open the question of whether D1R and D2R stimulation would also enhance rule WM activity in a saccadic task or whether the dissociable effects found with spatial WM would extend to rule representation specifying a saccade response. Here, we examined the physiological consequences of D1R/D2R stimulation on a version of the antisaccade task (Hallett, 1978), where a briefly memorized sensory rule cue specified the appropriate eye movement response: look toward (prosaccade) or away from (antisaccade) a visual stimulus. Antisaccade performance requires inhibiting the prepotent impulse to look toward a flashed visual stimulus (response inhibition) and reprogram the motor command to look to the opposite direction. Antisaccade performance deficits are a diagnostic indicator of schizophrenic pathology and correlate with Wisconsin card sorting performance deficits, indicative of frontal lobe dysfunction (Rosse et al., 1993). We stimulated D1Rs and D2Rs locally while recording DLPFC neurons from two rhesus macaques performing a task executing rule-guided pro- and antisaccades.

RESULTS

Effects of D1R and D2R Agonists on Overall Neuronal Activity

We performed 167 microiontophoretic recordings and obtained 326 neurons in the DLPFC of two male rhesus macaques. After discarding recordings with fewer than eight trials per saccade rule in each condition, 143 neurons tested with the D1R agonist SKF81297 and 160 neurons tested with the D2R agonist quinpirole were examined further (149 valid sessions). Figure S2 shows the breakdown of neurons by task-relevant activity type (classified by ANOVA) in the D1R and D2R populations.

SKF81297 decreased population activity, as reported previously (Ott et al., 2014; Vijayraghavan et al., 2007; Wang et al., 2004) (Figure 1C, left), whereas quinpirole induced significant activation (Figure 1C, right). Both low (0–15 nA) and high (15–100 nA) doses of SKF81297 induced significant suppression of mean normalized activity (Figure 1D, top left), with greater suppression at higher doses (Δ_{low} = −0.043, and

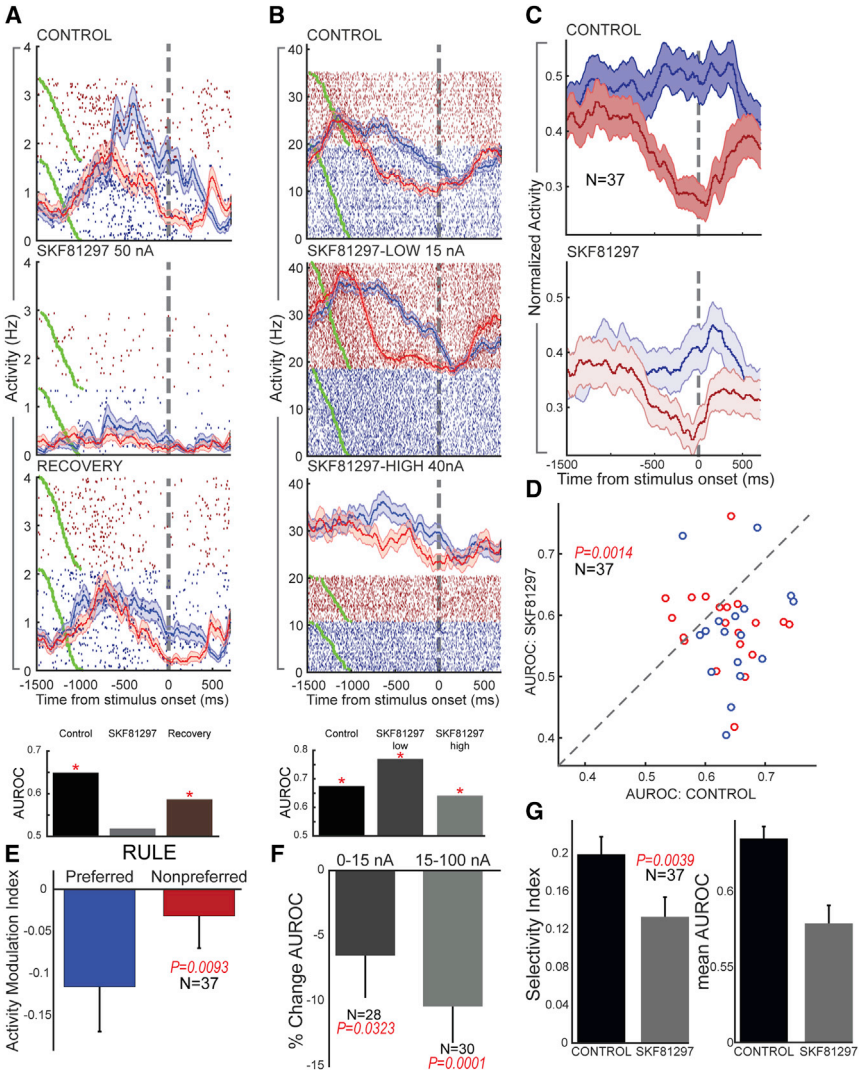

Figure 2. Effects of SKF81297 on Rule-Related Activity of DLPFC Neurons

(A) Rasters and spike density functions aligned on stimulus onset (dashed line) for a DLPFC neuron shown during control (top), SKF81297 (upper middle), and recovery (lower middle). This neuron fired more for prosaccade rule (blue) trials than antisaccades (red) in the rule-memory epoch, was suppressed by SKF81297, and was subsequently recovered. AUROC selectivity is shown (bottom) for control (black), SKF81297 (gray), and recovery (brown). Red asterisks indicate significant AUROC by bootstrap analysis ($p < 0.05$). Green dots represent rule-cue onset. Trials are sorted by randomized delay length.

(B) Rasters and spike density functions for another rule-selective neuron showing effects of low (upper middle) and high (lower middle) doses of SKF81297. Same conventions as in (A); AUROCs (bottom) show control (black), low doses (1–15 nA; dark gray), and high doses (16–100 nA; light gray) of SKF81297.

(C) Traces show population (n = 37) preferred (blue) and nonpreferred (red) rule activity aligned on stimulus onset (dashed line).

(D) Scatterplot shows neuronal AUROCs (blue circles, prosaccade rule-selective neurons; red, antisaccade rule-selective neurons) for control (abscissa) and SKF81297 (ordinate). Dashed line indicates equality.

(E) SKF81297 reduces the population activity modulation index (AMI) significantly more for preferred rule (blue) than nonpreferred rule (red).

(F) Percentage change in AUROC for population tested with low (light gray) and high (dark gray) doses of SKF81297.

(G) Mean selectivity index (SI; left) and AUROC (right; black indicates control, and gray indicates drug) are reduced significantly by SKF81297.

The p values in red are significant (WSR). Error bars indicate ±SEM.

$\Delta_{high} = -0.068$; normalized units). Quinpirole significantly increased activity at low (0–40 nA) and high (40–100 nA) doses (Figure 1D, top right; $\Delta_{low} = 0.124$, and $\Delta_{high} = 0.138$). Quinpirole-induced changes were not dose dependent. SKF81297-induced inhibition was reversed in post-drug recovery (Figure 1D, bottom left). Quinpirole-induced activation did not fully recover (Figure 1D, bottom right), although many individual examples substantially recovered.

