1521-0081/67/3/681–696$25.00
PHARMACOLOGICAL REVIEWS

http://dx.doi.org/10.1124/pr.115.010512
Pharmacol Rev 67:681–696, July 2015

ASSOCIATE EDITOR: JEFFREY M. WITKIN

Dopamine's Actions in Primate Prefrontal Cortex: Challenges for Treating Cognitive Disorders

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***Abstract*——The prefrontal cortex (PFC) elaborates and differentiates in primates, and there is a corresponding elaboration in cortical dopamine (DA). DA cells that fire to both aversive and rewarding stimuli likely project to the dorsolateral PFC (dlPFC), signaling a salient event. Since 1979, we have known that DA has an essential influence on dlPFC working memory functions. DA has differing effects via D1 (D1R) versus D2 receptor (D2R) families. D1R are concentrated on dendritic spines, and D1/5R stimulation produces an inverted U-shaped dose response on visuospatial working memory performance and Delay cell firing, the neurons that generate representations of visual space. Optimal levels of D1R stimulation gate out "noise," whereas higher levels, e.g., during stress, suppress Delay cell firing. These effects likely involve hyperpolarization-activated cyclic nucleotide-gated channel opening, activation of GABA interneurons, and reduced glutamate release. Dysregulation of D1R has been related to cognitive deficits in schizophrenia, and there is a need for new, lower-affinity D1R agonists that may better mimic endogenous DA to enhance mental representations and improve cognition. In contrast to D1R, D2R are primarily localized on layer V pyramidal cell dendrites, and D2/3R stimulation speeds and magnifies the firing of Response cells, including Response Feedback cells. Altered firing of Feedback neurons may relate to positive symptoms in schizophrenia. Emerging research suggests that DA may have similar effects in the ventrolateral PFC and frontal eye fields. Research on the orbital PFC in monkeys is just beginning and could be a key area for future discoveries.**

This review was supported in part by the National Institutes of Health National Institute on Aging Pioneer Award [DP1-AG047744-01].
A.F.T.A. and Yale University receive royalties from the sales of Intuniv (extended release guanfacine) by Shire Pharmaceuticals. They do not receive royalties from immediate release guanfacine or generic versions of Intuniv.
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dx.doi.org/10.1124/pr.115.010512.

I. General Introduction

The higher cognitive functions of the prefrontal cortex (PFC) are impaired in a range of mental disorders. The more severe cognitive disorders, such as schizophrenia, are a tremendous emotional and societal burden when patients are unable to safely care for themselves and others, and even milder cognitive disorders can limit a person's success in the information age when executive functions are essential to an accomplished career. Although there is great need, there have been few effective treatments developed for normalizing PFC cognitive abilities in humans. Research in nonhuman primates suggests that the dopamine (DA) D1 receptor family (D1R and D5R) may be an important therapeutic target for the treatment of PFC cognitive disorders, whereas the D2 receptor family (D2R, D3R, D4R) may be especially related to appropriate motor responding and possibly to the positive symptoms (hallucinations and delusions) of schizophrenia. Most of this research has been conducted in rhesus monkeys, although recent studies of the orbital PFC have begun in marmosets.

The breakthrough discovery by Brozoski et al. (1979) first revealed that DA is essential for PFC working memory functions, and that depletion of DA from the dorsolateral PFC (dlPFC) was as detrimental to cognition as removing the cortex itself. The advent of DA receptor pharmacology introduced more selective tools for dissecting DA actions at its various receptors. [Note: As currently available, pharmacological agents do not distinguish between D1R and D5R or D2R and D3R (Sealfon and Olanow, 2000), and thus descriptions of pharmacological data will refer to D1/5R and D2/3R actions.] Although early studies showed that blockade of D1/5R in PFC impairs working memory function (Sawaguchi and Goldman-Rakic, 1991, 1994), decades later, D1/5R agonists still have not successfully translated into clinical treatment. The challenges to the development of D1/5R agonists as therapeutics include a narrow inverted U-shaped dose response, whereby increasing doses actually impair cognition, e.g., as occurs with very high levels of endogenous DA release during uncontrollable stress (Arnsten, 1998). More recent data suggest that the D2 receptor family may also contribute to PFC function, where D4R influence GABA interneurons (Mrzljak et al., 1996), and D2/3R modulate response-related neuronal firing (Wang et al., 2004), including the feedback that allows the updating of appropriate responses. This review describes the complex and vital role of DA in the primate dlPFC, how its actions may differ from the simpler rodent PFC, and potential strategies for facilitating the development of therapeutics for higher cognitive disorders.

II. The Great Expansion of the Prefrontal Cortex and Cortical Dopamine in Primates

The neocortex greatly expands and differentiates over the course of evolution, and there is a corresponding increase in the extent and elaboration of the DA innervation of the cortical mantle in primates. Cortical DA is relatively restricted in rodents—there is dense innervation of the anterior cingulate, PFC, and rhinal cortices, but only sparse innervation of the sensorimotor cortex that makes up the majority of the rodent neocortex (Descarries et al., 1987; Berger et al., 1991). In contrast, there is an extensive DA innervation of most of the cortical mantle in nonhuman (rhesus macaque) and human primates, with densest distribution in the motor and premotor association areas, and extensive projections to most areas, with the exception of the primary visual cortex (Berger et al., 1991; Lewis, 2001). The primate PFC is densely innervated medially, with a more delicate innervation of the dorsolateral surface (Fig. 1A; Levitt et al., 1984; Berger et al., 1991; Lewis, 2001). However, even the regions with fewer DA projections contain high concentrations of DA, suggesting extensive DA synthesis by these axons (Brown et al., 1979). There are intriguing age-related changes in the DA innervation of the dlPFC, with an increased innervation of layer III during adolescence (Rosenberg and Lewis, 1994, 1995), a time of increased vulnerability to mental illness and addiction, and a marked loss of DA from the dlPFC commencing in middle age (Goldman-Rakic and Brown, 1981; Wenk et al., 1989).

The PFC is one of the brain areas that expands most in evolution, with an increase in the number and size of PFC subregions and an increase in the width and neuronal complexity of cortical layers. For example, layer III is especially broad in the primate dlPFC, whereas there is only a sparse layer II/III in rodent PFC (Preuss, 1995). In particular, there is a vast increase in the number and elaboration of pyramidal cells in deep layer III of the dlPFC, with an explosion of their basal dendritic fields and corresponding dendritic spines (Elston et al., 2006). As described below, these deep layer III pyramidal cell microcircuits are the ones that

ABBREVIATIONS: A77636, 1*R-cis*-1-(aminomethyl)-3,4-dihydro-3-tricyclo[3.3.1.13,7]dec-1-yl-[1*H*]-2- benzopyran-5,6-diol; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ADHD, attention deficit hyperactivity disorder; D1/5R, D1–D5 receptor; dlPFC, dorsolateral prefrontal cortex; DA, dopamine; FEF, frontal eye fields; HCN channels, hyperpolarization-activated cyclic nucleotide-gated channels; NMDAR, *N*- methyl-D-aspartate receptor; NE, norepinephrine; PET, positron emission tomography; PFC, prefrontal cortex; PSD, postsynaptic density; PV, parvalbumin; RGS4, regulator of G protein signaling 4; SCH23390, 7-chloro-3-methyl- 1-phenyl-1,2,4,5-tetrahydro-3-benzazepin-8-ol; SCH39166, (6*aS-trans*)-11-chloro- 6,6*a*,7,8,9,13*b*-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol; SKF38393, 1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol; SKF81297, (±)-6-chloro- 2,3,4,5-tetrahydro-1-phenyl-1*H*-3-benzazepine; vlPFC, ventrolateral prefrontal cortex.

