

## Review

# Catecholamine influences on prefrontal cortical function: Relevance to treatment of attention deficit/hyperactivity disorder and related disorders<sup>☆</sup>

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## ABSTRACT

The primary symptoms of attention deficit/hyperactivity disorder (ADHD) include poor impulse control and impaired regulation of attention. Research has shown that the prefrontal cortex (PFC) is essential for the “top-down” regulation of attention, behavior, and emotion, and that this brain region is underactive in many patients with ADHD. The PFC is known to be especially sensitive to its neurochemical environment; relatively small changes in the levels of norepinephrine and dopamine can produce significant changes in its function. Therefore, alterations in the pathways mediating catecholamine transmission can impair PFC function, while medications that optimize catecholamine actions can improve PFC regulation of attention, behavior, and emotion. This article reviews studies in animals showing that norepinephrine and dopamine enhance PFC function through actions at postsynaptic  $\alpha_{2A}$ -adrenoceptors and dopamine D1-receptors, respectively. Stimulant medications and atomoxetine appear to enhance PFC function through increasing endogenous adrenergic and dopaminergic stimulation of  $\alpha_{2A}$ -receptors and D1-receptors. In contrast, guanfacine mimics the enhancing effects of norepinephrine at postsynaptic  $\alpha_{2A}$ -receptors in the PFC, strengthening network connectivity. Stronger PFC regulation of attention, behavior, and emotion likely contributes to the therapeutic effects of these medications for the treatment of ADHD.

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Basic studies of catecholamine actions in the prefrontal cortex (PFC) have helped us understand how genetic insults in catechol-

amine signaling pathways may lead to symptoms of attention deficit/hyperactivity disorder (ADHD), and how current medications may alleviate symptoms of weak attention and impulse control in ADHD and related disorders. The following provides a brief review of PFC functions and their modulation by catecholamine signaling pathways.

## 1. The prefrontal cortex and attention deficit/hyperactivity disorder

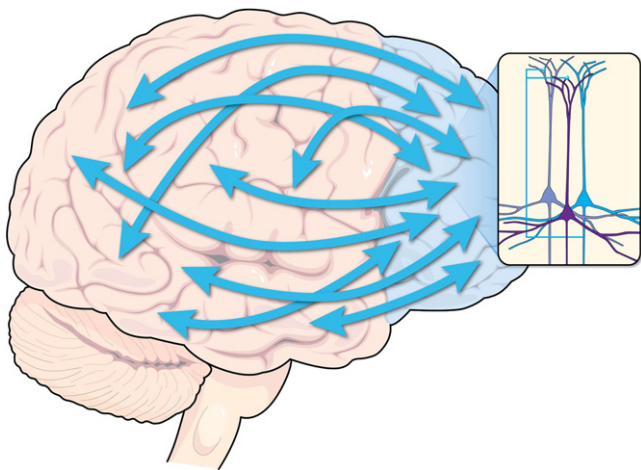
The PFC is the most recently evolved region of the brain, subserving our highest order cognitive abilities. The cellular networks of the PFC are able to maintain representations of goals and rules and

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use remembered information to guide attention, actions, and emotion (Goldman-Rakic, 1995). Current evidence supports the role of the PFC in the regulation of top-down attention, i.e. attention based on relevance (Buschman and Miller, 2007). Extensive projections to the sensory association cortices allow the PFC to suppress processing of irrelevant distractions and enhance processing of meaningful stimuli that may not be inherently captivating (e.g. homework) (Barbas et al., 2005; Yamaguchi and Knight, 1990) (Fig. 1). Depending on task demands, the PFC facilitates sustained attention on a single task (Wilkins et al., 1987) or manages rapid shifts in attention to accomplish multiple sequential tasks (Robbins, 2007). In addition to regulating attention, the PFC also regulates behavior and emotions. The right inferior PFC is especially important for reducing impulsive behavior and inhibiting inappropriate actions (Aron et al., 2004), while the orbital and ventromedial PFC is essential for the regulation of emotion, such as the inhibition of aggressive impulses (Best et al., 2002; Izquierdo et al., 2005; Price et al., 1996). These PFC regions act in concert to carry out the executive functions of planning and organizing appropriate actions, thoughts, and emotions.