Effects of Dopamine Agonists on Rule-Related Activity

We found task-rule-related differential discharges in 37 neurons (25%) tested with SKF81297. Two representative neurons are shown in Figures 2A and 2B. Figure 2A shows a DLPFC neuron with greater activity for prosaccade trials than antisaccades during the rule-memory epoch (2.1 versus 0.97 Hz; $p_{pro\text{-}anti} < 10^{-6}$, Wilcoxon rank-sum test [WRS]). SKF81297 strongly suppressed neuronal activity, more for prosaccades, and disrupted rule selectivity (0.39 versus 0.22 Hz; $p_{pro\text{-}anti} = 0.382$). Activity recovered post-drug, restoring rule selectivity (1.16 versus 0.66 Hz; $p_{pro\text{-}anti} = 0.0008$). Areas under the receiver-operating characteristic (ROC) curves (AUROCs) (Figure 2A, bottom) show the effects of SKF81297 on rule selectivity. In another neuron (Figure 2B) selective for prosaccades (17.75 versus 11.56 Hz; $p_{pro\text{-}anti} = 4.7 \times 10^{-5}$), low-dose SKF81297 application increased neuronal activity, comparatively more for the preferred rule, increasing rule selectivity (27.65 versus 20.08 Hz; $p_{pro\text{-}anti} < 10^{-6}$). Subsequent high-dose application increased activity further, but more for the nonpreferred rule, reducing selectivity (30.82 versus 26.14 Hz; $p_{pro\text{-}anti} = 0.011$). AUROCs (Figure 2B, bottom) show the dose-dependent changes in rule selectivity. Two more examples of opponent SKF81297 effects on rule selectivity—wherein the background activity of the neurons was negligibly affected by D1R stimulation while rule selectivity was affected by greater increases and decreases in preferred and nonpreferred rule activity, respectively—are shown in Figure S3. Population normalized activity curves for preferred and nonpreferred rules (n = 37; Figure 2C) revealed that SKF81297 application suppresses normalized activity (bottom versus top), with concomitant

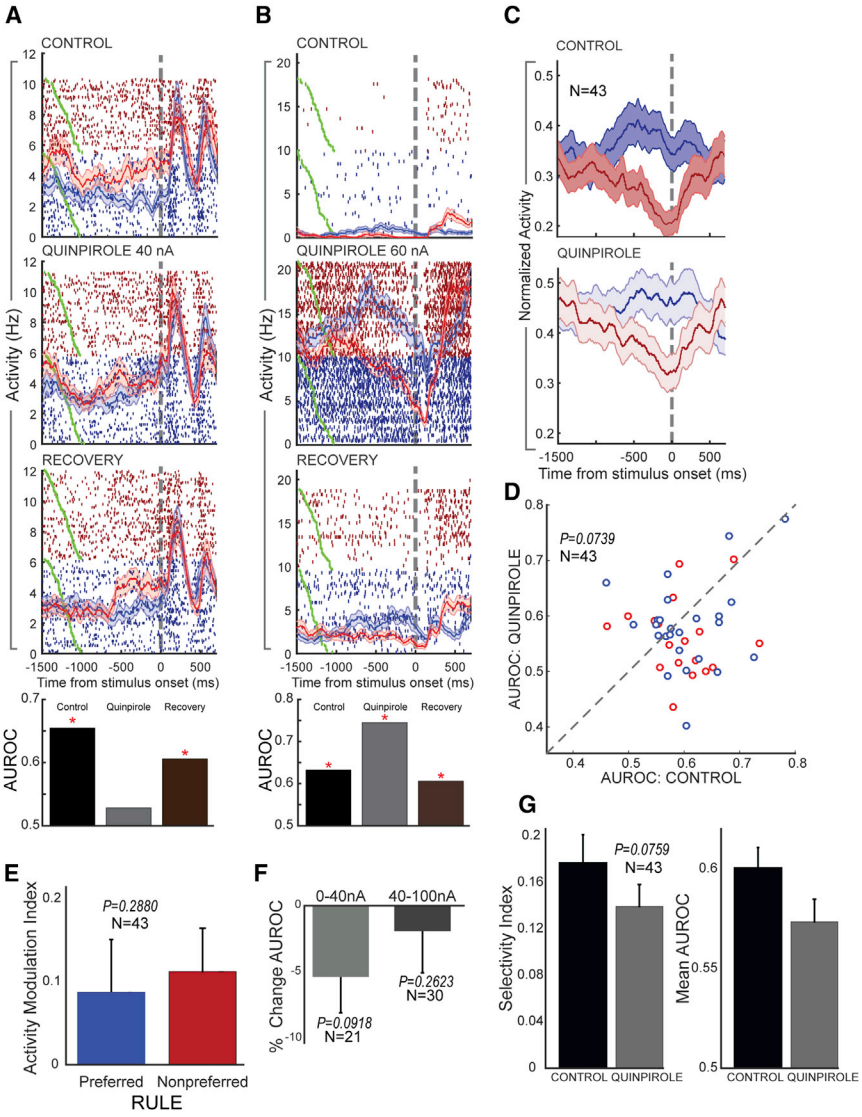

Figure 3. Effects of Quinpirole on Rule-Related Activity of DLPFC Neurons

Color and figure conventions are analogous to those in Figure 2.

(A) Rasters and spike density functions shown for neuron with rule-memory epoch preference for antisaccades tested with quinpirole and washout (top three panels; AUROC, bottom).

(B) Another neuron with weak prosaccade rule selectivity in control (top) tested with quinpirole (upper middle) and washout (lower middle). AUROC selectivity, bottom.

(C) Population (n = 43) normalized activity curves for preferred versus nonpreferred rules.

(D) AUROC scatterplot for population shows quinpirole effects on individual neuron AUROCs.

(E) Population AMI values for preferred/nonpreferred rule shown after quinpirole.

(F) Change in AUROC for low (0–40 nA) and high (40–100 nA) doses of quinpirole.

(G) Mean SI (left) and mean AUROC (right) for control and quinpirole shown.

The p values are from WSR. Error bars indicate ±SEM.

suppression of the population rule discriminability, as quantified by significant reduction of the population AUROC (Figure 2D; Figure 2G, right) and selectivity index (SI) during the drug condition (Figure 2G, left). SKF81297 degradation of AUROC selectivity was significant at both low- and high-dose ranges (Figure 2F), with comparatively greater diminishment for higher doses. To determine whether agonist-induced selectivity deterioration was due to excitability collapse for the preferred rule (e.g., Figure 2A) or increased activity for the nonpreferred rule (e.g., Figure 2B, high dose), we computed the activity modulation index (AMI). Population selectivity decreased due to significantly greater decrease in population AMI for the preferred rule (Figure 2E).