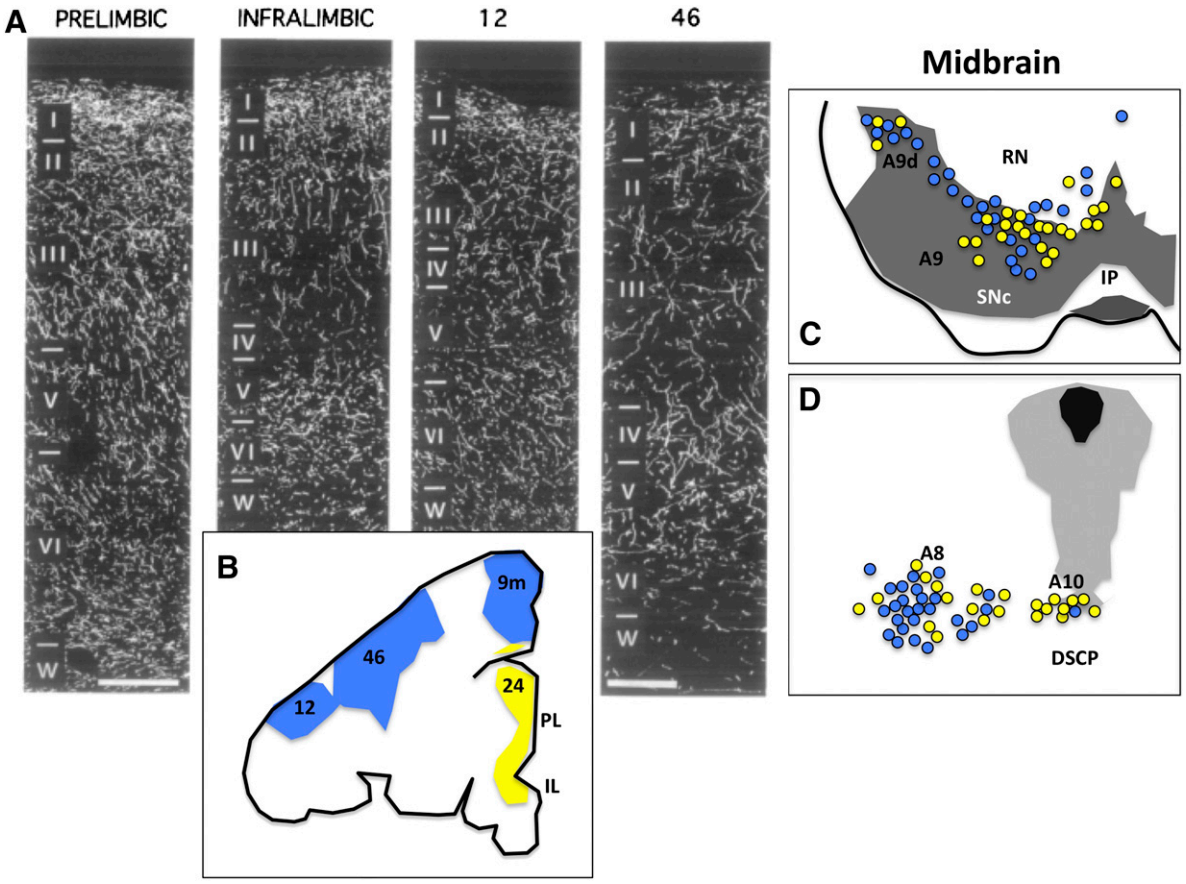

Fig. 1. The DA innervation of the primate PFC. (A) Dark-field microscopy of the extensive DA axonal projections in four PFC regions of the rhesus monkey brain. Note the relatively delicate innervation of the dlPFC (from Williams and Goldman-Rakic, 1993). (B) The PFC regions sectioned in (A), color-coded to indicate the DA cell groups in the midbrain (C and D) that project to the corresponding PFC region. (C and D) DA cell groups (A8, A9, A10) in the rostral (C) and caudal (D) midbrain project to PFC. In general, laterally localized neurons (blue circles) project to dorsal and lateral PFC, whereas the more medially localized neurons (yellow circles) project to the ventromedial PFC. However, there are exceptions. DSCP, decussation of the superior cerebellar peduncle; IL, infralimbic; IP, interpeduncular nucleus; PL, prelimbic; RN, red nucleus; SNc [shaded area in (C)], substantia nigra pars compacta. (B–D) Adapted from Williams and Goldman-Rakic (1998).

generate the mental representations that form the basis for abstract thought (Goldman-Rakic, 1995; Kritzer and Goldman-Rakic, 1995). Thus, it is of special interest that these pyramidal cell microcircuits are the most altered in schizophrenia, where there is loss of basal dendrites and spines (Glantz and Lewis, 2000) and signs of profound pyramidal cell hypometabolism (D. A. Lewis, personal communication).

III. Working Memory Circuits in the Dorsolateral Prefrontal Cortex

Working memory is precisely defined by cognitive psychologists as the simultaneous storage and processing of information (Baddeley, 1992). However, the term has come to be used more generally to refer to the ability to generate mental representations and keep information "in mind" in the absence of sensory stimulation, our "mental sketch-pad." The contents of working memory are constantly updated, reflecting an ever-changing pattern of cortical network firing (see Arnsten et al., 2012, for review). Working memory contrasts with long-term memory consolidation, where an event is captured in long-term storage and also differs from the habit and association memories that arise from sequence repetitions. In these more classic forms of plasticity, experiences are stored as architectural changes in synapses, e.g., with the formation of new spines or structural changes in existing immature spines, as documented in the sensory cortices, hippocampus, amygdala, and striatum. In contrast, higher cognition involves a transient firing pattern of neurons in the association cortex: keeping an event in short-term memory, bringing information to mind from long-term stores, generating novel, flexible events from the vast library of mental experience. The ability to generate mental representations is the foundation of cognitive operations such as high-order decision-making, top-down control and behavioral inhibition, insight, and planning, and thus, has far-reaching influence on human cognitive abilities.

Highly-evolved dlPFC microcircuits generate the mental representations that subserve working memory (Fig. 2). Goldman-Rakic (1995) first studied this mechanism in regard to visuospatial working memory and the