Several imaging studies have shown that the dorsolateral PFC has a smaller volume and reduced activity in patients with ADHD compared with controls (Castellanos et al., 2002, 2008; Mostofsky et al., 2002; Rubia et al., 1999; Seidman et al., 2005). Decreased PFC activity is particularly evident in the performance of tasks that require sustained attention or inhibition of inappropriate movement (Rubia et al., 2005). In patients with ADHD, the white matter tracts that link the PFC to other brain regions also appear less well organized (Casey et al., 2007; Makris et al., 2008), and functional connectivity is reduced (Castellanos et al., 2008). Thus, PFC regulation of posterior cortical and subcortical structures is likely to be less effective in patients with ADHD, leading to decreased top-down regulation of attention, behavior, and emotion. In addition, the volumes of other brain regions, such as the caudate and cerebellum, which have reciprocal connections with the PFC, have been reported to be smaller in children with ADHD than in control subjects in some studies (Castellanos et al., 2002). The PFC is slow to mature, reaching adult dimensions in the early 20s (Giedd, 2004). There is evidence of delayed maturation of the PFC in children with ADHD (Shaw et al., 2007). This delayed maturation may vary in degree, which may explain why ADHD continues into adulthood for some individuals, yet may resolve in others. Recent studies have found slower maturation of PFC in typically developing adolescents with weaker impulse control, indicating that this is a dimensional characteristic related to the integrity of PFC gray matter (Shaw et al., 2011).



**Fig. 1.** The PFC regulates attention, behavior, and emotion through extensive network connections with other brain regions. Networks of neurons within the PFC (inset) excite each other to maintain representations of goals and rules used to guide attention, behavior, and emotion.

The PFC regulates attention, behavior, and emotion through networks of pyramidal neurons that interconnect on dendritic spines (Fig. 1, inset). PFC networks are able to excite each other in the absence of external environmental stimulation, thus representing information such as goals for behavior, our “mental sketch pad” (Goldman-Rakic, 1995). However, recurrent PFC network activity is fragile, and extremely sensitive to the neurochemical environment. Thus, small changes in the arousal systems can markedly alter the connectivity of PFC networks (Arnsten et al., 2010). In particular, these PFC connections require that catecholamine concentrations be maintained at optimal levels (Arnsten, 2007).

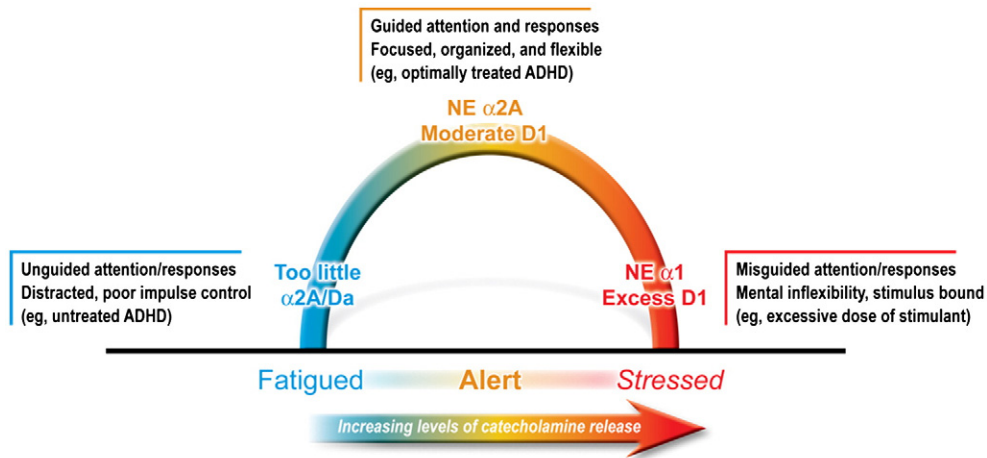
## 2. Catecholamine effects on PFC function

