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Stimulants: Therapeutic Actions in ADHD

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Stimulants such as methylphenidate and amphetamine are currently the most common treatment for attention deficit hyperactivity disorder (ADHD). For years, it was assumed that stimulants had paradoxical calming effects in ADHD patients, whereas stimulating 'normal' individuals and producing locomotor activation in rats. It is now known that low doses of stimulants focus attention and improve executive function in both normal and ADHD subjects. Furthermore, the seminal work of Kuczenski and Segal showed that low, oral doses of methylphenidate reduce locomotor activity in rats as well. Berridge *et al* have now shown that these low doses produce marked increases in norepinephrine and dopamine release in the prefrontal cortex, whereas having only subtle effects on subcortical catecholamine release. ihe prefrontal cortex regulates behavior and attention using representational knowledge, and imaging and neuropsychological studies have shown that the prefrontal cortex is weaker in subjects with ADHD. This cortical area is very sensitive to levels of catecholamines: moderate levels engage postsynaptic α2A-adrenoceptors and D1 receptors and improve prefrontal regulation of behavior and attention, while high levels impair prefrontal function via α1-adrenoceptors and excessive D1 receptor stimulation. Administering low doses of methylphenidate to rats improves the working memory and attentional functions of the prefrontal cortex, while high doses impair working memory and produce a perseverative pattern of errors similar to that seen in patients. The low dose improvement is hiocked by either an α2-adrenoceptor or Dl receptor antagonist, suggesting that both norepinephrine and dopamine contribute to the beneficial actions of stimulant medications.
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INTRODUCTION

For decades, basic research on the neurochemical and behavioral actions of stimulants has focused on higher doses that induce locomotor hyperactivity and promote dopamine release in ventral and/or dorsal striatum. This body of work has been the foundation for many of the dopaminergic hypotheses of schizophrenia and drug abuse. In particular, the sensitizing effects of repeated, high-dose stimulant administration have been a major focus of this work. Much of David Segal's career was spent characterizing the behavioral and neurochemical differences that emerge following repeated, high-dose amphetamine administration (see, for example, Segal and Kuczenski, 1987, 1997a, b)

In contrast to these basic studies in rats, humans given stimulant medications for the treatment of attention deficit hyperactivity disorder (ADHD) display reduced locomotor activity and improved attentional focus. For years, it was presumed that stimulant medications had paradoxical effects in ADHD. However, it is now established that the focusing effects of stimulants in ADHD are not paradoxical; these agents have the same effect in 'normal' human subjects (albeit a more subtle response given ceiling effects) (Rapoport and Inoff-Germain, 2002). However, the discrepancies between locomotor-activating effects in rodents and the focusing effects in humans remained: it was assumed that the locomotor-activating effects of stimulants in rodents must be owing to species differences, thus weakening the validity of rodent models of ADHD.

A major advance for the field of ADHD was the finding by Kuczenski and Segal (2002) that low, oral doses of methylphenidate—doses that produce blood levels similar to those in ADHD patients—can decrease locomotor activity in juvenile rats. Thus, it was not that rats and humans had opposite responses to stimulants, but rather that rats had previously been given doses far in excess of those equivalent to human therapeutic medications. This key finding redirected the entire field, and has allowed us to study the therapeutic mechanisms of stimulant medications using valid rodent models.

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THE BIOCHEMICAL EFFECTS OF LOW-DOSE STIMULANT ADMINISTRATION

Previous research with higher doses of stimulants focused on the dopaminergic effects of these compounds in

subcortical structures. Methylphenidate and amphetamine were known to block the dopamine transporter and enhance dopamine release, and robust increases in dopamine release were observed in the nucleus accumbens (Segal and Kuczenski, 1999) and dorsal striatum (Kuczenski and Segal, 1997) of rats given high doses of stimulants. Supportive evidence was found in human imaging studies, where intravenous stimulant administration displaced D2 receptor PET ligands, an indication of increased endogenous dopamine release (Volkow *et al*, 2002b). This measure of D2 receptor stimulation correlated with measures of reinforcement, consistent with the rodent work (Volkow *et al*, 2002b). In contrast, oral administration of lower doses of stimulants produces more subtle and slower effects on striatal dopamine release (Volkow *et al*, 2002a). The amount of dopamine release in the nucleus accumbens is especially pertinent to drug abuse, and thus rodent studies focused on this brain region to try to determine whether the doses of stimulants given to children would alter dopamine release in this structure. Kuczenski and Segal (2002, 2005) first identified the dose regimen of orally administered, low doses that produced blood levels similar to those observed in children taking stimulants to treat ADHD symptoms. They found that these low, oral doses had little or no effect on DA release in the nucleus accumbens, and they found no evidence of stimulant sensitization following low-dose chronic usage. These results in rats are consistent with observations of children taking stimulants: ADHD medications do not produce euphoria (indeed, dysphoria is the more likely side effect), and the incidence of drug abuse is actually reduced in properly medicated ADHD patients (Hechtman and Greenfield, 2003; Katusic *et al*, 2005).