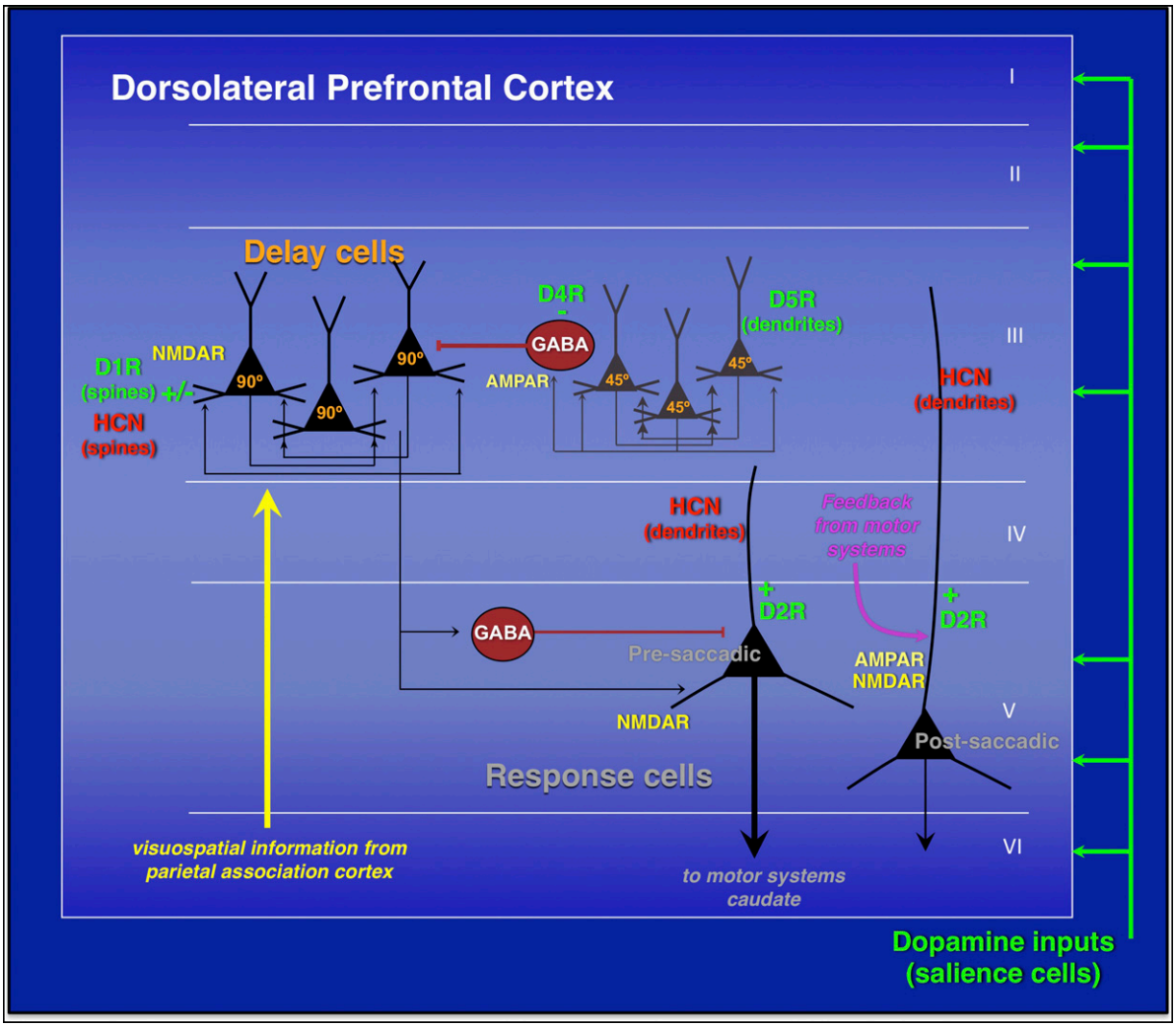

Fig. 2. The dlPFC microcircuits underlying spatial working memory as discovered by Goldman-Rakic. A schematized figure illustrating a simplified version of the neuronal microcircuitry thought to contribute to spatial working memory. The dlPFC receives DA inputs to layers I–III and V–VI, likely from DA "salience cells" that respond to aversive as well as rewarding stimuli. dlPFC Delay cells generate persistent representations of visual spatial position across the delay epoch and are thought to be concentrated in deep layer III (and possibly superficial layer V), whereas Response-related cells are thought to be concentrated in layer V. The persistent firing of Delay cells across the delay epoch in a spatial working memory task is thought to arise from recurrent excitation among pyramidal cells with similar spatial tuning. dlPFC neurons receive highly processed visuospatial information from area 7 of the parietal association cortex. Pyramidal cells in deep layer III interconnect on spines via NMDAR synapses, including those with NR2B subunits. The spatial tuning of these neurons is enhanced by lateral inhibition from GABAergic interneurons. Delay cells are modulated by DA D1/5R, but not D2/3R stimulation. D1R colocalize with HCN channels in spines of deep layer III, where they contribute to the sculpting and suppressive actions of D1/5R stimulation. In contrast D5R are concentrated in dendrites and associate with internal calcium stores, whereas D4R are concentrated on interneurons. In contrast to Delay cells, Response-related cells are modulated by D2/3R but not D1/5R stimulation. Response cells fire either just before the saccadic motor response (presaccadic) or during or just after the response (postsaccadic); these cells are very reliant on AMPAR as well as NMDAR. Post-saccadic Response cells likely receive and respond to feedback regarding the motor response (corollary discharge). Both types of Response-related cells show increased and speeded firing with D2/3R stimulation. D2R are localized in pyramidal cell dendrites where they may modulate inhibitory influences (see Fig. 4). Pyramidal cells in layer V often have HCN channels concentrated in their distal apical dendrites; however, the role of HCN channels in Response cell firing is not known. See Goldman-Rakic (1995) for more in-depth discussion of dlPFC microcircuitry.

dlPFC region that receives visuospatial inputs from the parietal association cortex but found that the same organization extended to other processing domains (O Scalaidhe et al., 1997), with spatial information localized more dorsally and feature information more ventrally (Romanski et al., 1999; Arnsten, 2013). She found that clusters of pyramidal cells receive highly processed information from the sensory association cortex and then were able to maintain the representation of the stimulus in the absence of sensory stimulation through their recurrent excitation within pyramidal cell networks (Goldman-Rakic, 1995). Neurons that are able to maintain representations in the absence of sensory stimulation across the delay epoch are termed Delay cells. These cells likely reside in deep layer III and possibly superficial layer V, because there are extensive horizontal connections between pyramidal cells in deep layer III (but not superficial layer III) and to a lesser extent in superficial layer V (Kritzer and Goldman-Rakic, 1995). The maintenance of neuronal firing across the delay period is often referred to as persistent firing. It should be noted that this persistent

firing shows a precise temporal and spatial pattern that can only be created by a circuit of neurons and not by a simple increase in the excitability of a single neuron. For example, a cluster of pyramidal cells all with a preferred direction of 90° will excite each other to maintain firing across the delay period on trials where the monkey is trying to remember a 90° cue (Fig. 2). This recurrent excitation is mediated by *N*-methyl-D-aspartate receptor (NMDAR) synapses on spines (see below). The specificity of information held in working memory is shaped and refined through lateral inhibition from parvalbumin (PV)-containing, fast-spiking GABA interneurons (Goldman-Rakic, 1995; Constantinidis and Goldman-Rakic, 2002). For example, as shown in Fig. 2, a cluster of pyramidal cells with a preferred direction of 45° will fire in response to a 45° cue and will activate nearby PV basket and chandelier interneurons to inhibit pyramidal cells with preferred direction other than 45°, e.g., with a preferred direction of 90°. Dopamine D1R also contribute to these sculpting actions, as described below. Delay cells can fire across the entire delay period or can begin "ramping up" later in the delay period, building toward the motor response. Delay cells likely convey their information to perisaccadic Response cells, which, in turn, project to motor systems to guide a thoughtful response. Delay cells appear to inhibit Response cells during the delay period, and thus reduced Delay cell firing can lead to disinhibited Response cell firing (Goldman-Rakic, 1995). Finally, there are Response cells that fire during or slightly after the motor response. These neurons are thought to provide feedback that a response has occurred, i.e., corollary discharge or efference copy. This feedback may convey a confirmatory signal, which allows the brain to track its own actions, and/or resets circuits to allow the subsequent updating of working memory (Funahashi et al., 1991). These neurons are of increasing interest, because altered feedback may contribute to symptoms of hallucinations and delusions (Ford et al., 2002).

A. Delay Cells

The persistent firing of Delay cells is generated by deep layer III pyramidal cell circuits that interconnect with synapses on long, thin spines. These dlPFC thin spines have the features consistent with mature, stable spines (a well developed spine apparatus, synapse encased by perisynaptic glia), in contrast to the immature "learning spines" that predominate in hippocampus and have the capacity to become mushroom spines after long-term potentiation (Bourne and Harris, 2007). The long, thin shape of dlPFC spines likely provides the geometry needed for effective gating by potassium channels to dynamically alter the pattern of network connections underlying working memory. Delay cells generate persistent firing via NMDAR synapses (Wang et al., 2013). These include NMDAR with NR2B subunits found exclusively within the postsynaptic density (PSD)—this contrasts with hippocampus and V1, where NMDAR-NR2B have a large extrasynaptic component (Wang et al., 2013). Blocking these NMDAR in monkey dlPFC completely arrests persistent firing, whereas blocking α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) has only subtle effects on Delay cell firing (Wang et al., 2013). Low, systemic doses of the NMDAR antagonist ketamine that impair working memory performance also decrease the firing of Delay cells (Wang et al., 2013). Given the subtle contribution of AMPAR to Delay cell firing, what depolarizes the membrane to eject Mg^{2+} from NMDAR and allow them to open? This vital function is performed by α_7-nicotinic acetylcholine receptors, which are localized in the PSD of glutamate synapses (Yang et al., 2013). These findings are particularly relevant to schizophrenia, given genetic links to α_7-nicotinic acetylcholine receptors, and the finding that most patients with schizophrenia smoke (Martin and Freedman, 2007). Importantly, thin spines in dlPFC layer III also contain a constellation of feedforward calcium-cAMP signaling proteins anchored next to the spine apparatus in close proximity to hyperpolarization-activated cyclic nucleotide-gated (HCN) (h-current or Ih) and KCNQ (m-current or Im) potassium channels in the spine membrane (Arnsten et al., 2012; Paspalas et al., 2013). These channels are opened by cAMP and protein kinase A, respectively, weakening the efficacy of synaptic connections and reducing neuronal firing (Arnsten et al., 2012). As described below, D1R in spines are also localized near this complex, e.g., next to HCN channels and the synapse (Paspalas et al., 2013; Gamo et al., 2015), and Delay cells are powerfully modulated by D1/5R but not D2/3R stimulation (Wang et al., 2004).