The release of the catecholamines norepinephrine (NE) and dopamine (DA) in the PFC is related to arousal state (Fig. 2). Low arousal conditions are associated with very low levels of NE cell firing (Aston-Jones et al., 2000; Foote et al., 1980). In contrast, under conditions of alert interest, there is moderate tonic firing, and increased phasic firing of NE and DA to relevant stimuli (Aston-Jones et al., 2000, 1994; Finlay et al., 1995; Foote et al., 1980; Schultz, 1998). Under stressful conditions, there are high levels of catecholamine release in PFC (Deutch and Roth, 1990; Finlay et al., 1995), which may arise from high, tonic firing of NE neurons (Aston-Jones et al., 2000, 1994), and DA neurons that respond to aversive events (Matsumoto and Hikosaka, 2009). Thus, the level and timing of catecholamine release in PFC can coordinate arousal state and PFC function.

The effects of NE and DA on arousal, mood, and behavior are mediated through interactions with an extensive range of receptors that demonstrate varying affinities for these catecholamines. DA acts at both the D1 (D1- and D5-receptors) and D2 (D2-, D3-, and D4-receptors) families of receptors. These receptors have distinct localizations in primate PFC. D2-receptors in the PFC are concentrated in layer V neurons where they also increase response-related firing (Wang et al., 2004). DA also acts at D4-receptors in the PFC, where it inhibits interneurons (Mrzljak et al., 1996; Wang et al., 2002). However, the most prominent dopaminergic actions in the PFC arise from actions at D1-receptors, which are found in both superficial and deep layers of the primate PFC (Lidow et al., 1991). D1-receptors have fundamental excitatory effects on PFC function, but also modify inputs to pyramidal cells (Vijayraghavan et al., 2007).

NE acts chiefly at  $\alpha_1$ -,  $\alpha_2$ -, and  $\beta$ -receptors; the  $\alpha_2$ -receptors are further subdivided as  $\alpha_{2A}$ ,  $\alpha_{2B}$ , and  $\alpha_{2C}$ . These subtypes are located presynaptically on noradrenergic neurons, dendrites, or axon terminals, and postsynaptically on neurons receiving noradrenergic input. Although presynaptic receptors are the most recognized, the majority of  $\alpha_2$ -receptors in the brain are postsynaptic (U'Prichard et al., 1979). Among noradrenergic receptors, NE has the highest affinity for  $\alpha_2$ -receptors, with lower affinity for  $\alpha_1$ - and  $\beta$ -receptors (Arnsten, 2000). Studies in animals indicate that NE engages predominantly  $\alpha_2$ -receptors in the PFC when the subject is alert and interested (Li and Mei, 1994), while actions at  $\alpha_1$ -receptors and possibly  $\beta$ -receptors are predominant under stressful conditions (Birnbbaum et al., 2004; Ramos et al., 2005). Among the  $\alpha_2$ -receptors, the  $\alpha_{2A}$  subtype is the most prevalent in the PFC and is found both presynaptically on noradrenergic terminals and postsynaptically on the dendritic spines of PFC pyramidal cells that receive network inputs (Aoki et al., 1998; Wang et al., 2007). Although previous research focused on presynaptic receptor actions, research has established that the beneficial effects of  $\alpha_2$ -agonists arise from stimulation of postsynaptic  $\alpha_{2A}$ -receptors in the PFC (Arnsten and Goldman-Rakic, 1985; Cai et al., 1993).