Although Kuczenski and Segal (2002) found only subtle effects of low-dose oral methylphenidate on dopamine release in the nucleus accumbens, they did observe increased release of norepinephrine in the hippocampus. Based on this seminal paper, Berridge *et al* (2006) then explored low-dose stimulant effects on dopamine and norepinephrine release in the prefrontal cortex, a brain region closely linked to ADHD, as well as in the nucleus accumbens and medial septal area. A summary of these results can be seen in Figure 1. As with Kuczenski and Segal, only subtle effects were observed in accumbens dopamine release. There was also some subcortical norepinephrine release in the medial septal area. However, the greatest effects were observed in prefrontal cortex, where there were especially high levels of norepinephrine release (400% increase; Figure 1a), and significant levels of dopamine release (250% increase; Figure 1b). The functional ramifications of enhanced catecholamine release in prefrontal cortex are discussed below. It is noteworthy that atomoxetine (Strattera) also increases norepinephrine and dopamine release in the prefrontal cortex (Bymaster *et al*, 2002); thus, catecholamine release in the prefrontal cortex may be a common action for many ADHD therapeutics. It should be noted that available PET and SPECT neuroreceptor ligands are generally unable to detect the delicate catecholamine input to cortex. Thus, current imaging methods are limited to the striatum. Research is in progress to visualize catecholamine actions in the prefrontal cortex of human subjects.

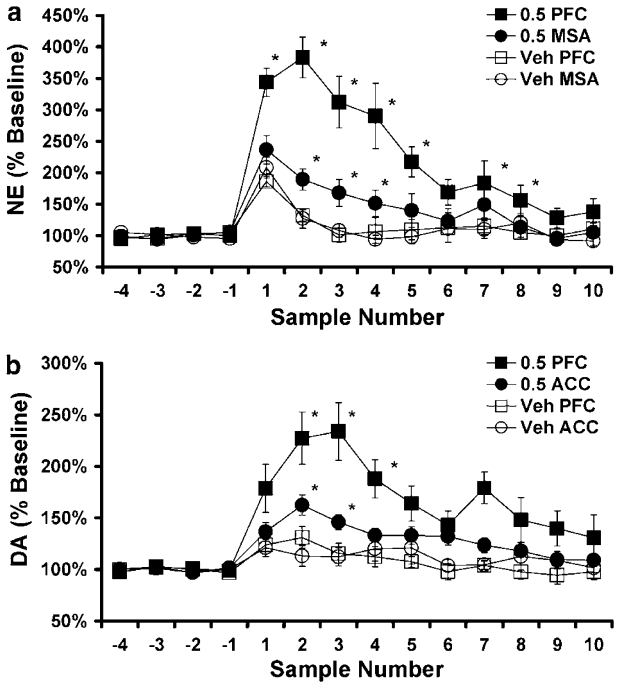

Figure 1 Effects of low-dose methylphenidate (MPH) on extracellular levels of NE and DA within and outside the PFC. (a) NE levels within the PFC and the medial septal area (MSA). (b) DA levels within the PFC and nucleus accumbens (ACC). In each panel, the mean (±SEM) NE or DA levels within 16-min samples collected before (negative numbers) and following (positive numbers) injection of vehicle or 0.5 mg/kg (i.p.) MPH are displayed. Values are expressed as a percentage of baseline (calculated as the average of four pre-infusion samples). Low-dose MPH produces substantially larger increases in NE and DA within the PFC relative to the MSA and Acc, respectively. At this dose, but not 0.25 mg/kg, MPH produces a larger increase in PFC NE levels relative to PFC DA. Similar preferential actions of MPH on PFC catecholamines were observed with oral administration (2.0 mg/kg). $^*P<0.05$ compared to vehicle-treated animals. Data from Berridge *et al* (2006).

THE ROLE OF THE PREFRONTAL CORTEX IN EXECUTIVE FUNCTIONS

The prefrontal cortex guides behavior and attention using working memory, applying representational knowledge to inhibit inappropriate actions, thoughts, and feelings. These processes are the basis of the so-called executive functions, including regulation of attention, planning, impulse control, mental flexibility, and the initiation and monitoring of action. Lesions to the prefrontal cortex produce symptoms such as forgetfulness, distractibility, impulsivity, perseveration, and disorganization. Lesions in the ventromedial prefrontal cortex can impair regulation of emotion, and result in inappropriate social behaviors such as aggression (Anderson *et al*, 1999).

The role of prefrontal cortex in attention regulation has been appreciated for many years. The prefrontal cortex regulates what we attend to based on represented goals. The prefrontal cortex inhibits responses to distracting stimuli and suppresses irrelevant thoughts such as proactive interference. Thus, patients with prefrontal cortex lesions are easily distracted (Woods and Knight, 1986; Godefroy and Rousseaux, 1996), are impaired at gating sensory stimuli (Knight *et al*, 1989; Yamaguchi and Knight, 1990),

have poor concentration and organization, and are more vulnerable to disruption from proactive interference (Thompson-Schill *et al*, 2002). Prefrontal cortex lesions impair the ability to sustain attention, particularly over long delays (Wilkins *et al*, 1987). Lesions of the dorsolateral prefrontal cortex impair the ability to shift attentional set (Manes *et al*, 2002). Prefrontal cortex lesions also impair divided attention, and these attentional deficits have been associated with lesions in the left, superior prefrontal cortex (Godefroy and Rousseaux, 1996). Similar results have been seen in animals, where prefrontal cortex lesions impair attentional regulation in monkeys (Malmo, 1942; Bartus and Levere, 1977; Dias *et al*, 1996), and rats (Muir *et al*, 1996).