Next, we examined quinpirole's impact on rule selectivity. Figures 3A and 3B show individual rule-selective neurons tested with quinpirole and drug recovery. The first neuron had greater rule-memory epoch activity for anti- than for prosaccade trials (Figure 3A; 2.45 versus 4.5 Hz; $p_{pro\text{-}anti}$ = 0.0001, WRS). Quinpirole application increased nonpreferred (prosaccade) rule activity (p = 0.0018, WRS), sparing preferred activity (antisaccade; p = 0.767), thus disrupting rule selectivity (4.01 versus 4.5 Hz; $p_{pro\text{-}anti}$ = 0.466). Nonpreferred activity was reduced comparatively more during the subsequent recovery, restoring selectivity (3.13 versus 4.51 Hz; $p_{pro\text{-}anti}$ = 0.0045). The neuron in Figure 3B had prosaccadic rule selectivity (0.85 versus 0.15 Hz; $p_{pro\text{-}anti}$ = 0.0002, WRS). Quinpirole strongly augmented activity, more for the preferred rule (p = 0.0003) than for the nonpreferred rule ($p < 10^{-6}$), increasing rule selectivity (14.3 versus 6.89 Hz; $p_{pro\text{-}anti} < 10^{-6}$). Neuronal activity subsided during recovery with rule selectivity diminution (3.37 versus 1.54 Hz; $p_{pro\text{-}anti}$ = 0.02). AUROCs (Figures 3A and 3B, bottom) show the effects of quinpirole and recovery on rule selectivity for both neurons. However, when the rule-selective neuronal population (n = 43, 27% total neurons) was examined, while normalized curves (Figure 3C) showed overall quinpirole-induced excitation, SI (Figure 3G, left) and AUROC metrics (Figure 3D; Figure 3G, right; p = 0.07) showed overall reduction in selectivity that failed to reach significance. AUROC nonsignificantly decreased for both low and high doses, with no dose relationship (Figure 3F). Population AMI increased for both preferred and nonpreferred rules with nonsignificant differences (Figure 3F).

Thus, the D1R agonist decreased overall population rule selectivity, with a greater decrease in activity for preferred rule, whereas the D2R agonist, while augmenting population activity, had ambivalent effects on population rule selectivity.

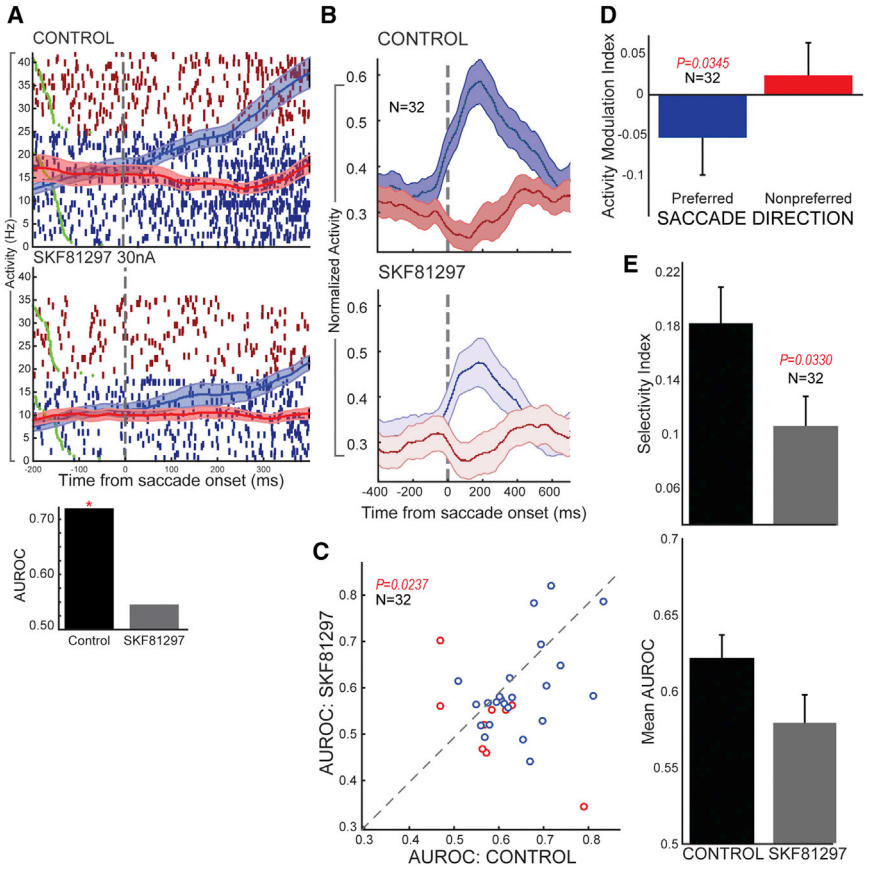

Figure 4. Effects of SKF81297 on Saccade-Related Activity of DLPFC Neurons in the Stimulus-Response Epoch

Color conventions in (A): blue, contralateral saccade; red, ipsilateral saccade; green dots, peripheral stimulus onset; In (B) and (D): blue, preferred saccade direction; red, nonpreferred. In (C): blue, contralateral-saccade-selective neurons; red, ipsilateral-saccade-selective neurons.

(A) Rasters and spike density functions are aligned to saccade onset (dashed line) for a neuron showing elevated activity for the contralateral saccade in the stimulus-response epoch that extends postsaccadically. SKF81297 (30 nA) eliminated saccade direction selectivity of the neuron (AUROC, bottom; red asterisk indicates significant AUROC).

(B) Saccade-selective population (n = 32) normalized activity aligned on saccade onset (dashed line) for preferred/nonpreferred saccade direction for control and SKF81297.

(C) Saccade-selective AUROC values for population (n = 32) in control and during SKF81297 application shown for contralateral- and ipsilateral-saccade-selective neurons (dashed line indicates equality).

(D) Population AMI after SKF81297 for preferred/nonpreferred saccade direction shown.

(E) Mean SI and AUROC for saccade direction during control and SKF81297.

The p values are from WSR. Error bars indicate ±SEM.

Effects of Dopamine Agonists on Perisaccadic and Stimulus-Related Activity

Next, we examined SKF81297 modulation of perisaccadic activity in the stimulus-response epoch. Figure 4A shows a neuron with differential postsaccadic activity ($p_{contra\text{-}ipsi}$ = 0.0001) for contralateral (blue) versus ipsilateral (red) saccades. SKF81297 decreased saccade direction selectivity, with greater decrease in contralateral activity ($AUROC_{control}$ = 0.72, p = 0.0001; $AUROC_{drug}$ = 0.54, p = 0.38; $\Delta_{Activity\text{-}contra}$ = −9.9 Hz; $\Delta_{Activity\text{-}ipsi}$ = −3.75 Hz). SKF81297 effects were analyzed on 32 DLPFC neurons with saccade selectivity (22%; 23 contralateral-saccade-preferring). Population normalized curves for preferred versus nonpreferred saccade direction (Figure 4B) show that this population started possessing directional selectivity around saccade onset. SKF81297 reduced activity and significantly reduced saccade direction SI (Figure 4E, top) and AUROCs (Figure 4C; Figure 4E, bottom). Mean AMI for the preferred saccade direction decreased, while that for the nonpreferred direction marginally increased (Figure 4D). Thus, selectivity deterioration was effected by greater activity reduction for the preferred saccade direction.