The effectiveness of PFC network connections relies on noradrenergic stimulation of  $\alpha_{2A}$ -receptors on the spines of PFC pyramidal cells (Wang et al., 2007). These  $\alpha_{2A}$ -receptors are localized on the dendritic spines near ion channels that control the impact of synaptic inputs on

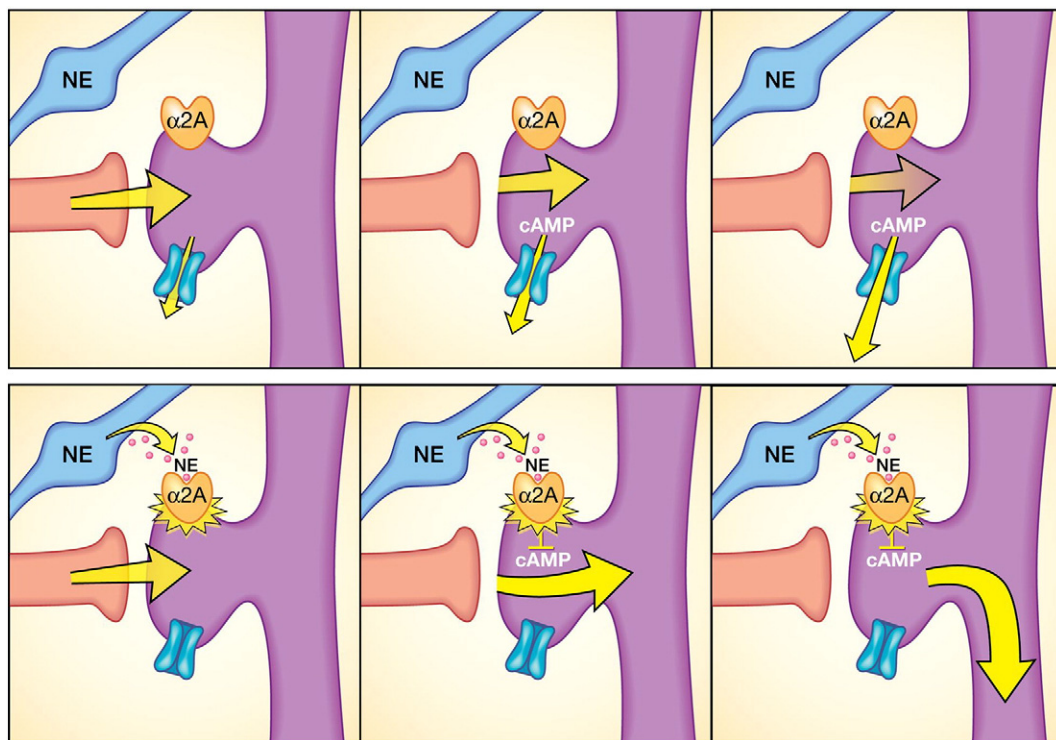


**Fig. 2.** The PFC is very sensitive to its neurochemical environment; both insufficient and excessive catecholamine release impair PFC function. The catecholamines norepinephrine (NE) and dopamine (DA) are released in the PFC according to arousal state: very little during fatigue (and boredom?), a moderate amount of phasic release to relevant stimuli during alert, nonstressed waking, and high tonic release under stressful conditions. Moderate levels of NE engage postsynaptic  $\alpha_{2A}$ -receptors to improve PFC function, while higher levels engage  $\alpha_1$ - and  $\beta$ -receptors, which impair PFC function. Thus, optimal regulation of PFC function depends on postsynaptic  $\alpha_{2A}$ - and moderate D1-receptor stimulation. Animal studies suggest that therapeutic doses of stimulants improve PFC function by increasing endogenous noradrenergic and dopaminergic stimulation of  $\alpha_{2A}$ - and D1-receptors, respectively. ADHD = attention deficit/hyperactivity disorder.