The prefrontal cortex also allows us to regulate overt behaviors including locomotor activity. The right inferior prefrontal cortex is particularly important for behavioral inhibition (reviewed in Aron *et al*, 2004). Both imaging (Konishi *et al*, 1999; Rubia *et al*, 2003) and lesion studies indicate that the right prefrontal cortex in humans is critical for inhibitory abilities, for example, performance of the stop or go–no go tasks. The importance of the prefrontal cortex to inhibitory control has also been shown in monkeys with lesions to the prefrontal cortex (Petrides, 1986), and in electrophysiological (Watanabe, 1986) and imaging studies (Morita *et al*, 2004). There is also a classic literature demonstrating that prefrontal cortex lesions cause locomotor hyperactivity in monkeys (Kennard *et al*, 1941; French, 1959; Gross, 1963; Gross and Weiskrantz, 1964). Thus, some of the locomotor hyperactivity observed in ADHD may arise from prefrontal cortex dysfunction.

The cellular basis for prefrontal cortical regulation of attention and behavior has been an arena of intensive research in animals. Prefrontal neurons are able to represent spatial and feature information in the absence of environmental stimulation (Goldman-Rakic, 1995). This firing is often measured during the delay period of working memory tasks when information must be kept in mind for correct performance. Prefrontal neurons can also fire in relationship to an abstract rule that is used to govern action (Wallis *et al*, 2001). A unique feature of prefrontal neurons is their ability to maintain information in the presence of interference from distracting stimuli (Miller *et al*, 1993). Delay-related firing also can serve as the basis for behavioral inhibition, as examined in an anti-saccade task in which monkeys must look away from a remembered visual stimulus (Funahashi *et al*, 1993). Thus, delay-related activity is observed both when an animal must make a memory-guided action and when an animal must withhold a prepotent response based on representational knowledge. Weakening of these abilities likely contributes to ADHD.

PREFRONTAL CORTICAL DYSFUNCTION IN ADHD

Evidence from a variety of perspectives demonstrates that prefrontal cortical function is weaker in subjects with ADHD (reviewed in Arnsten *et al*, 1996; Barkley, 1997; Aron and Poldrack, 2005). Neuropsychological analyses have shown that patients with ADHD are impaired on the same tasks as those with prefrontal lesions, for example, tasks of behavioral inhibition, reward reversal, and working memory (Itami and Uno, 2002; Bedard *et al*, 2003; McLean *et al*, 2004). Although some neuropsychological studies disagree with the importance of executive function deficits in ADHD, these studies are often flawed by the use of inappropriate tasks for evaluating children (eg the Stroop color-naming interference task, which assumes that reading is a prepotent response that must be inhibited, an assumption often invalid in children; van Mourik *et al*, 2005), disagreement on which processes constitute executive functions (eg not including attention regulation parameters as executive functions; Schoechlin and Engel, 2005), or by the use of tasks with ceiling effects for this patient population. Deficits in attention can also lead to secondary impairments on widespread cognitive abilities that depend on proper perception and encoding. Thus, it is difficult to ascertain specificity in this patient population (Boonstra *et al*, 2005). It is likely that ADHD does not involve global prefrontal deficits in all ADHD patients, as subcircuits within prefrontal cortex are likely differentially sensitive to genetic mutations and/or developmental abnormalities. This heterogeneity in types of PFC dysfunction would account for a weaker effect size on any one task. However, when viewed as a whole, the literature indicates that functions dependent on the PFC are weaker in ADHD patients. Numerous structural imaging studies have shown reduced size of the prefrontal cortex in ADHD patients, particularly in the right hemisphere (Castellanos *et al*, 1996; Casey *et al*, 1997; Filipek *et al*, 1997; Giedd *et al*, 2001; Kates *et al*, 2002; Hill *et al*, 2003; Sowell *et al*, 2003). Many of these studies have also found reduced volume of cerebellum, caudate, and corpus callosum (Seidman *et al*, 2005; Castellanos *et al*, 2002). A large study of children aged 5–18 showed that the developmental trajectories for these structures, except caudate, remained parallel for patients and controls during childhood and adolescence, and were observed in children who had never received stimulant treatment (Castellanos *et al*, 2002). These findings emphasize the biological nature of ADHD. Functional imaging studies have also shown evidence of inefficient or reduced blood flow or metabolism in prefrontal cortex of ADHD patients, deficits that correspond with poor prefrontal cortical cognitive function (Rubia *et al*, 1999; Yeo *et al*, 2000; Bush *et al*, 2005).