Figure 5A shows a neuron with contralateral perisaccadic selectivity induced by quinpirole. This neuron had nonsignificant control period contralateral perisaccadic selectivity ($p_{contra\text{-}ipsi}$ = 0.4238, WRS; AUROC = 0.52). Quinpirole augmented neuronal activity ($p < 10^{-6}$) and induced significant contralateral selectivity ($p_{contra\text{-}ipsi}$ = 0.0205; AUROC = 0.61). During post-drug recovery, neuronal activity subsided ($p < 10^{-6}$), and selectivity was reduced but remained significant ($p_{contra\text{-}ipsi}$ = 0.01636; AUROC = 0.604). Population normalized curves (Figure 5B; n = 46, 28%; 35 contralateral-saccade-preferring) show activity augmentation with increases in mean SI (Figure 5F; p = 0.0051) and mean saccade direction AUROC upon quinpirole application (Figures 5C and 5G; p = 0.0032). Mean AUROC increased nonsignificantly with lower doses (Figure 5E; p = 0.1808), whereas higher doses were significantly augmented (p = 0.0472). Selectivity increase was due to greater AMI increase for the preferred saccade direction than for the nonpreferred direction (Figure 5D; p = 0.005). Thus, SKF81297 moderately decreased, while quinpirole sharply increased, saccade direction selectivity.

Next, we tested whether quinpirole's effects on perisaccadic activity were different for pro- versus antisaccades. Figure 6A shows a neuron with perisaccadic activity. Contralateral and ipsilateral prosaccade activity (Figure 6A, left) and antisaccade activity (Figure 6A, right; contralateral is indicated by dark traces, and ipsilateral is indicated by light traces) are shown. This neuron displayed saccade direction selectivity on control trials for prosaccades starting prior to saccade onset and for antisaccades just after saccade onset. Quinpirole augmented activity for both pro- and antisaccades in this neuron ($p < 10^{-6}$). Control direction selectivity in the presaccadic epoch for both trial types

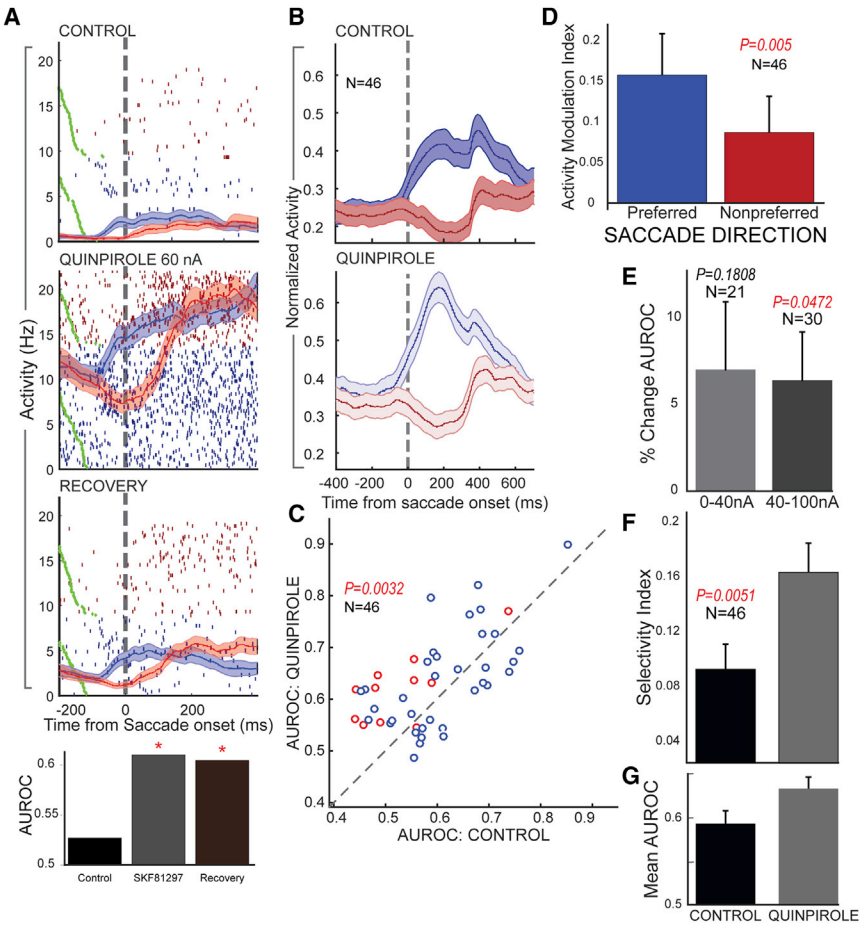

Figure 5. Effects of Quinpirole on Saccade-Related Activity of DLPFC Neurons in the Stimulus-Response Epoch

Color and figure conventions are analogous to those in Figure 4.

(A) Rasters and spike density functions for a neuron displaying mild contralateral saccadic activity in the stimulus-response epoch in control and tested with quinpirole and post-drug recovery (AUROC saccade selectivity, bottom).

(B) Saccade-selective population (n = 46) normalized activity curves for preferred and nonpreferred saccade direction for control and quinpirole.

(C) Saccade-selective AUROC values for population during control and quinpirole application shown for contralateral- and ipsilateral-saccade-selective neurons.

(D) Population AMI for preferred and nonpreferred saccade direction shown. Quinpirole increased preferred direction activity significantly more than nonpreferred direction activity.

(E) Change in AUROC for saccade direction after iontophoresis of low (0–40 nA) and high (40–100 nA) doses of quinpirole.

(F) Mean population saccade direction SI during control and quinpirole.

(G) Mean population saccade direction AUROC during control and quinpirole. p values from WSR. Error bars indicate ± SEM.

was nonsignificant (p_{pro} = 0.174, and p_{anti} = 0.49). Quinpirole significantly increased directional presaccadic selectivity for prosaccades (p_{pro} = 0.0007, Δ_{SI} = 0.10, and Δ_{AUROC} = 0.10), whereas selectivity was unchanged for antisaccades (p_{anti} = 0.704, Δ_{SI} = −0.01, and Δ_{AUROC} = 0.03). In contrast, directional selectivity increased during the postsaccadic epoch for both trial types (prosaccades: $p_{pro} < 10^{-6}$, Δ_{SI} = 0.01, and Δ_{AUROC} = 0.07; antisaccades: p_{anti} = 0.0007, Δ_{SI} = 0.01, and Δ_{AUROC} = 0.07). Quinpirole increased saccade direction cumulative selectivity over time in the presaccadic epoch for this neuron (Figure 6B), whereas differences in antisaccadic selectivity were smaller and began postsaccadically. Presaccadic SI changes were significantly greater for prosaccades than for antisaccades (Figure 6C, left), whereas postsaccadic SI changes were also greater for prosaccades (Figure 6C, right). Thus, perisaccadic selectivity effects were stronger during prosaccades than antisaccades, with latency shifts absent in the latter and more pronounced in the presaccadic epoch.