B. Response Cells

In contrast to Delay cells, Response cells respond to DA D2/3R but not to D1/5R stimulation (Wang et al., 2004). The Response cells likely reside in layer V, because this layer is the focus of neurons that synthesize D2R (Lidow et al., 1989), and Response-related firing has been recorded from deeper rather than superficial layers in similar cognitive tasks (Opris et al., 2011). The post-saccadic "feedback" Response cells are activated by AMPAR stimulation in addition to NMDAR (Wang et al., 2013), and systemic ketamine increases their firing, similar to what is described in rodents (Jackson et al., 2004). Response cells appear to be most commonly recorded in studies of rodents and ferrets (Caetano et al., 2012), but this may be due to the larger size of these neurons making them easier to record. Layer V pyramidal cells express HCN channels extensively on their distal apical dendrites (Lörincz et al., 2002). This feature is seen across species and cortical regions (He et al., 2014). In primate dlPFC, these dendritic HCN channels are not associated with cAMP-related proteins,

suggesting they are regulated by voltage but not by cAMP concentrations (Paspalas et al., 2013). In mouse PFC, HCN channel opening on layer V pyramidal cells increases their firing, whereas HCN1 knockdown decreases persistent firing (Thuault et al., 2013). It is noteworthy that this is opposite to what is recorded in primate Delay cells, where low dose HCN channel blockade increases persistent firing, whereas cAMP opening of HCN channels markedly *reduces* firing, likely through disconnection of recurrent excitatory circuits synapsing on spines in deep layer III (Wang et al., 2007) [although high-dose HCN channel blockade reduces firing, suggesting that dendritic Ih may play a less sensitive role in Delay cells as well (Wang et al., 2007)]. Thus, Delay cells and Response cells are modulated in fundamentally different ways, including qualitatively differing effects of DA. As layer III grows increasingly larger in primates, Delay cells may come to dominate cognitive processing in primates compared with rodents, allowing much greater powers of abstraction and the ability to represent information independently from sensory experience.

IV. Dopamine Neuron Anatomy and Physiology

DA projects throughout the cortical mantle in primates, with the densest projections to motor association areas and primary motor cortex (Levitt et al., 1984; Lewis et al., 1987; Williams and Goldman-Rakic, 1993). The dlPFC (e.g., areas 46 and 12, as shown in Fig. 1A) receives a delicate, bilaminar projection, whereas the DA projections to medial PFC areas are more dense (Williams and Goldman-Rakic, 1993). In monkey dlPFC, the DA innervation of layer III increases during adolescence (Rosenberg and Lewis, 1994); if there are similar increases in humans, they may lower the threshold for stress-induced mental illness in adolescence, e.g., for addiction or schizophrenia. In both monkey (Lewis et al., 2001) and human (Ciliax et al., 1999) dlPFC, DA fibers express DA transporters, although there are far fewer than in the striatum. Small alterations in the carboxyl-terminal tail of the DA transporters can make it less specific for DA (Lee et al., 1996) and this may explain why DA and norepinephrine (NE) transporters in the PFC appear to take up both catecholamines (Schmeichel et al., 2013). In monkey dlPFC, DA axons establish symmetric synapses with the soma, dendritic shafts, and spines of pyramidal cells, the latter participating in synaptic triads where both a DA symmetric synapse and a glutamate-like asymmetric synapse converge onto a single spine (Goldman-Rakic et al., 1989). As D1R are concentrated on spines (see below), these triadic complexes have been a focus of DA research in nonhuman primate cognition (Goldman-Rakic, 1999).

As illustrated in Fig. 1, B–D, the DA projections to the monkey PFC arise from a wide swath of the midbrain, including the dorsal tier of the substantia nigra pars compacta (A9 cell group). In general, projections to the dorsal and lateral parts of the PFC arise from more lateral aspects of the A8 and A9 DA cell groups, whereas projections to the medial PFC arise from more medial aspects of A9 and A10 cell groups (Fig. 1, B–D) (Haber and Fudge, 1997; Williams and Goldman-Rakic, 1998). The dlPFC projects back down to the DA cells in midbrain to regulate its own input, although these projections are sparse (Frankle et al., 2006), and the majority of PFC influence on DA neurons is likely via the striatum (Haber, 2014).

Recordings from DA neurons in monkeys have uncovered two general types of cells, those that fire based on the *value* of a stimulus and those that fire based on its *salience* (Matsumoto and Hikosaka, 2009; Bromberg-Martin et al., 2010). The original recordings by Schultz focused on DA Value cells and found that they fired in relationship to prediction error, increasing their firing to unexpected rewards or to cues that predict reward, decreasing firing when a reward is predicted but does not occur and responding very little to expected rewards (Schultz et al., 1993; Schultz, 1998). The Hikosaka group recorded additional types of DA neurons in the midbrain, termed Salience cells, which show elevated firing to either rewards or punishments, e.g., increased firing to a mildly aversive air-puff (Bromberg-Martin et al., 2010). Aversive information is relayed to the Salience cells via the lateral habenula (Hong et al., 2011; Lammel et al., 2012). Based on the general location of these different types of neurons, it is hypothesized that DA Salience cells project to dorsal PFC, whereas DA Value cells project to ventromedial and orbital PFC and the nucleus accumbens, although this is currently speculative (Bromberg-Martin et al., 2010). Of particular relevance to the current review, DA neurons fire to the visual cue in monkeys performing a visual spatial working memory task (Schultz et al., 1993). Thus, there is likely dopamine release in the dlPFC just in time to modulate neuronal firing during the delay period and possibly the response epoch as well.

The discovery of Salience DA cells is consistent with a previous body of biochemical research in rats showing that even mild stress increases DA release in the PFC, while having more subtle effects on DA release in striatum (Roth et al., 1988; Deutch and Roth, 1990), and that this increase impairs PFC cognitive function (see below; Arnsten, 1998, 2009). Recent studies have also shown that aversive stimulation increases DA release in mouse medial PFC (Lammel et al., 2011). Most recently, stress-induced release of DA in the PFC has been documented in primates. A study in monkeys found that the delivery of unexpectedly small rewards leads to increased DA release in the dlPFC (Kodama et al., 2014). Indirect measures of DA release using positron emission tomography (PET) imaging have also found evidence of stress-induced DA release in the PFC in

humans (Lataster et al., 2011; Nagano-Saito et al., 2013). Significant changes were focused in the medial PFC, which may be a function of the denser DA innervation of this region. Humans with the weaker (met/met) catechol-*O*-methyltransferase genotype are also more vulnerable to stress-induced PFC dysfunction (Qin et al., 2012), consistent with increased DA levels impairing PFC function during stress. The subjects with met/met genotype had impaired performance on a numerical N-back working memory task and reduced fMRI BOLD response in dlPFC after exposure to upsetting imagery, consistent with high levels of DA suppressing dlPFC neuronal firing during stress (Qin et al., 2012). Thus, there is excellent translation from rodent to monkey to human, suggesting that these effects of stress are conserved over evolution.

V. Dopamine Influences on Dorsolateral Prefrontal Cortex Physiology and Cognition (D1/D5 versus D2/D3 Receptors)

Catecholamines are essential to dlPFC function, and their depletion from the rhesus monkey (Brozoski et al., 1979) or marmoset (Collins et al., 1998) dlPFC greatly impairs spatial working memory performance (note that norepinephrine's effects on dlPFC function and neuronal firing are just as powerful as DA; see Arnsten and Li, 2005, and Wang et al., 2007, for reviews). Depletion of catecholamines from the lateral PFC in marmosets also impairs attentional set formation (Roberts et al., 1994; Robbins and Roberts, 2007) but not performance on a self-ordering task (Collins et al., 1998).

The cellular basis for DA's effects in PFC has begun to be examined in rhesus monkeys. Dopamine has differentiated effects on dlPFC neuronal physiology in monkeys performing a spatial working memory task: D1/5R, but not D2/3R, stimulation influences Delay cell firing, whereas D2/3R, but not D1/5R, influences Response cell firing (Wang et al., 2004). This contrasts with rodent medial PFC, where certain physiologic studies find layer V neurons responding to both D1/5R and D2/3R manipulations (Parfitt et al., 1990; Zheng et al., 1999; Trantham-Davidson et al., 2004), although in situ hybridization studies have yet to definitively document coexpression within a single rodent PFC neuron (Santana et al., 2009). It is not known if this is a species difference or a regional difference (medial PFC versus dlPFC), because DA effects on medial PFC have yet to be studied in primates. The following describes DA D1/5R and D2/3R influences on the primate dlPFC in relationship to both working memory and associative learning tasks.