the spine (Wang et al., 2007). When these ion channels are open, nearby synaptic inputs are diverted and the incoming information escapes, weakening the synaptic connection (Fig. 3). Alternatively, noradrenergic stimulation of  $\alpha_{2A}$ -receptors initiates a cascade of chemical events that close these ion channels, strengthening the synaptic connection. The strengthened synaptic connections enable the PFC to regulate attention, behavior, and emotion more effectively. Blockade of  $\alpha_{2A}$ -receptors in the monkey PFC with local yohimbine infusions markedly impairs PFC regulation of attention and behavior,

inducing poor impulse control and locomotor hyperactivity (Li and Mei, 1994; Ma et al., 2005, 2003). In humans, lower activity of dopamine  $\beta$ -hydroxylase, the enzyme that synthesizes NE, is associated with poor sustained attention (Greene et al., 2009), poor executive function (Kieling et al., 2008), and impulsiveness (Hess et al., 2009), demonstrating that endogenous NE is important for proper PFC regulation.

In the PFC, DA plays a role complementary to that of NE, decreasing PFC neuronal activity in response to irrelevant stimuli (Vijayraghavan



**Fig. 3.** Stimulation of postsynaptic,  $\alpha_{2A}$ -receptors on PFC neurons by norepinephrine (NE) or guanfacine strengthens the functional connections between prefrontal cortex (PFC) neurons. Many  $\alpha_{2A}$ -receptors are found on the dendritic spines where PFC neurons form network connections. Top row: When there is no  $\alpha_{2A}$ -receptor stimulation, cyclic adenosine monophosphate (cAMP) levels are high, potassium channels open, weakening nearby synaptic inputs. As a result, PFC network firing decreases, and there is weakened capability to regulate attention, behavior, or emotion. Bottom row: When  $\alpha_{2A}$ -receptors are stimulated by NE or by guanfacine, they close nearby potassium channels, increasing the efficacy of network inputs, and facilitating PFC function.

et al., 2007). Dopaminergic stimulation of D1-receptors opens ion channels on a set of dendritic spines that receive inputs irrelevant to focused working memory and attention. Opening channels on these spines weakens irrelevant network connections, reducing noisy input to the neuron and enhancing the efficiency of PFC function. However, diminishing these connections excessively may be harmful in situations that require broad attention or creative solutions. In these instances, a wider range of synaptic inputs may be helpful. In addition, DA D1-receptor overstimulation (e.g., under a stressful condition) may lead to disconnection of all network inputs and the cell may stop firing. As a result, PFC neurons require a specific amount of DA to function optimally (Arnsten et al., 2009; Vijayraghavan et al., 2007).

PFC function is also impaired by excessive NE release. High levels of NE release, such as those encountered during a stressful condition, engage  $\alpha_1$ -receptors that suppress PFC cell firing (Birnbaum et al., 2004).  $\alpha_1$ -Receptor stimulation impairs working memory by activating protein kinase C intracellular signaling, which is thought to be overactive in patients with bipolar disorder (Birnbaum et al., 2004).

### 3. Likely mechanisms of action of ADHD medications

All medications currently approved by the U.S. Food and Drug Administration to treat ADHD enhance catecholamine transmission in the PFC. The stimulants methylphenidate and amphetamine block reuptake at NE and DA transporters, while atomoxetine more selectively targets the NE transporter. However, as the NE transporter clears both NE and DA in the PFC, atomoxetine increases both DA and NE in the rat PFC (Bymaster et al., 2002).