We analyzed saccade direction selectivity during prosaccades and antisaccades in the 35 neurons with contralateral saccade preference tested with quinpirole. Figure 7A shows population normalized curves (contra- versus ipsilateral) aligned on stimulus onset (left) and saccade onset (right) for prosaccades (top) and antisaccades (bottom). Selectivity onset in control was comparable between rules when aligned on saccade onset. After quinpirole, selectivity was more robust and had earlier onset for prosaccades only. Onset of direction selectivity for antisaccades did not change. Population sliding AUROC analysis (Figure 7B) of the perisaccadic epoch shows a selective increase in AUROC in the presaccadic period after quinpirole for prosaccades but not for antisaccades. Quinpirole significantly increased mean presaccadic AUROC for prosaccades only (Figure 7C). Furthermore, quinpirole-induced AUROC increases on prosaccade trials were reversed during recovery in 12 neurons (Figure 7D). We also examined quinpirole's effects on misdirected saccades to determine whether contralateral selectivity was present and augmented when the saccade was a response error. Normalized population curves for ipsi- and contralateral error prosaccades (Figure S4A) show no presaccadic selectivity and small postsaccadic selectivity for ipsilateral errors (contralateral saccade) during control. Quinpirole did not change AUROC selectivity for contralateral error saccades pre- and postsaccadically (Figure S4B). This indicates that quinpirole-sensitive saccadic responses were not directly motor feedback related, because purely motor-feedback responses should not depend on whether the identical motor response was made correctly or in error. Further, population analysis of SKF81297 application on pro- versus antisaccadic selectivity in 24 contralateral-saccade-selective neurons revealed weaker but significant deterioration of selectivity during the presaccadic epoch (see Figure S5).

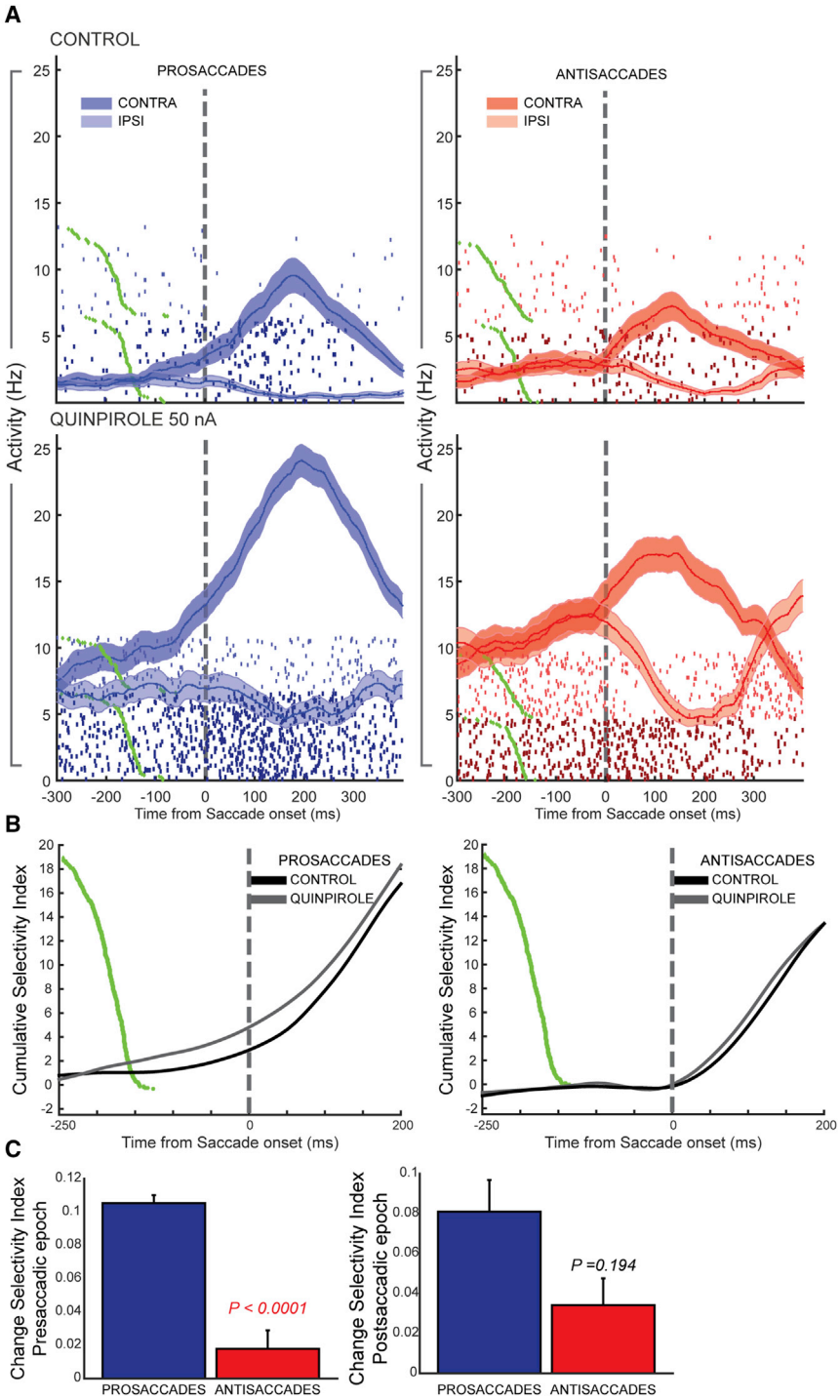

Figure 6. Rule-Dependent Augmentation of Contralateral Saccadic Selectivity of a DLPFC Neuron by Quinpirole

(A) Rasters and spike density functions for DLPFC neuron showing contralateral-saccade-related activity shown for prosaccade trials (left: dark blue, contralateral; light blue, ipsilateral) and antisaccades (right: dark red, contralateral; light red, ipsilateral). Dashed lines indicate saccade onset; green dots stimulus onset.

(B) Cumulative saccadic SI shown for prosaccades (left) and antisaccades (right) for neuron in (A) during control and quinpirole time course of quinpirole-induced selectivity changes. Similar analysis using cumulative sliding AUROC showed similar results, with significant presaccadic augmentation for prosaccades ($p_{pro} = 2 \times 10^{-6}$; WSR), but not for antisaccades ($p_{anti} = 0.288$; WSR), while postsaccadic selectivity changes were significant for both ($p_{pro} = 0.0002$, and $p_{anti} = 0.0005$).

(C) Change in saccade direction SI for prosaccades (blue) and antisaccades (red) in the presaccadic (left) and postsaccadic (right) epochs. The p values (red, significant; WSR) indicate comparisons of SI between pro- and antisaccades on a 50 ms sliding window and 10 ms step in each epoch between control and drug.

Error bars indicate ±SEM.

Similarly, an analysis of stimulus-related selectivity in visually responsive DLPFC neurons revealed that SKF81297 enhanced, while quinpirole did not enhance, neuronal stimulus direction selectivity (Figure S6 and legend). Thus, quinpirole's effects on saccade-related selectivity were unaccompanied by comparable changes in stimulus-related responsiveness.