GENETICS OF ADHD: FOCUS ON CATECHOLAMINES

ADHD is often an inherited disorder, and many of the genes associated with ADHD code for molecules involved with catecholamine transmission (reviewed in Faraone *et al*, 2005). Initial genetic studies focused on molecules involved with dopamine transmission. Researchers have consistently found associations between ADHD and the genes encoding for the dopamine transporter, and the D1, D4, and D5 receptors. More recently, genetic studies have turned to genes associated with norepinephrine transmission. The norepinephrine synthetic enzyme dopamine beta hydroxylase (DBH) and the gene encoding for the α2A adrenoceptor have been associated with ADHD (Roman *et al*, 2003; Park *et al*, 2005). It should be noted that the D4 receptor has very high affinity for norepinephrine (Van Tol *et al*, 1991) and should really be considered a catecholamine receptor. Patients with ADHD show a greater prevalence of the seven repeat polymorphism form of the D4 receptor that renders this receptor less effective. Intriguingly, a recent study has associated changes in the D4 receptor with

reduced prefrontal volume (Durston *et al*, 2005), and with poor performance of a sustained attention task (Bellgrove *et al*, 2005). Similarly, genetic alterations in DBH are associated with impaired sustained attention in ADHD (Bellgrove *et al*, 2006). These relationships between genetic changes in catecholamine signaling and prefrontal cognitive deficits are consistent with the important role of dopamine and norepinephrine in prefrontal cognitive function.

CATECHOLAMINE MODULATION OF PREFRONTAL CORTICAL FUNCTION

The working memory abilities of the prefrontal cortex are greatly influenced by the levels of catecholamines released in prefrontal cortex. Either insufficient or excessive catecholamine receptor stimulation can markedly impair prefrontal cortex cognitive function. For more extensive reviews of this topic, see Arnsten and Robbins (2002) and Arnsten and Li (2005).

Dopamine

Dopamine modulates prefrontal cortex functions through actions at the D1 (D1, D5) and D2 (D2, D3, D4) families of receptors. Research elucidating the role of the D2 family is still in progress, but a clear picture is emerging with regard to the D1 receptor family. There are no drugs that distinguish between D1 and D5 receptors, and thus all references to 'D1' generally refer to either the D1 or D5 subtype. Stimulation of D1/D5 receptors produces an inverted 'U'-shaped dose–response on the working memory and attention regulation processes of the prefrontal cortex (Zahrt *et al*, 1997; Granon *et al*, 2000). Whereas modest levels of D1 receptor stimulation are essential for prefrontal cortex function, high levels of dopamine release occur during exposure to stress, and impair working memory and attention regulation. Many of these D1/D5 actions appear to be mediated via cAMP/protein kinase A intracellular signaling mechanisms (Arnsten *et al*, 2005). A similar inverted 'U' has been described at the cellular level in monkeys performing a spatial working memory task. Moderate levels of D1/D5 receptor stimulation suppress delay-related firing for nonpreferred spatial directions (ie 'noise'), and thus enhance spatial tuning (Williams and Goldman-Rakic, 1995; Vijayraghavan *et al*, 2006). However, high levels of D1/D5 receptor stimulation suppress delay-related firing for all directions, and thus erode spatial tuning (Vijayraghavan *et al*, 2006). Limited studies have been performed in humans owing to the lack of selective D1/D5 compounds available for human use. However, studies with nonselective compounds have suggested that an inverted 'U' may be evident in humans as well as animals (Kimberg *et al*, 1997), and that compounds that prefer D1 receptors may be more helpful than D2 agonists in improving working memory (Muller *et al*, 1998). Taken together, these studies suggest that genetic alterations in the D1 or D5 receptor, or in molecules that influence the level of DA available in the synapse (eg the dopamine transporter, the catabolic enzyme COMT) could influence the strength of prefrontal cortical regulation of behavior.