A. D1/D5 Receptors Have an Inverted U Influence on Working Memory and Delay Cell Firing

Autoradiographic studies of D1/5R binding in primate dlPFC show a bilaminar distribution, with high levels of binding both in superficial layers I–IIIa and in deep layers V and VI (Lidow et al., 1991). Methods that can distinguish D1R from D5R show that there are higher levels of D1R than D5R in primate dlPFC (Lidow et al., 1997). Immunoelectron microscopy has revealed the complementary distribution of D1R and D5R in the primate dlPFC neuropil (Arnsten et al., 2009). D1R are typically located perisynaptically in spines of pyramidal neurons (Smiley et al., 1994; Bergson et al., 1995) where they are occasionally captured within the PSD of glutamate-like synapses (Fig. 3A), and are also found in glutamate-like axon terminals (Paspalas and Goldman-Rakic, 2005) and the dendrites of PV-containing GABA interneurons (Glausier et al., 2009). In contrast, D5R have been found mostly in dendrites of pyramidal neurons (Paspalas and Goldman-Rakic, 2004) and calretinin-containing interneurons (Glausier et al., 2009) and more rarely in spines and axon terminals, including some that coexpress D1R (Bordelon-Glausier et al., 2008). D5R in the proximal portion of pyramidal dendrites associate with internal calcium stores and inositol trisphosphate receptors (Paspalas and Goldman-Rakic, 2004), suggesting that DA volume transmission may influence internal calcium release and thus alter neuronal excitability. The finding of D5R in calretinin-containing interneurons, a class of interneurons that often inhibit other interneurons, suggests that D5R may also increase the excitability of pyramidal cells through an indirect mechanism (Glausier et al., 2009).

The earliest studies of D1/5R actions in primate dlPFC revealed the important beneficial effects of DA D1/5R stimulation, whereby D1/5R blockade (by SCH23390 [7-chloro-3-methyl-1-phenyl-1,2,4,5-tetrahydro-3-benzazepin-8-ol] or SCH39166 [(6*aS-trans*)-11-chloro-6,6*a*,7,8,9,13*b*-hexahydro-7-methyl-5*H*-benzo[*d*]naphth [2,1-*b*]azepin-12-ol]) within the dlPFC markedly impaired spatial working memory abilities (Sawaguchi and Goldman-Rakic, 1994; Sawaguchi, 1998). Consistent with these findings, low systemic doses of the very first full D1/5R agonist, dihydrexidine, improved working memory performance in monkeys (Arnsten et al., 1994). However, it was soon discovered that high doses of D1/5R agonists, or very high levels of DA release in PFC, as occurs during stress exposure, could be as detrimental to cognitive function as DA depletion, and the detrimental effects of stress involved excessive stimulation of D1/5R (Arnsten and Goldman-Rakic, 1990, 1998; Murphy et al., 1996). The administration of D1/5R-selective agonists (SKF38393 [1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol], SKF81297 [(±)-6-chloro- 2,3,4,5-tetrahydro-1-phenyl-1*H*-3-benzazepine], A77636 [1*R-cis*-1-(aminomethyl)-3,4-dihydro-3-tricyclo[3.3.1.13,7] dec-1-yl-[1*H*]-2- benzopyran-5,6-diol]) revealed an inverted U-shaped dose response, where either high-dose D1/5R antagonist or D1/5R agonist treatment impaired performance after systemic or intra-PFC infusions, whereas low doses of agonist improved performance, especially in monkeys with DA depletion (Arnsten et al., 1994;

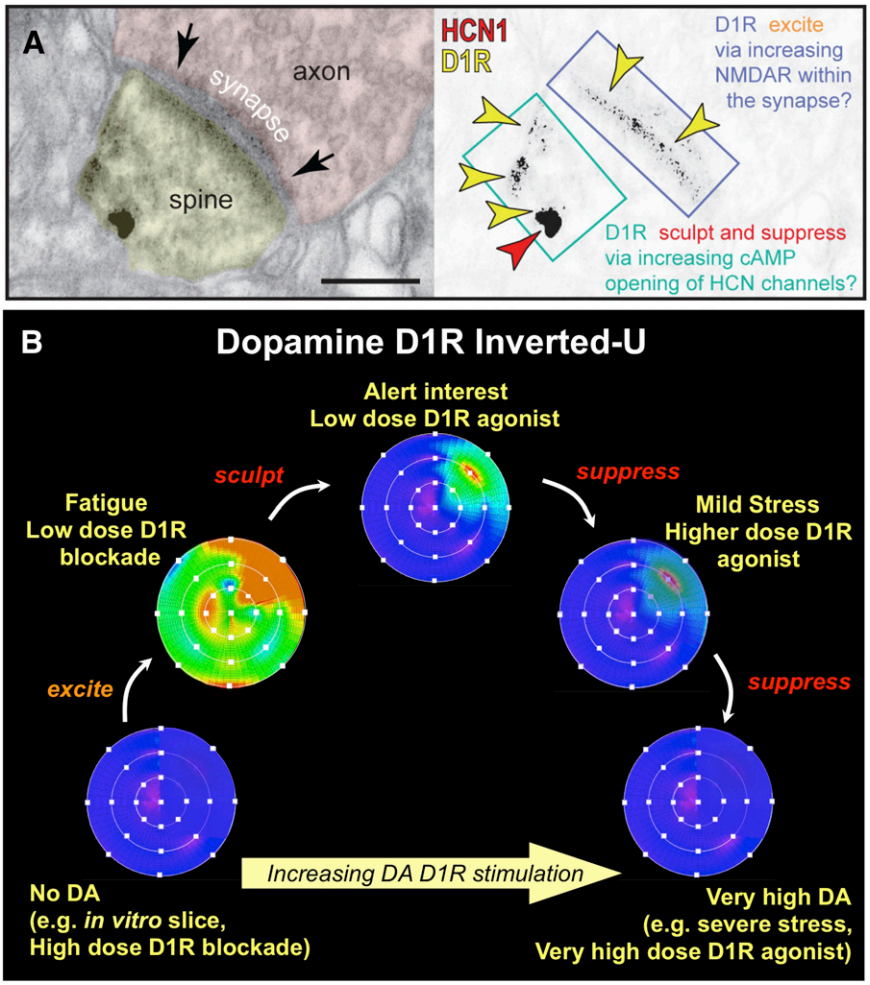

Fig. 3. DA D1R powerfully influence Delay cell firing in dlPFC. (A) D1R and HCN channels colocalize in spines in deep layer III of the monkey dlPFC. This paired image was edited to facilitate visualization of the immunoperoxidase label for D1R. Yellow arrowheads point to D1R on the extrasynaptic and perisynaptic spine membrane and within the synapse per se (between arrows). Red arrowhead points to HCN1 channel subunits visualized with immunogold. Scale bar, 100 nm. (B) A schematic illustration of the DA D1R inverted U influence on the "memory fields" of dlPFC Delay cells. Under optimal arousal conditions, Delay cells generate persistent representations of visual space, displaying high rates of firing (orange-red) to the memory of one spatial location and low rates of firing (blue) to the memory of all other spatial locations. Low levels of D1R stimulation appear to be excitatory, e.g., phosphorylating NMDAR to increase their trafficking into the synapse. This can produce noisy firing for all directions, as represented by the generalized green-orange coloring of the memory field. With optimal levels of D1R stimulation, there are additional sculpting actions, gating out "noise." This may involve opening of HCN channels, enhancement of lateral inhibition, and possibly selective reductions in glutamate release. At still higher levels of D1R stimulation as occurs during stress, neuronal firing is generally suppressed, and the neuron is unable to generate persistent representations of visual space.

Cai and Arnsten, 1997; Zahrt et al., 1997; Gamo et al., 2015). Later studies found parallel, inverted U-shaped influences on dlPFC neuronal physiology (Williams and Goldman-Rakic, 1995; Vijayraghavan et al., 2007; Arnsten et al., 2009), as described in detail below.