Behavioral Effects of Dopamine Agonists

Microiontophoresis results in focal drug delivery with circumscribed spatial spread and is not expected to have behavioral effects in areas with diffuse functional specialization, such as the DLPFC (Gamo et al., 2015). Nevertheless, given reports of reaction time effects upon iontophoresis of dopamine agonists (Ott et al., 2014), we examined their behavioral effects in our main paradigm (Figure S7). SKF81297 significantly increased total post-delay error rates (anticipatory and misdirected saccade errors) across sessions (Figure S7A) in a dose-dependent manner (Figure S7B), whereas quinpirole application did not significantly change total post-delay errors (Figure S7A) at both doses (Figure S7B). Contrasting with their dissociable error-rate effects, both SKF81297 (Figure S7C, top) and quinpirole (Figure S7C, bottom) significantly increased both prosaccade and antisaccade saccade reaction times (SRTs) at low and high doses, barring a nonsignificant increase in antisaccade SRTs at high doses of quinpirole. Figure S7C tabulates a breakdown of effects of both agonists on misdirected response errors, premature (anticipatory) saccade errors, memory epoch fixation breaks, and express saccade

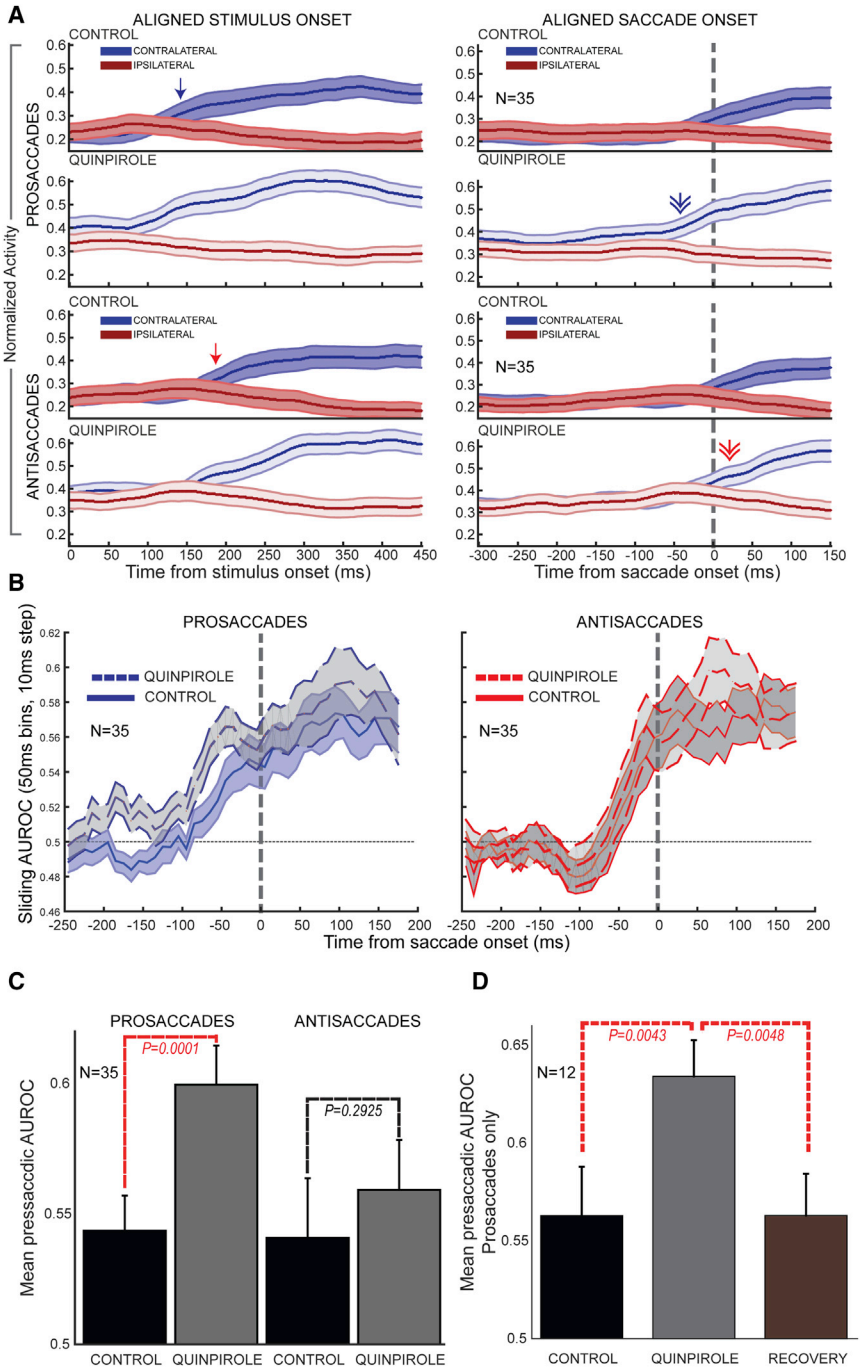

Figure 7. Population Analysis of Rule-Contingent Saccadic Selectivity Changes Induced by Quinpirole

(A) Normalized activity for control and quinpirole shown for 35 neurons that preferred contralateral saccades in the perisaccadic epoch. Curves are shown for prosaccades (top) and antisaccades (bottom), aligned on stimulus onset (left) and saccade onset (right; dashed lines). Blue, contralateral activity; red, ipsilateral activity. When aligned to stimulus onset, during control, selectivity onset occurred earlier for prosaccades (120 ms post-stimulus onset) than for antisaccades (190 ms), approximately corresponding to mean SRT differences between pro- and antisaccades (blue arrow, mean prosaccade SRT; red arrow, mean antisaccade SRT), indicating that selectivity latency onset is correlated with the saccade onset and not influenced by visual stimulus onset (blue and red double arrows, activation onset latency).

(B) Sliding-window AUROC for control and quinpirole for pro- and antisaccades (left and right, respectively) showing the time course of selectivity accumulation.

(C) Presaccadic average population AUROC is significantly augmented by quinpirole for prosaccades but not antisaccades.

(D) Quinpirole augmentation of presaccadic AUROCs was reversed in 12 contralateral-saccade-selective neurons tested for drug recovery.

The p values in (C) and (D) are for WSR-HB, and p values in red are significant. Error bars indicate ±SEM.

proportions (Everling and Munoz, 2000). Both agonists significantly increased fixation breaks during the rule-memory period before fixation spot offset. SKF81297, but not quinpirole, increased anticipatory saccades selectively for prosaccade trials and not antisaccade trials. SKF81297 also mildly, but significantly, augmented misdirected antisaccade error rate. Quinpirole significantly reduced, while SKF81297 had nonsignificant effects on, express saccade proportions and prosaccade velocities, and SKF81297 mildly reduced antisaccade velocities. Thus, only D1R stimulation increased erroneous responding, whereas quinpirole changed behavioral metrics related to the saccade.

DISCUSSION

We found that local stimulation of dopamine D1Rs and D2Rs has complex, dissociable effects on rule, sensory, and saccadic activity of DLPFC neurons engaged in rule-guided pro- and antisaccade performance. Contrasting with a previous report that both D1R and D2R iontophoretic stimulation enhanced DLPFC neuronal selectivity for rules guiding numerical comparisons (Ott et al., 2014), we found that D1R stimulation markedly suppressed neuronal rule selectivity in DLPFC at all doses in a saccadic task and increased behavioral choice errors and premature, impulsive responding. Further, D2R stimulation had ambivalent effects on neuronal rule selectivity while augmenting saccade direction selectivity with subtle effects on saccade metrics. Additionally, D1R stimulation, but not D2R stimulation, increased stimulus selectivity in DLPFC neurons. We also found that D2R augmentation of saccade direction selectivity in DLPFC neurons

(Wang et al., 2004) was more pronounced during prosaccade than antisaccade trials, and selectivity augmentation was stronger prior to the saccade. We reason this implies that D2R may not modulate corollary discharge (CD) signals conveyed to DLPFC from mediodorsal thalamus (MD), as has been previously hypothesized (Wang et al., 2004). Instead, our results suggest that D2R may modulate layer V DLPFC output neurons, influencing circuitry in subcortical structures involved in saccade dynamics (Noudoost and Moore, 2011), including superior colliculus (SC).