Norepinephrine

As with dopamine, moderate levels of NE are critical for proper prefrontal cortical function, whereas high levels released during stress impair prefrontal cortical function. The beneficial effects of NE may be especially relevant to medications used to treat ADHD (see below). Norepinephrine improves prefrontal cortex function through actions at post-synaptic, α2A receptors. Although the older literature emphasized the prevalence of pre-synaptic α2 receptors that inhibit NE release and reduce noradrenergic cell firing, it is now known that the vast majority of α2 receptors are localized post-synaptic to norepinephrine terminals. It is these post-synaptic receptors that mediate the enhancing effects of α2 agonists on prefrontal cognitive function (Arnsten and Goldman-Rakic, 1985; Cai *et al*, 1993). Studies in genetically modified mice have demonstrated that the α2A subtype, rather than the α2B or α2C subtype, underlies the enhancement in prefrontal cognitive function (Franowicz *et al*, 2002). These enhancing effects appear to result from inhibiion of cAMP intracellular signaling (Ramos *et al*, 2006). The α2A agonist, guanfacine, improves many aspects of prefrontal cortical function, including working memory, attention regulation, behavioral inhibition, and planning, and these effects have been seen in rats (Tanila *et al*, 1996; Ramos *et al*, 2006), monkeys (Arnsten *et al*, 1988; Mao *et al*, 1999), and humans (Jakala *et al*, 1999). The enhancing effects of α2A agonists are most evident in subjects with PFC dysfunction, and these compounds can be less efficacious and/or potent in young adult animals (Franowicz and Arnsten, 1998) or humans (Muller *et al*, 2005) with healthy endogenous noradrenergic systems. SPECT imaging has shown that systemic administration of guanfacine activates dorsolateral prefrontal cortex in monkeys performing a spatial working memory task (Mao *et al*, 1999; Avery *et al*, 2000). Importantly, guanfacine appears to improve the functioning of both lateral (Mao *et al*, 1999; Wang *et al*, 2004) and ventromedial (Steere and Arnsten, 1997) prefrontal circuits, and thus strengthens regulation of both intellectual and emotional responses. α2A-Adrenoceptor stimulation also strengthens prefrontal function at the cellular level. Thus, α2A agonists enhance, whereas antagonists erode, delay-related prefrontal cell firing (Sawaguchi, 1998; Li *et al*, 1999; Wang *et al*, 2006). In contrast to stimulation of DA D1 receptors that suppress 'noise', norepinephrine α2A receptor stimulation enhances spatial tuning by increasing 'signals', that is, increasing delay-related firing for the preferred spatial direction. Studies in progress indicate that guanfacine increases delay-related firing and improves prefrontal cognitive function by strengthening the functional connectivity of microcircuits in the prefrontal cortex via inhibition of cAMP intracellular signaling (Wang *et al*, 2006). In contrast, blockade of α2 receptors in the prefrontal cortex of monkeys erodes delay-related cell firing and recreates all the symptoms of ADHD: poor impulse control (Ma *et al*, 2003), locomotor hyperactivity (Ma *et al*, 2005), and weakened working memory (Li and Mei, 1994) underlying increased distractibility. From these basic studies, it is clear that genetic alterations in NE synthetic enzymes (DBH) or in α2A adrenoceptors may contribute to ADHD symptomology by weakening endogenous noradrenergic α2A-adrenoceptor signaling.

In contrast to these beneficial effects at moderate concentrations, high levels of norepinephrine release (eg during stress) impair prefrontal function through actions at α1 receptors (Birnbaum *et al*, 1999, 2004) and possibly β1

receptors as well (Ramos *et al*, 2005). Based on this work, the α1 receptor blocker, prazosin, is now in use for the treatment of post-traumatic stress disorder (Raskind *et al*, 2003). Recordings of prefrontal neurons have found that α1-adrenoceptor stimulation decreases delay-related cell firing for the preferred direction (Birnbaum *et al*, 2004). These detrimental actions are mediated by activation of protein kinase C intracellular signaling (Birnbaum *et al*, 2004). Interestingly, excessive protein kinase C signaling has been associated with mania (Manji and Lenox, 1999), and bipolar disorder and ADHD are often confused in children with high levels of distractibility, impulsivity, and hyperactivity (Biederman *et al*, 2000). In this regard, it is of interest that most 'atypical' anti-psychotic medications have potent α1 blocking properties. Thus, prefrontal deficits associated with high levels of stress or with bipolar disorder may benefit from inhibition of α1/protein kinase C signaling.

LOW-DOSE STIMULANTS IMPROVE PREFRONTAL CORTICAL FUNCTION IN HUMANS AND ANIMALS

Given the role of prefrontal cortical deficits in ADHD, studies have examined whether stimulant medication can ameliorate prefrontal deficits in patients and in animals. Methylphenidate has now been found to improve spatial working memory, response inhibition, set-shifting, and other prefrontal cognitive functions in both 'normal' college students (Elliott *et al*, 1997; Mehta *et al*, 2000) and in children and adults with ADHD (Aron *et al*, 2003; Bedard *et al*, 2003; Mehta *et al*, 2004). In adults with ADHD, childhood ratings of ADHD correlated with response to methylphenidate on the spatial working memory task (Turner *et al*, 2005). Thus, studies of spatial working memory performance are likely relevant to the therapeutic actions of this compound in ADHD.

Spatial working memory is classically assessed in rats using delayed alternation testing on a T maze (Larsen and Divac, 1978). Low doses of methylphenidate, which increase catecholamine release in prefrontal cortex, have recently been shown to improve delayed alternation performance in rats (Figure 2; Arnsten and Dudley, 2005; Berridge *et al*, 2006). Low doses of methylphenidate also improved performance of a sustained attention task, the five-choice attention task that similarly depends upon prefrontal cortex (Berridge *et al*, 2006). In contrast to low doses of methylphenidate, higher doses impaired performance of the delayed alternation task (eg Figure 2a), consistent with excessive catecholamine receptor stimulation impairing prefrontal cortical cognitive function. These impairing effects at higher doses may correspond to the mental inflexibility often described in patients taking excessive doses of stimulant medication.