There are still no Food and Drug Administration–approved D1/5R selective compounds that can be used to conduct parallel studies in humans. However, research using nonselective compounds (Gibbs and D'Esposito, 2006; Cools and D'Esposito, 2011) suggests an inverted U-shaped dose response in humans as well. A similar dose response has been seen in humans in regard to catechol-*O*-methyltransferase genotype, an enzyme that catabolizes catecholamines and is weakened by a methionine-valine substitution (Bellgrove et al., 2005; Bertolino et al., 2006; Williams-Gray et al., 2007; Jacobs and D'Esposito, 2011). As described above, weaker enzymatic activity can be helpful to cognition under basal conditions, but worsens working memory abilities under conditions of stress exposure, consistent with the inverted U-shaped dose response (Qin et al., 2012).

2A D1/5R inverted U-shaped dose response also has been seen at the cellular level in monkeys, where the precisely patterned and timed firing of Delay cells is enhanced by a moderate level of D1/5R stimulation, whereas either inadequate or excessive D1/5R stimulation erodes the neural representation of visual space (Williams and Goldman-Rakic, 1995; Vijayraghavan et al., 2007; Arnsten et al., 2009). As schematically illustrated in Fig. 3B, 1) low levels of D1/5R stimulation have an excitatory effect, and blocking these actions with high doses of D1/5R antagonist markedly reduces all neuronal firing, 2) moderate levels of D1/5R stimulation sculpt away noise but leave firing to the

neuron's preferred direction intact, thus enhancing representations of visual space, whereas 3) high levels of D1/5R stimulation suppress all neuronal firing. The ultrastructural locations of D1R and D5R in dlPFC may relate to the D1/5R inverted U-shaped physiologic dose-response as covered in the next paragraphs.

Low levels of D1/5R stimulation may enhance the excitability of pyramidal cells through D1R within the PSD (Fig. 3A), increasing NMDAR actions. This hypothesis is based on in vitro recordings from rodent PFC slices, where D1/5R stimulation increases NMDAR-induced EPSCs (Seamans et al., 2001; Gonzalez-Islas and Hablitz, 2003) and increases the insertion of NMDAR into the synapse (Li et al., 2010). Similar actions in primate may enhance firing and be blocked by high doses of D1/5R antagonists (Williams and Goldman-Rakic, 1995). These excitatory actions have yet to be seen with low doses of D1/5R agonist in monkey dlPFC. This may be because the excitatory effects are already saturated in the awake, behaving monkey, and/or because all currently available D1/5R agonists have very high affinity for the D1/5R that may produce excessive stimulation even at very low doses. Thus, the development of low-affinity D1/5R agonists that better mimic endogenous DA will be needed to test this hypothesis more directly. It is also possible that the general excitatory effects of D1/5R also involve D5R excitation of calretinin-containing interneurons, which, in turn, inhibit other interneurons and disinhibit pyramidal cells, especially as DA has higher affinity for D5R than D1R (Glausier et al., 2009). Thus, these actions may be preferentially engaged under conditions of low-level DA concentrations.

Moderate levels of D1/5R stimulation may sculpt away "noise" through a variety of mutually interactive mechanisms. The reduction in firing to nonpreferred inputs may include 1) increased opening of HCN and KCNQ channels on spines, 2) a reduction in glutamate release from axon terminals as has been seen in ferret (Gao et al., 2001), and 3) facilitation of the lateral inhibition provided by GABAergic interneurons. D1R in spines are typically found next to glutamate-like synapses, where they are colocalized with HCN channels (Paspalas et al., 2013; Gamo et al., 2015) (Fig. 3A). Stimulation of D1/5R increases cAMP signaling, which in turn increases the open state of HCN channels, gating out nearby network connections (Arnsten et al., 2012; Gamo et al., 2015). If D1R are preferentially localized on the spines receiving nonpreferred network inputs, they may gate out "noisy inputs" and narrow the spatial tuning of Delay cell firing. Preliminary data indicate that D1/5R-cAMP-protein kinase A–mediated increases in KCNQ channel opening contribute as well (data not shown). Enhanced spatial tuning may also arise from increased lateral inhibition from GABA interneurons: in vitro recordings from layer II/III of monkey dlPFC showed that D1/5R stimulation increases the excitability of fast-spiking, nonadapting interneurons (Kroner et al., 2007), consistent with an earlier finding that DA-like fibers target PV-containing interneurons in deep layer III (Sesack et al., 1998). We have seen high doses of D1/5R agonist decreasing rather than increasing the firing of fast-spiking neurons in vivo (Arnsten et al., 2009), but this may be due to the overwhelming suppressive effects of high levels of D1/5R stimulation of pyramidal cells removing the excitatory drive on interneurons. In vitro recordings from monkey dlPFC suggest that D1/5R may also decrease "noise" for fast-spiking cells in dlPFC (Gonzalez-Burgos et al., 2005), suggesting that optimal doses of D1/5R stimulation may refine the firing patterns of the entire microcircuit.

High levels of D1/5R stimulation suppress all neuronal firing. This may simply be an amplification of the sculpting actions leading to a more generalized suppression of firing or may involve qualitatively different actions, e.g., higher levels of DA release reaching more distant spines that receive preferred network inputs and were unaffected by moderate levels of DA release. High levels of DA release during stress exposure may be able to spread more widely due to cortisol blocking the extraneuronal catecholamine transporters that normally would limit its diffusion (Grundemann et al., 1998). The generalized suppressive effects of high levels of D1/5R stimulation involve D1/5R-cAMP opening of HCN channels (Fig. 3A; Gamo et al., 2015). These effects are blocked, but not readily reversed, by D1/5R antagonists, suggesting that downstream phosphorylation of ion channels may lead to a sustained increase in their open state. These actions likely contribute to stress-induced working memory impairments, because working memory deficits in stressed rats can be prevented by blocking HCN channels in PFC (Gamo et al., 2015).

B. D1/D5 Receptors Have Parallel Actions on Associative Learning by the Ventrolateral Prefrontal Cortex and Attentional Regulation by the Frontal Eye Fields

Although the vast majority of research on D1/5R actions in primates has used working memory paradigms, there is one study showing parallel findings with an associative learning task (Puig and Miller, 2012). This task used visual features rather than visual space and was performed in the ventrolateral PFC (vlPFC) region that receives visual feature information from the inferior temporal cortex (Goldman-Rakic, 1987). Infusion of a D1/5R antagonist into this region of vlPFC impaired the learning of new associations but did not alter the memory of previously learned associations (Puig and Miller, 2012). These behavioral changes were accompanied by a corresponding decrease in neural selectivity for novel associations (Puig and Miller, 2012), consistent with the increased "noise" seen after D1/5R antagonist administration in working memory paradigms (Fig. 3B). Although this is only one study, it suggests that there

may be parallel D1/5R actions in dlPFC and vlPFC in the cognitive manipulation of spatial and feature information.

Finally, D1/5R antagonist infusion into the frontal eye fields (FEF) has been shown to alter the attentional regulation of the FEF on visual processing in posterior visual cortices. Microstimulation of the FEF can enhance processing of visual stimuli in a corresponding area in visual cortical region V4 (Moore and Armstrong, 2003). Similar effects were seen when a D1/5R antagonist was infused into the FEF (Noudoost and Moore, 2011), perhaps due to increasing the firing of FEF neurons. Similar effects were seen with a saccadic choice task, where blocking D1/5R in the FEF increased the tendency to choose targets in the response field of the affected site (Soltani et al., 2013). Computational analysis suggested that this effect was due to increasing the strength of inputs to the FEF and on recurrent connectivity, similar to the increased Delay cell firing after low dose D1/5R blockade in the dlPFC. Thus, at least some aspects of D1/5R actions appear to translate across nearly lateral PFC regions.

C. D2/D3 Receptor Stimulation Increases Response Cell Firing during Working Memory

There has been less research on the D2 receptor family in the primate PFC. There was a flurry of research on the D4R when clozapine was discovered to have high affinity for this receptor (Van Tol et al., 1991), but the lack of clinical effects with selective D4R antagonists diminished interest in this field (please note that NE has very high affinity for the D4R, so it should really be called a "catecholamine receptor"). There are relatively low levels of D2R and especially of DR3 in the primate dlPFC, where their mRNA is concentrated in layer V neurons (Goldman-Rakic et al., 1990; Lidow et al., 1998). The binding of the D2/3R antagonist raclopride is also highest in layer V (Lidow et al., 1991). The ultrastructural localization of D3R has yet to been examined, but immunoelectron microscopy has shown that D2R are primarily localized in the higher order dendrites of pyramidal cells (Fig. 4A). D2R are also found in glutamate-like axons that may include axons projecting to the striatum (Paspalas et al., 2006). Thus, some DA actions at D2R in striatum involve modulation of dlPFC influence on striatal function.