We found that D1R stimulation mostly suppresses DLPFC activity and that D2R stimulation increases neuronal excitability, which is consonant with previous reports (Ott et al., 2014; Vijayraghavan et al., 2007; Wang et al., 2004). However, our observed effects of dopamine receptor stimulation on rule selectivity contrast with Ott et al. (2014), who found that "greater/less than" rule representation in DLPFC neurons in a numerical comparison task was augmented by stimulation of SKF81297 at low doses (15 nA) and quinpirole. Here, we find rule selectivity deterioration at all doses of SKF81297 and nonsignificant reduction with quinpirole. One possible reason for our contrasting findings with both agonists is that our recordings were in a different subzone of the DLPFC. A majority of our rule-selective neurons was found in a patch dorsal to the caudal principal sulcus, and the overlap with rule-selective loci in the numerical study is unknown. Further, the task used by Ott et al. (2014) was a numerical comparison with non-oculomotor lever responses, whereas we recorded in a region with strong connectivity with the FEF in an oculomotor paradigm. We discount the possibility that the differential prestimulus activity we recorded was not rule related, as we found that differential rule activity was similar with color cues and a modified uncued task. It is possible that cognitive representation in DLPFC is generated by different mechanisms depending on task contingencies, and neuromodulatory effects may depend on the nature of inputs generating rule selectivity. Alternatively, differences in task difficulty between the numerical comparison task and our saccadic task could lead to differences in baseline neuromodulatory tone (Arnsten et al., 2012), contributing to divergent agonist effects. This study suggests that dopamine modulation of rule representation in DLPFC is heterogeneous and dependent on the sensorimotor context.

Meanwhile, our results are partly consonant with previous reports of D1R and D2R stimulation on spatial WM activity in DLPFC neurons (Vijayraghavan et al., 2007; Wang et al., 2004). At low doses, the D1R agonist SKF81297 augments spatial tuning of memory period activity by suppressing activity for nonpreferred spatial directions, while higher doses suppress tuning by suppressing preferred direction activity (Vijayraghavan et al., 2007). The D2R agonist quinpirole has no appreciable effects on this memory activity (Wang et al., 2004). We found deterioration of rule selectivity with SKF81297 at both dose ranges (defined based on previous studies), with larger decreases at higher doses due to greater effects on preferred-rule activity. Apart from individual examples, we failed to find population inverted-U dose effects on rule-memory activity, as reported for spatial memory selectivity (Vijayraghavan et al., 2007). This may be a consequence of differences in the prefrontal representation of parametric spatial and categorical rule activity.

Contrasting with rule selectivity, we found enhancement of peripheral stimulus direction selectivity with D1R, but not with D2R, stimulation. Dopamine neurons fire in response to the sensory cue in delayed response tasks after training (Schultz et al., 1993), and dopamine enhances sensory stimulus signal to noise in DLPFC neurons (Jacob et al., 2013). D1R blockade, and not D2R stimulation, in the FEF enhances stimulus selectivity and reliability of V4 neurons similar to attentional top-down effects (Noudoost and Moore, 2011), arguing for a selective role of D1Rs in sculpting sensory signals. Our observations with stimulus-direction selectivity contribute to this developing consensus on D1R modulation of sensory activity in DLPFC.

Contrastingly, we found that quinpirole enhanced saccade direction selectivity by increasing preferred direction activity, consistent with a previous report with spatial delayed response (Wang et al., 2004), whereas we found weaker deterioration in saccade selectivity due to D1R stimulation. However, unlike memory-guided saccades in the previous study, the antisaccade paradigm allowed us to examine saccade activity related to directionally identical saccades congruent with or spatially dissociated from visual stimuli, allowing analysis of activity for visually guided saccades versus saccades to internally generated incongruent targets. We found that D2R stimulation had greater effects on contralateral saccade direction activity for prosaccades than for antisaccades. Moreover, saccade direction selectivity effects were greater in the presaccadic epoch, not reaching significance postsaccadically.

The functional role of DLPFC perisaccadic activity has been fraught with interest, with many hypothetical roles proposed (Funahashi, 2014). The previous study delineating D2R-selective modulation of saccadic activity (Wang et al., 2004) hypothesized that perisaccadic discharge, especially postsaccadic, could represent CD feedback from the SC via MD, updating DLPFC spatial representations about an upcoming saccade (Sommer and Wurtz, 2008). However, D2R expression in DLPFC is sparse, with strongest expression restricted to layer V (Lidow et al., 1998), whereas MD-DLPFC projections specifically target deep layer III and layer IV (Giguere and Goldman-Rakic, 1988), thus rendering direct D2R modulation of MD inputs less plausible. Also, if D2Rs directly modulated CD inputs, then we would expect comparable effects on pre- and postsaccadic activity independent of the type of saccade (pro- or antisaccades), contrary to our findings. Furthermore, we found that perisaccadic selectivity is diminished and unaffected by quinpirole when an identical saccade was erroneously produced. If D2R-sensitive activity were purely motor feedback, we would expect commensurate enhancement of activity on error trials where identical saccades were generated. Thus, at least some D2R effects on saccade activity appear unrelated to CD regarding the saccade motor command. CD deficits are proposed to exacerbate hallucinatory behavior in schizophrenia (Ford et al., 2001), quinpirole induces hallucinatory-like behavior in monkeys (Arnsten et al., 1995), and D2R blockade is correlated with antipsychotic treatment efficacy (Kapur et al., 2000). However, our findings suggest that D2R/CD involvement in hallucinogenesis may not be localized in DLPFC. Mechanistically, we hypothesize that D2R stimulation had greater effects on saccade direction selectivity on prosaccade trials, because D2R-expressing neurons in layer V

of DLPFC microcolumns receive input from superficial layers carrying contralateral stimulus information (Kritzer and Goldman-Rakic, 1995). D2R stimulation leads to enhancement of visuomotor integration within the microcolumn. In antisaccade trials, D2R-expressing layer V contralateral-saccade-selective neurons do not receive direct visual information, which is instead represented in the opponent hemisphere. Thus, D2R stimulation does not augment perisaccadic selectivity for antisaccades. Further experiments are needed to test this hypothesis.