The receptor mechanisms underlying the therapeutic effects of low, oral doses of methylphenidate have recently begun to be examined. As shown in Figure 2, studies in rats have shown that the cognitive-enhancing effects of methylphenidate on spatial working memory are prevented by blockade of either noradrenergic α2-adrenoceptors (Figure 2b) or dopamine D1 receptors (Figure 2c) (Arnsten and Dudley, 2005). Thus, stimulants likely facilitate endogenous catecholamine stimulation of D1 and α2A receptors in prefrontal cortex. The receptor mechanisms

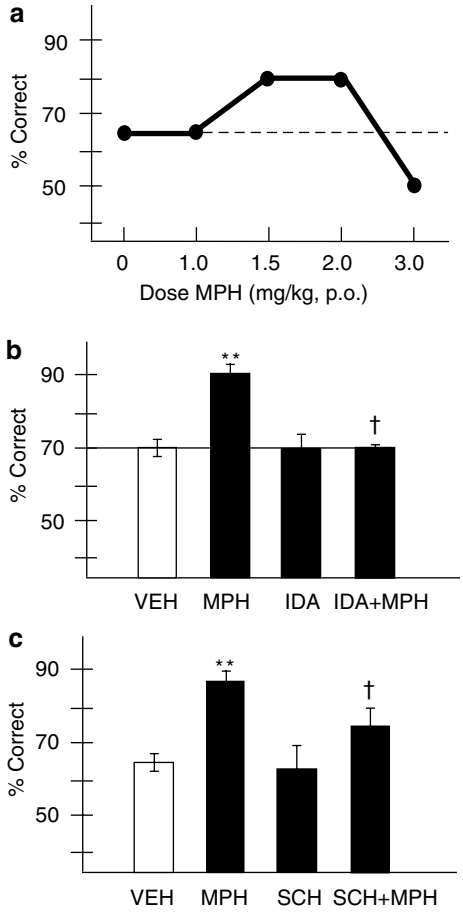

Figure 2 The effects of oral administration of MPH on delayed alternation performance in male rats. (a) A representative dose–response curve from an individual rat. For most rats, a lower dose (1.0–2.0 mg/kg, p.o. 30 min) was found to improve performance, whereas higher doses often impaired performance (1.5–3.0 mg/kg). (b) The enhancing effects of methylphenidate (1.0–2.0 mg/kg) were blocked by co-administration of the α2 adrenoceptor antagonist idazoxan (IDA, 0.1 mg/kg), which had no effect on its own. Results represent mean ± SEM percent correct on the delayed alternation task. **significantly different from VEH; †significantly different from MPH. (c) The enhancing effects of methylphenidate were blocked by co-administration of the dopamine D1 receptor antagonist SCH23390 at doses (0.01–0.1 mg/kg) that had no effect on their own. **Significantly different from VEH; †significantly different from MPH. Data adapted from Arnsten and Dudley (2005).

underlying the cognitive errors observed following high-dose methylphenidate administration are currently under investigation. These may involve excessive D1, α1, and/or β1 receptor stimulation in prefrontal cortex. Thus, we now have rodent models to examine the neurochemistry and neuropharmacology of stimulant actions in ADHD. The results so far, when viewed in combination with genetic studies of ADHD, suggest that stimulants may ameliorate weaknesses in catecholamine signaling in the prefrontal cortex of ADHD subjects.

SUMMARY

Thanks to the patient work of Kuczenski and Segal (2002), the correct path has been illumined to pursue the neural mechanisms underlying the therapeutic effects of stimulant

medications in rodent models. The spotlight has turned to much lower doses, and a logical picture emerges, bridging genetics and neurobiology with the pharmacological treatment of ADHD.

A final comment—those who knew David observed his extraordinary energy, focus, and commitment to his work and family. I would like to thank him for teaching me to be a dedicated scientist and a devoted parent, all at once.

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REFERENCES

Anderson SW, Bechara A, Damasio H, Tranel D, Damasio AR (1999). Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nat Neurosci* **2**: 1032–1037.

Arnsten AFT, Cai JX, Goldman-Rakic PS (1988). The alpha-2 adrenergic agonist guanfacine improves memory in aged monkeys without sedative or hypotensive side effects. *J Neurosci* **8**: 4287–4298.

Arnsten AFT, Dudley AG (2005). Methylphenidate improves prefrontal cortical cognitive function through a2 adrenoceptor and dopamine D1 receptor actions: relevance to therapeutic effects in Attention Deficit Hyperactivity Disorder. *Behav Brain Funct (Biomed Central)* **1**: 2.

Arnsten AFT, Goldman-Rakic PS (1985). Alpha-2 adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. *Science* **230**: 1273–1276.

Arnsten AFT, Li B-M (2005). Neurobiology of executive functions: catecholamine influences on prefrontal cortical function. *Biol Psychiatry* **57**: 1377–1384.

Arnsten AFT, Ramos B, Birnbaum SB, Taylor JR (2005). Protein kinase A as a therapeutic target for memory disorders: rationale and challenges. *Trends Mol Med* **11**: 121–128.