#### 3.1. Stimulants enhance both DA and NE actions in PFC

Historically, studies of stimulant actions in ADHD have focused on the effects on DA (Swanson and Volkow, 2002). This focus has arisen, in part, from the fact that positron emission tomography (PET) imaging studies can visualize DA receptors in the striatum, but these studies are unable to visualize changes in NE or DA in the PFC. This view is also based on older biochemical studies in rats that used high doses of stimulants, which increased locomotor activity and had pronounced effects on DA release throughout the brain. However, more recent biochemical studies in rats have shown that lower doses of stimulants, which produce blood levels similar to those in patients with ADHD, preferentially increase NE in the PFC (Berridge et al., 2006). These lower doses in rats improve PFC attention and working memory function, enhance PFC neuronal response, and reduce locomotor hyperactivity in juveniles (Arnsten and Dudley, 2005; Berridge et al., 2006; Kuczenski and Segal, 2002). Importantly, these doses have less effect on subcortical DA release in areas such as the nucleus accumbens (Berridge et al., 2006), which may explain why they do not cause addiction when they are used as prescribed. Animal studies have shown that therapeutic doses of methylphenidate and atomoxetine improve PFC function by increasing endogenous NE stimulation of  $\alpha_2$ -receptors and DA stimulation of D1-receptors in rats (Arnsten and Dudley, 2005) and monkeys (Gamo et al., 2010). These agents produce an inverted U dose response, whereby higher doses can actually impair PFC cognitive performance in monkeys (Gamo et al., 2010). Stimulant medications might also exert therapeutic effects through actions in striatum (e.g. caudate), and in the posterior association cortices in addition to the PFC. PET imaging studies have shown that therapeutic doses of stimulant medications engage DA receptors in striatum (Swanson and Volkow, 2002), consistent with the small but significant increases in DA release measured in rodent striatum (Berridge et al., 2006). Since PET imaging is unable to detect catecholamine actions in the cortex, drug actions in the sensory association cortices remain speculative. However, excessive doses of stimulants impair PFC function, which may account for the cognitive

inflexibility observed when patients with ADHD are administered these doses of stimulant medication (Dyme et al., 1982).

Contrary to common views on stimulant medications, the effects of stimulants for the treatment of ADHD are not paradoxical. When administered in appropriate doses, these medications improve PFC function both in healthy human subjects (Elliott et al., 1997) and in animals (Arnsten and Dudley, 2005), including the reduction of locomotor hyperactivity in juvenile rats (Kuczenski and Segal, 2002). Higher doses of stimulants induce hyperactivity and addiction in rat models, but these doses exceed those given clinically (Segal and Kuczenski, 1987). Indeed, imaging studies have shown that methylphenidate enhances the efficiency of PFC activity both in healthy college students (Mehta et al., 2000) and in subjects with ADHD (Bush et al., 2008). These measureable positive effects of stimulants on attention in subjects without ADHD reflect the sensitivity of the PFC to relatively small changes in catecholamine levels. Interestingly, recent data have shown that stimulant medication can normalize gray matter volume in the developing PFC of patients with ADHD (Shaw et al., 2009). This finding counters fears that stimulant medications could interfere with brain development.

#### 3.2. Atomoxetine enhances NE and DA transmission in PFC

Atomoxetine increases extracellular availability of both NE and DA in the rat PFC (Bymaster et al., 2002). Atomoxetine improves measures of PFC cognitive function in rats (Newman et al., 2008; Robinson et al., 2008; Seu et al., 2009), monkeys (Gamo et al., 2010; Seu et al., 2009), and humans (Chamberlain et al., 2007, 2006). Recent studies in monkeys performing a working memory task show that atomoxetine produces an inverted U dose response, similar to that seen with stimulants (Gamo et al., 2010). Thus, optimal doses improved working memory performance in monkeys, while higher doses impaired performance. The enhancing effects were blocked by co-administration of either an NE  $\alpha_2$  or DA D1 antagonist (Gamo et al., 2010). Interestingly, the optimal dose varied widely, which may explain variability of drug response in patients (Castellanos and Kelly, 2010). An inverted U dose response was also observed at the neuronal level when atomoxetine was iontophoretically applied onto PFC neurons in monkeys performing a working memory task. Lower “optimal” amounts of atomoxetine enhanced “signals” (neuronal firing during the delay period for the neuron’s preferred direction) via indirectly increasing NE stimulation of  $\alpha_2$  receptors, and/or decreased “noise” (neuronal firing for nonpreferred directions) via indirectly increasing DA stimulation of D1 receptors (Gamo et al., 2010). In humans, both normal subjects (Chamberlain et al., 2006) and patients with ADHD (Chamberlain et al., 2007) show improved PFC inhibition of behavior following atomoxetine, consistent with the animal data.