There are few studies of the behavioral effects of D2/3R manipulations in monkey PFC. The same study that showed that D1/5R antagonist infusions into dlPFC impaired spatial working memory performance showed no effects with infusions of a D2/3R antagonist (sulpiride or raclopride) (Sawaguchi and Goldman-Rakic, 1994). These monkeys were performing near perfectly under control conditions, so ceiling effects could have precluded possible *improvements* with D2/3R blockade. There have been no studies of D2/3R agonist infusions into monkey PFC, so we do not know how stimulation of these receptors would alter working memory performance. Systemic administration of a D2/3R agonist has a triphasic effect on working memory performance, with low doses impairing performance likely through presynaptic D2R drug actions (i.e., the effects were not evident in reserpine-treated animals), moderate doses improving performance through postsynaptic actions (i.e., the effects were enhanced in reserpine-treated animals) and the highest doses impairing performance and inducing prominent side effects, including dyskinesias, hypotension, and occasional hallucinatory-like behaviors (Arnsten et al., 1995). As drug was administered systemically, many of these pharmacological actions may have occurred outside of PFC, e.g., in caudate.

The physiologic effects of D2/3R stimulation in dlPFC are especially interesting. Consistent with their concentration in layer V pyramidal cells, D2/3R stimulation or blockade selectively alters the firing of Response cells in the dlPFC of monkeys performing a spatial working memory task, whereas changes in D1/5R stimulation

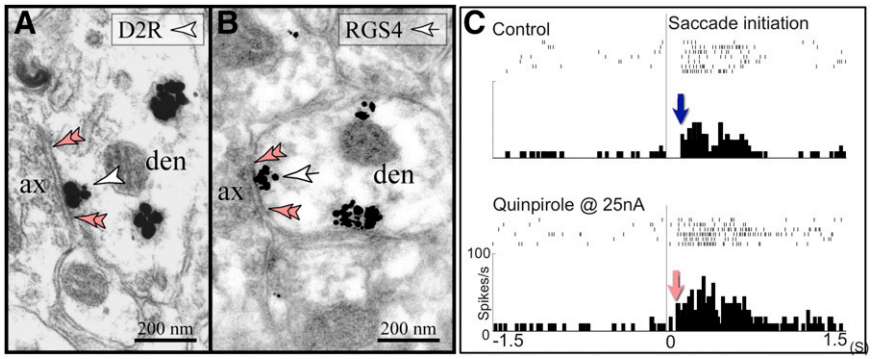

Fig. 4. DA D2R excite Response cells in dlPFC. (A) D2R localization in a high-order pyramidal cell dendrite in monkey dlPFC. The receptor (arrowhead) is captured at the synaptic membrane (double arrowheads). (B) RGS4 is typically found in high-order pyramidal dendrites in association with synapses (arrow) to regulate G receptor signaling within the synapse (double arrowheads). Note how this pattern of localization corresponds to that shown for the D2R in (A). Further research is needed to establish whether RGS4 inhibits D2R signaling in primate dlPFC. (C) Stimulation of D2R in dlPFC by iontophoresis of quinpirole increases the amplitude and speeds the firing of Response cells in monkeys performing a visuospatial working memory task. In postsaccadic Response cells such as this one, neuronal firing likely represents feedback regarding the motor response ("corollary discharge"). Alterations in the timing and magnitude of this feedback may have important yet unexplored ramifications for cognitive function.

have no effect on Response cell firing (Wang et al., 2004). As shown in Fig. 2, there are two general types of Response cells, those that fire immediately before the motor response and are likely conveying signals to the motor system, and those that fire during or immediately after the motor response and are likely conveying feedback (i.e., efference copy or corollary discharge) regarding the motor event. D2/3R stimulation influences both types of Response cells, whereby D2/3R stimulation speeds and increases response-related firing (e.g., Fig. 4C), whereas blockade reduces and slows the response (Wang et al., 2004; Arnsten et al., 2009). It is surprising that infusions of D2/3R antagonists had no effect on oculomotor delayed response performance given these large effects on Response cell firing. It may be that a more challenging task, or one that required novel motor responses, may have shown an effect of D2/3R blockade.

Corollary discharge has been studied in the eye movement system, where feedback regarding the movement returns to the PFC via the mediodorsal thalamus (Sommer and Wurtz, 2008). Mediodorsal thalamic terminals target layers IV and deep III in the monkey dlPFC, where they target dendrites as well as spines (Negyessy and Goldman-Rakic, 2005). In this regard it is of interest that D2R are also concentrated on dendrites (Paspalas et al., 2006), where they may modulate the feedback inputs from thalamus.

The intracellular actions governing D2/3R actions on Response cell firing have not been studied, but it is curious that RGS4 (regulator of G protein signaling 4) has a pattern of localization on high-order dendrites similar to D2R (Fig. 4B). RGS4 inhibits $G_{i/o}$ or G_q signaling, both of which have been implicated with D2/3R actions. Spatial interactions of D2R with RGS4 have not been studied, but would be especially interesting if confirmed given the great reduction in RGS4 expression in the dlPFC of patients with schizophrenia (Mirnics et al., 2001; Erdely et al., 2006) and the genetic links to this molecule in schizophrenia associated with weaker PFC function (Morris et al., 2004; Buckholtz et al., 2007). Loss of RGS4 could disinhibit D2R actions and alter the timing and magnitude of Response cell firing, including the disruption of feedback on neural actions, which, as described below, may contribute to the positive symptoms of schizophrenia.

The effects of D2/3R stimulation on the postsaccadic Response feedback cells are particularly intriguing, because alterations in the timing and magnitude of neural feedback could have important consequences to cognitive performance. In particular, if the feedback represents the corollary discharge (efference copy) that a specific response has occurred, the distortion of this information could compromise working memory abilities. For example, ineffective feedback could interfere with the clearance and updating of information held in working memory and lead to perseveration and/or impairments in error correction. Studies of patients with schizophrenia suggest that impaired corollary discharge between the PFC (Broca's area) and temporal cortex (Wernicke's area) contributes to auditory hallucinations (Ford et al., 2002). Impaired feedback and prediction error may also contribute to the formation of delusions (Corlett et al., 2004). D2/3R antagonists are particularly effective in reducing hallucinations and delusions (Seeman, 1987), whereas high-dose amphetamine sensitization can induce psychotic behaviors in human subjects (Lieberman et al., 1990). Although many of these actions likely occur in striatum (Howes et al., 2009), it is intriguing to speculate that some of their beneficial actions of antipsychotics may involve correcting neuronal feedback (corollary discharge) in the PFC by normalizing D2R signaling. Conversely, high levels of D2/3R stimulation may induce hallucinatory-like behaviors by distorting neural feedback in PFC, perhaps underlying the hallucinatory-like behaviors induced by high-dose D2/3R agonist administration (Arnsten et al., 1995). This will be an important arena for future research.

D. D3 Receptors May Impair Prefrontal Cortex Function by Decreasing Acetylcholine Release in Prefrontal Cortex

A new pharmacology is emerging with the creation of D3R-preferring agents, driven by cognitive-enhancing effects with D3R antagonists (Gross et al., 2013). D3R antagonists, e.g., S33138, increase catecholamine and acetylcholine efflux in rodent PFC (Lacroix et al., 2003; Millan et al., 2008). S33138 improved working memory and attentional set-shifting performance when given systemically to monkeys with cognitive deficits arising from low-dose MPTP, which causes mild DA depletion (Millan et al., 2010). Thus, D3R antagonists are being considered as therapeutics for both attention-deficit hyperactivity disorder (ADHD) and schizophrenia (Barth et al., 2013; Gross et al., 2013). Dissection of D2R versus D3R actions within the primate PFC will be an important challenge for future studies and may be aided by the development of D3R negative allosteric modulators.