Arnsten AFT, Robbins TW (2002). Neurochemical modulation of prefrontal cortical function in humans and animals. In: Stuss DT, Knight RT (eds). *Principles of Frontal Lobe Function*. Oxford University Press: New York. pp 51–84.

Arnsten AFT, Steere JC, Hunt RD (1996). The contribution of alpha-2 noradrenergic mechanisms to prefrontal cortical cognitive function: potential significance to Attention Deficit Hyperactivity Disorder. *Arch Gen Psychiatry* **53**: 448–455.

Aron AR, Dowson JH, Sahakian BJ, Robbins TW (2003). Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry* **54**: 1465–1468.

Aron AR, Poldrack RA (2005). The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. *Biol Psychiat* **57**: 1285–1292.

Aron AR, Robbins TW, Poldrack RA (2004). Inhibition and the right inferior frontal cortex. *Trends Cogn Sci* **8**: 170–177.

Avery RA, Franowicz JS, Studholme C, van Dyck CH, Arnsten AFT (2000). The alpha-2A-adenoceptor agonist, guanfacine, increases regional cerebral blood flow in dorsolateral prefrontal cortex of monkeys performing a spatial working memory task. *Neuropsychopharmacology* **23**: 240–249.

Barkley RA (1997). *ADHD and the Nature of Self-Control*. Guilford Press: New York.

Bartus RT, Levere TE (1977). Frontal decortication in rhesus monkeys: a test of the interference hypothesis. *Brain Res* **119**: 233–248.

Bedard AC, Ickowicz A, Logan GD, Hogg-Johnson S, Schachar R, Tannock R (2003). Selective inhibition in children with attention-deficit hyperactivity disorder off and on stimulant medication. *J Abnorm Child Psychol* **31**: 315–327.

Bellgrove MA, Hawi Z, Gill M, Robertson IH (2006). The cognitive genetics of attention deficit hyperactivity disorder (ADHD): sustained attention as a candidate phenotype. *Cortex* (in press).

Bellgrove MA, Hawi Z, Lowe N, Kirley A, Robertson IH, Gill M (2005). DRD4 gene variants and sustained attention in attention deficit hyperactivity disorder (ADHD): effects of associated alleles at the VNTR and -521 SNP. *Am J Med Genet B Neuropsychiat Genet* **136**: 81–86.

Berridge CW, Devilbiss DM, Andrzejewski ME, Arnsten AFT, Kelley AE, Schmeichel B *et al* (2006). Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biol Psychiatry* [Epub ahead of print].

Biederman J, Mick E, Faraone SV, Spencer T, Wilens TE, Wozniak J (2000). Pediatric mania: a developmental subtype of bipolar disorder? *Biol Psychiatry* **48**: 458–466.

Birnbaum SB, Yuan P, Bloom A, Davis D, Gobeske K, Sweatt D *et al* (2004). Protein kinase C overactivity impairs prefrontal cortical regulation of working memory. *Science* **306**: 882–884.

Birnbaum SG, Gobeske KT, Auerbach J, Taylor JR, Arnsten AFT (1999). A role for norepinephrine in stress-induced cognitive deficits: alpha-1-adrenoceptor mediation in prefrontal cortex. *Biol Psychiatry* **46**: 1266–1274.

Boonstra AM, Oosterlaan J, Sergeant JA, Buitelaar JK (2005). Executive functioning in adult ADHD: a meta-analytic review. *Psychol Med* **35**: 1097–1108.

Bush G, Valera EM, Seidman LJ (2005). Functional neuroimaging of attention-deficit/hyperactivity disorder: a review and suggested future directions. *Biol Psychiatry* **57**: 1273–1284.

Bymaster FP, Katner JS, Nelson DL, Hemrick-Luecke SK, Threlkeld PG, Heiligenstein JH *et al* (2002). Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* **27**: 699–711.

Cai JX, Ma Y, Xu L, Hu X (1993). Reserpine impairs spatial working memory performance in monkeys: reversal by the alpha-2 adrenergic agonist clonidine. *Brain Res* **614**: 191–196.

Casey BJ, Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Schubert AB *et al* (1997). Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolescent Psychiatry* **36**: 374–383.

Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP *et al* (1996). Quantitative brain magnetic resonance imaging in attention deficit/hyperactivity disorder. *Arch Gen Psychiatry* **53**: 607–616.

Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS *et al* (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA* **288**: 1740–1748.

Dias R, Roberts A, Robbins TW (1996). Dissociation in prefrontal cortex of affective and attentional shifts. *Nature* **380**: 69–72.

Durston S, Fossella JA, Casey BJ, Hulshoff Pol HE, Galvan A, Schnack HG *et al* (2005). Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. *Mol Psychiatry* **10**: 678–685.

Elliott R, Sahakian BJ, Matthews K, Bannerjea A, Rimmer J, Robbins TW (1997). Effects of methylphenidate on spatial working memory and planning in healthy young adults. *Psychopharmacology* **131**: 196–206.

Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA *et al* (2005). Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry* **57**: 1313–1323.

Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J (1997). Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. *Neurology* **48**: 589–601.