#### 3.3. Guanfacine mimics NE at postsynaptic PFC $\alpha_{2A}$ -receptors

Guanfacine is the most selective  $\alpha_{2A}$ -adrenoceptor agonist currently available, with higher affinity for the  $\alpha_{2A}$ - than for the  $\alpha_{2B}$ - or  $\alpha_{2C}$ -adrenoceptor subtypes (Uhlén et al., 1995; Uhlen and Wikberg, 1991), and little affinity for the brainstem imidazoline I1 receptors that contribute to the potent hypotensive actions of clonidine (van Zwieten and Chalmers, 1994). In addition, guanfacine has weaker actions at presynaptic  $\alpha_2$ -receptors, where its activity is only one-tenth that of clonidine (Engberg and Eriksson, 1991). Not only does guanfacine mimic noradrenergic actions at  $\alpha_{2A}$ -receptors, its activity at postsynaptic  $\alpha_2$ -receptors may restore PFC function in patients with ADHD (Biederman et al., 2008; Scahill et al., 2001). Conversely, yohimbine blockade of  $\alpha_2$ -receptors in the PFC recreates the symptoms of ADHD: inducing locomotor hyperactivity (Ma et al., 2005), poor impulse control (Ma et al., 2003), and weaker working memory (Li and Mei, 1994).

Guanfacine enhances various PFC functions in animals, including improvements in working memory (Arnsten et al., 1988), behavioral inhibition (Steere and Arnsten, 1997), and reduced distractibility (Arnsten and Contant, 1992). These improvements are observed immediately when guanfacine is infused directly into the PFC (Mao et al., 1999) and when administered systemically (Arnsten et al., 1988; O'Neill et al., 2000; Rama et al., 1996). Dose–response studies in monkeys suggest that guanfacine-induced enhancement of PFC function can be completely dissociated from the sedative effects of guanfacine (Arnsten et al., 1988). The sedative effects of guanfacine may arise from a variety of actions, including stimulation of presynaptic  $\alpha_{2A}$ -receptors on noradrenergic cell bodies and terminals as well as postsynaptic  $\alpha_{2B}$ -receptors in the thalamus (Berridge et al., 2003; McCormick et al., 1991).

The improvements in PFC function observed in animal studies of guanfacine treatment appear to extend to human subjects; double-blind placebo-controlled studies have demonstrated that guanfacine is effective in treating ADHD symptoms. In 2 short-term, placebo-controlled, double-blind pivotal trials, an extended-release formulation of guanfacine (Intuniv™, Shire US Inc.) has shown efficacy as monotherapy for reducing symptoms of ADHD based on clinician-rated ADHD Rating Scale IV (ADHD-RS-IV) total score as well as the hyperactivity/impulsivity and inattentiveness subscale scores (Biederman et al., 2008; Sallee et al., 2009). Immediate-release guanfacine has also demonstrated positive effects in other disorders characterized by impaired PFC function, such as children with ADHD and tic disorders (Scahill et al., 2001). In that study, immediate-release guanfacine was superior to placebo on teacher ratings of inattention and hyperactivity on the ADHD-RS-IV. Finally, there are 2 trials in children with pervasive developmental disorder accompanied by hyperactivity and impulsiveness in which immediate-release guanfacine shows promise, though more study is needed in this population (Handen et al., 2008; Scahill et al., 2006).

#### 4. Summary and future directions

In summary, improved understanding of catecholamine actions in the PFC has helped to lead to new treatments for ADHD. Important directions for the future include better understanding of PFC subregions, and deeper understanding of second messenger actions that regulate PFC circuits. As altered “top-down” PFC control of behavior, thought and emotion is central to most neuropsychiatric disorders, these studies are relevant to many cognitive disorders. We must respect that cognition is not a unitary phenomenon, and that different brain circuits and cognitive operations may have distinct neurochemical needs.

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