E. D2/D3 Receptor Actions on Associative Learning by the Ventrolateral Prefrontal Cortex and Attentional Regulation by the Frontal Eye Fields

Similar to studies of D1/5R effects on associative learning, a recent study has shown that blockade of D2/3R in the vlPFC impaired the learning of new associations while leaving familiar associations intact (Puig and Miller, 2014). This study found that D2/3R blockade also impaired behavioral flexibility and reduced motivation (Puig and Miller, 2014). At the cellular level, D2/3R blockade reduced firing to the neuron's preferred saccadic direction, eroding direction selectivity (Puig and Miller, 2014). As this was an

associative learning task, the motor response became evident during the cue epoch, and so it is hard to compare these findings directly to dlPFC neurons during a working memory task. However, a reduction in response direction selectivity after D2/3R blockade was found with both studies (Wang et al., 2004; Puig and Miller, 2014).

Perseverative responses were also observed when D2/3R were stimulated in the FEF of monkeys performing a saccadic choice task (Soltani et al., 2013). Thus, either stimulation or blockade of D2R may interfere with flexible responding and lead to perseveration. Network simulation suggested that this effect was due to changes in the excitability of FEF output neurons (Soltani et al., 2013), similar to what is seen with Response cells in the nearby dlPFC.

VI. Dopamine Effects on the Orbital Prefrontal Cortex

The findings discussed so far have all been in regard to the lateral PFC in primates. However, there is a rich DA innervation of medial and orbital PFC, and it is important to learn how DA alters the functioning of these PFC circuits. As described above, it is hypothesized that the orbital and medial PFC regions may receive DA innervation from DA Value neurons rather than Salience neurons, although this has yet to be proven. Studies in marmoset monkeys have begun to explore the role of DA in the orbital PFC. Depletion of catecholamines from the orbital PFC had no effect on performance of a serial reward reversal task (Clarke et al., 2007); however, it did alter sensitivity to reinforcement (Walker et al., 2009). Marmoset monkeys with DA depletion were insensitive to conditioned reinforcers and showed persistent responding in the absence of reward during the extinction phase of the task. These deficits are consistent with impaired associative processing of reward. It is possible that the loss of a DA Value signal in the orbital PFC decreased the ability of these neurons to generate representations of reward needed to guide reinforcement-directed behavior. A more recent study has shown that depletion of DA in the orbital PFC also leads to increased tonic DA levels in caudate, which may contribute as well (Clarke et al., 2014). Given the importance of DA to reward signaling, the importance of orbital and medial PFC circuits in guiding behavior based on reward, the elaboration of these PFC areas in primates, and their relationship to mood disorders, this seems a particularly rich arena for future exploration.

VII. Relevance to Human Disorders

Changes in DA signaling in the PFC are relevant to a host of clinical disorders that involve PFC cognitive dysfunction, including addiction, Parkinson's disease, ADHD, and schizophrenia. Although a comprehensive discussion of these disorders is beyond the scope of the current review, a few comments are warranted.

Although the motor deficits arising from striatal DA depletion are the most pronounced symptoms of Parkinson's disease, there is also loss of DA in the PFC, and deficits in PFC cognition are common albeit complex (Owen et al., 1992; Narayanan et al., 2013; Robbins and Cools, 2014). Treatment of such cognitive deficits can be challenging, because the doses of DA medications that normalize striatal function are often too high for optimal PFC function (Gotham et al., 1988). In extreme cases, medication can cause cognitive deficits that are more problematic than the motor impairment they are treating, e.g., impulse disorders such as compulsive gambling or shopping addictions (Moore et al., 2014). These extreme behavioral changes may arise from a combined loss of PFC guidance and increased striatal habitual drive similar to what is seen in drug addiction (Everitt and Robbins, 2005; Olausson et al., 2007) and may be especially related to increased stimulation of D3R (Moore et al., 2014). A recent study suggests that treatment with the NE transporter inhibitor atomoxetine may be helpful in strengthening PFC regulatory control in patients with Parkinson's disease (Kehagia et al., 2014). Thus, understanding the neurochemical needs of the PFC may provide alternatives for superior treatment.

ADHD is often referred to as a DA disorder, although for most patients this is likely not the case. Genetic studies indicate that ADHD is highly heritable but is a polygenetic disorder with thousands of genes likely implicated, all with small effect size (Elia et al., 2012; Akutagava-Martins et al., 2013). Candidate gene studies have shown a small linkage with the DA-related genes DR5 and the DA transporter DAT1, as well as the catecholamine-related genes DRD4 and catechol-*O*-methyltransferase and the NE-related genes DBH and ADRA2A (Caylak, 2012). However, it is likely that most genes implicated in ADHD have other roles, e.g., involvement in PFC development and function independent of DA. The focus on DA and ADHD has largely been based on the success of stimulant medications such as methylphenidate in treating this disorder. However, it is important to note that low therapeutic doses of methylphenidate actually have a much greater effect on NE than DA release in the PFC (Berridge et al., 2006; Berridge and Devilbiss, 2011). These recent data should provide a more refined view of ADHD.

Schizophrenia has long been described as a DA disorder based on the success of D2R antagonists as antipsychotics. The "dopamine hypothesis" of schizophrenia comes in and out of fashion as more information becomes available. Although it is widely accepted that there is excessive DA release in the caudate of patients with schizophrenia (Laruelle et al., 1996; Kegeles et al.,

2010), the integrity of the DA innervation of the PFC has been harder to evaluate given the difficulty in imaging this very delicate system. Postmortem studies show that DA fibers are reduced in the dlPFC of patients with schizophrenia, but only from layer VI and not from more superficial layers (Akil et al., 1999). PET imaging findings also show evidence that D1/5R are increased in the dlPFC early in the illness in unmedicated patients (Abi-Dargham et al., 2002, 2012), possibly as compensation for reduced DA release (Slifstein et al., 2015). Dihydrexidine (now referred to as DAR-0100A) is currently being tested in schizotypal patients who have cognitive deficits that are qualitatively similar to patients with schizophrenia. DAR-0100A improved performance of a Paced Auditory Serial Addition Task, but had mixed effects on an N-back test of working memory, in part due to the drug-impairing performance on the 0-back, control condition (Rosell et al., 2015). The question of whether there is too much or too little D1R stimulation in the PFC may be moot, because rodent studies show that DA depletion actually leads to an increase in stress-induced DA release in the PFC (Deutch et al., 1990). Thus, a patient may have excessive DA stimulation of D1R in PFC during stress exposure even if there are lower levels of basal DA.

VIII. Future Challenges

There is a great need for further research on DA's effects in primates, because there has been relatively little research in this field and so much remains to be understood. The DA innervation encompasses most of the cerebral mantle, and yet studies so far have been confined to the PFC. Thus, the entire posterior cortex remains unexplored. In particular, it will be important to study DA actions in the motor cortices, because there are intensive DA projections to the primary and motor association cortices in primates (but not in rodents). It is possible that DA D1/5R stimulation in the motor cortex plays a role similar to that in dlPFC, sculpting and refining representations to allow fine movements, e.g., the ability to move the index finger separate from a thumb, a function not developed in rodents.

Understanding DA's actions at specific receptor subtypes in the PFC—D1R, D2R, D3R, D4R, and D5R—will depend on the creation of selective pharmacological agents, because genetic approaches are not currently feasible in monkeys. This venture also may have clinical benefits, e.g., a selective D3R antagonist or D1R agonist may have cognitive-enhancing properties. Because DA has relatively low affinity for D1R (Sunahara et al., 1991), there is a particular need for a low-affinity/highly selectivity D1R agonist that may better mimic DA's endogenous, beneficial actions. A lower affinity agonist may also broaden the inverted U-shaped dose response and have a greater dose range for therapeutic effects. A positive allosteric modulator of the D1R may have the same effect. The effective development of cognitive enhancers for humans requires the understanding that the goal is to enhance a highly specific pattern of neuronal firing, i.e., the neural representations of information, and that this is usually accomplished by very low doses of drug. In particular, a higher dose of drug may have generalized effects that obscure the pattern of information, i.e., be too high a dose for cognitive enhancement, although it has no obvious side effects. This more sophisticated view of drug development is needed for success in the cognitive arena.

Finally, there should be further research on the roles of D2/3Rs in modulating the firing of neurons that are providing essential feedback within PFC circuits, because altered firing of these neurons may contribute to symptoms such as hallucinations and delusions. Although the neural basis of these symptoms has previously been thought to be beyond scientific inquiry, we begin to see how this may be possible as we uncover the complex roles of primate cortical circuits.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Arnsten, Wang, Paspalas.

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