Microinfusion studies with D1R and D2R ligands have shown that spatial WM performance is deteriorated by both D1R blockade and stimulation in rodents and monkeys (Arnsten et al., 2015; Gamo et al., 2015; Sawaguchi and Goldman-Rakic, 1994; Zahrt et al., 1997), whereas D1R, but not D2R, stimulation facilitated visuospatial WM in humans (Müller et al., 1998). D2R DLPFC infusion does not affect oculomotor delayed-response performance (Sawaguchi and Goldman-Rakic, 1994). Here, we found D1R-agonist-induced, significant dose-dependent increases in premature anticipatory saccades on prosaccade trials, suggesting increased impulsive responding when the trial rule specifies prosaccades. We believe the rule specificity of impulsive responding we observed is due to differences in inhibitory control in the saccadic system between the two trial contingencies: increased prestimulus inhibitory tone in the SC during antisaccade trials (Everling et al., 1999) counteracts D1R-mediated effects in DLPFC, resulting in less change in premature responding during the gap period. Dopamine dysregulation has been implicated in impulsive responding in disorders like attention deficit hyperactivity disorder and schizophrenia, and D1R blockade and stimulation in rat medial PFC increases impulsive responding (Loos et al., 2010). Our data support modulation of inhibitory response control in primate DLPFC by D1Rs. We also found that D1R stimulation increased post-stimulus misdirected saccade errors, reaching significance in the more difficult antisaccade condition, suggesting that D1R stimulation disrupted WM representation of trial rule, similar to spatial WM modulation (Vijayraghavan et al., 2007). D1Rs are localized on both layer II/III and infragranular layer V circuits in DLPFC, and based on prior spatial WM studies (Gamo et al., 2015; Noudoost and Moore, 2011; Vijayraghavan et al., 2007; Wang et al., 2004), we propose that the SKF81297-induced increase in post-stimulus errors are a consequence of dysregulated layer II/III circuits. This is consonant with the physiological degradation of rule WM activity we observed here. Increased premature responding could be due to D1R disruption of layer V output neuronal activity targeting oculomotor striatum and SC.

Interestingly, both Ott et al. (2014) and this study found increased SRTs with both agonists, while the former did not find error rate effects and posited that longer SRTs reflected enhanced rule-coding stability. However, in this study, error rates increased for the D1R agonist only, while SRTs increased for both agonists. Furthermore, unlike dose dependence of error rate changes, increases in SRTs occurred regardless of agonist dose, suggesting that this may not reflect enhanced rule processing. It cannot be ruled out that the SRT increases we observed with both agonists could be consequent to ongoing changes in the motivational state of the animal or fatigue.

We found that D2R stimulation had no effect on anticipatory and misdirected saccade errors at any dose, consistent with previous spatial WM studies showing lack of D2R effects on delayed-response performance with microinfusions (Sawaguchi and Goldman-Rakic, 1994). Quinpirole selectively decreased the proportion of express saccades and decreased prosaccade velocities, suggesting an involvement in saccade-related circuitry after the saccade target has been specified. D2Rs are proposed to modulate target selection in layer V output neurons in the FEF (Noudoost and Moore, 2011). Here, we found modest effects on saccadic errors and, instead, found effects on express saccade proportions and velocities, delineating a more specific, unexplored role for DLPFC D2Rs. We propose that rule-specific augmentation of saccadic activity and concomitant latency shifts during prosaccades account for the effects on express saccade frequencies. Further experiments, including cortical microinfusions (Noudoost and Moore, 2011), may help clarify this hypothesis.

In summary, contrary to previous findings positing a beneficial role of dopamine receptor stimulation in DLPFC for WM representation of rules, we found that D1R and D2R effects on rule WM are dissociable, with D1R stimulation predominantly disrupting rule-guided task performance and activity. D1R stimulation increased premature responding, delineating a role for DLPFC D1Rs in impulse control. Contrastingly, D2Rs specifically gate perisaccadic activity that may be unrelated to movement feedback with modest behavioral effects, pointing to a role in modulating subcortical motor control circuitry. Our results contribute to the growing body of literature on the functional and physiological consequences of dopamine neuromodulation of prefrontal circuitry (Jacob et al., 2013; Noudoost and Moore, 2011; Ott et al., 2014; Puig et al., 2014; Vijayraghavan et al., 2007) and shed light on dopamine regulation of the performance of antisaccades, a paradigm highly correlated with cognitive deficits in psychiatric disorders.

EXPERIMENTAL PROCEDURES

For detailed procedures, please refer to the Supplemental Experimental Procedures.

Surgical Procedures

All behavioral and physiological procedures were performed on two adult male rhesus monkeys (*Macaca mulatta*). Procedures were performed in accordance with the Canadian Council of Animal Care policy and a protocol approved by the Animal Use Subcommittee of the University of Western Ontario Council on Animal Care. Recording chambers were implanted over the right DLPFC (Figure 1A), as previously described (Skoblenick and Everling, 2012).

Behavioral Paradigm

The subjects performed variants of the pro- and antisaccade tasks (Hallett, 1978). They executed prosaccades toward or antisaccades away from a peripheral stimulus, guided by a memorized colored rule cue that specified the appropriate response after a randomized gap period (n = 113 recording sessions; Figure 1B). To ensure that rule-selective activity was not a consequence of sensory attributes of the rule cues, we used an uncued task variant involving self-ordered switching of the rule (Everling and DeSouza, 2005) in some recording sessions (n = 18; Figure 1B, right). Neurons displaying rule activity in the color-cued rule task also displayed differential activity in the uncued task (Figure S1). We pooled physiological data from all recording types. Behavioral analysis was only performed on the gap-cued task.

Microiontophoretic Physiology

Multi-barrel tungsten-in-glass electrodes were custom fabricated and filled with D1R agonist SKF81297, D2R agonist quinpirole, and saline as previously described (Tocris Bioscience, Sigma-Aldrich; Vijayraghavan et al., 2007; Wang et al., 2004). SKF81297 and quinpirole were locally ejected at positive currents (10–100 nA). At least eight correct trials were obtained per rule/saccade direction.

Data Analysis

We conducted an analysis of drug effects on SRTs and different types of error rates observed in the task. We also examined drug effects on express saccade proportions (Everling and Munoz, 2000). After excluding neurons with negligible overall activity (<1 Hz), we performed an ANOVA on each neuron in the dataset for each drug with three factors: rule, saccade or visual direction, and drug condition and classified neuronal selectivity thereof. Proportions of DLPFC neurons displaying individual activity types (rule, saccade, and visual) in the overall population were determined (Figure S2).

We examined neuronal task-related selectivity by constructing ROC curves and computing the AUROC as a discriminability index (Everling and DeSouza, 2005). We also computed selectivity by using a different metric, the selectivity index (SI), from spike density functions normalized within control, drug, and recovery conditions.

We examined how population activity for preferred and nonpreferred conditions changed in response to the drug by normalizing the activity for each neuron across the whole recording session. We examined the relative effects of the drug on preferred versus nonpreferred activity for the activity type of interest by computing the AMI for normalized preferred and nonpreferred activity.

The WRS and paired signed-rank test (WSR) were used with the Holm-Bonferroni correction (HB) for multiple comparisons to examine drug effects in individual neuronal examples, population metrics, and behavior.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures and seven figures and can be found with this article online at http://dx.doi.org/10.1016/j.celrep.2016.06.031.

AUTHOR CONTRIBUTIONS

Conceptualization, S.V. and S.E.; Methodology, S.V., A.J.M., and S.E.; Investigation, S.V., A.J.M., and S.E.; Writing – Original Draft, S.V., A.J.M., and S.E.; Writing – Review & Editing, S.V., A.J.M., and S.E.; Funding Acquisition, S.E.; Resources, S.E.; Supervision, S.E.

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