Franowicz JCS, Arnsten AFT (1998). The alpha-2A noradrenergic agonist, guanfacine, improves delayed response performance in young adult rhesus monkeys. *Psychopharmacology* **136**: 8–14.

Franowicz JS, Kessler L, Dailey-Borja CM, Kobilka BK, Limbird LE, Arnsten AFT (2002). Mutation of the alpha2A-adrenoceptor impairs working memory performance and annuls cognitive enhancement by guanfacine. *J Neurosci* **22**: 8771–8777.

French GM (1959). Locomotor effects of regional ablation of frontal cortex in rhesus monkeys. *J Comp Physiol Psychol* **52**: 18–24.

Funahashi S, Chafee MV, Goldman-Rakic PS (1993). Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature* **365**: 753–756.

Giedd JN, Blumenthal J, Molloy E, Castellanos FX (2001). Brain imaging of attention deficit/hyperactivity disorder. *Ann NY Acad Sci* **931**: 33–49.

Godefroy O, Rousseaux M (1996). Divided and focused attention in patients with lesion of the prefrontal cortex. *Brain Cognition* **30**: 155–174.

Goldman-Rakic PS (1995). Cellular basis of working memory. *Neuron* **14**: 477–485.

Granon S, Passetti F, Thomas KL, Dalley JW, Everitt BJ, Robbins TW (2000). Enhanced and impaired attentional performance after infusion of D1 dopaminergic receptor agents into rat prefrontal cortex. *J Neurosci* **20**: 1208–1215.

Gross CG (1963). Locomotor activity following lateral frontal lesions in rhesus monkeys. *J Comp Physiol Psychol* **56**: 232–236.

Gross CG, Weiskrantz L (1964). Some changes in behavior produced by lateral frontal lesions in the macaque. In: Warren JM, Akert K (eds). *The Frontal Granular Cortex and Behavior*. McGraw-Hill Book Co: New York. pp 74–101.

Hechtman L, Greenfield B (2003). Long-term use of stimulants in children with attention deficit hyperactivity disorder: safety, efficacy, and long-term outcome. *Paediatr Drugs* **5**: 787–794.

Hill DE, Yeo RA, Campbell RA, Hart B, Vigil J, Brooks W (2003). Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. *Neuropsychology* **17**: 496–506.

Itami S, Uno H (2002). Orbitofrontal cortex dysfunction in attention-deficit hyperactivity disorder revealed by reversal and extinction tasks. *NeuroReport* **13**: 2453–2457.

Jakala P, Riekkinen M, Sirvio J, Koivisto E, Kejonen K, Vanhanen M *et al* (1999). Guanfacine, but not clonidine, improves planning and working memory performance in humans. *Neuropsychopharmacology* **20**: 460–470.

Kates WR, Frederikse M, Mostofsky SH, Folley BS, Cooper K, Mazur-Hopkins P *et al* (2002). MRI parcellation of the frontal lobe in boys with attention deficit hyperactivity disorder or Tourette syndrome. *Psychiatry Res* **116**: 63–81.

Katusic SK, Barbaresi WJ, Colligan RC, Weaver AL, Leibson CL, Jacobsen SJ (2005). Psychostimulant treatment and risk for substance abuse among young adults with a history of attention-deficit/hyperactivity disorder: a population-based, birth cohort study. *J Child Adolesc Psychopharmacol* **15**: 764–776.

Kennard MA, Spencer S, Fountain G (1941). Hyperactivity in monkeys following lesions of the frontal lobes. *J Neurophysiol* **4**: 512–524.

Kimberg DY, D'Esposito M, Farah MJ (1997). Effects of bromocriptine on human subjects depend on working memory capacity. *NeuroReport* **8**: 3581–3585.

Knight RT, Scabini D, Woods DL (1989). Prefrontal cortex gating of auditory transmission in humans. *Brain Res* **504**: 338–342.

Konishi S, Nakajima K, Uchida I, Kikyo H, Kameyama M, Miyashita Y (1999). Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain* **122**: 981–991.

Kuczenski R, Segal DS (1997). Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. *J Neurochem* **68**: 2032–2037.

Kuczenski R, Segal DS (2002). Exposure of adolescent rats to oral methylphenidate: preferential effects on extracellular norepinephrine and absence of sensitization and cross-sensitization to methamphetamine. *J Neurosci* **22**: 7264–7271.

Kuczenski R, Segal DS (2005). Stimulant actions in rodents: implications for attention-deficit/hyperactivity disorder treatment and potential substance abuse. *Biol Psychiatry* **57**: 1391–1396.

Larsen JK, Divac I (1978). Selective ablations within the prefrontal cortex of the rat and performance of delayed alternation. *Physiol Psychol* **6**: 15–17.

Li B-M, Mao Z-M, Wang M, Mei Z-T (1999). Alpha-2 adrenergic modulation of prefrontal cortical neuronal activity related to spatial working memory in monkeys. *Neuropsychopharmacology* **21**: 601–610.

Li B-M, Mei Z-T (1994). Delayed response deficit induced by local injection of the alpha-2 adrenergic antagonist yohimbine into the dorsolateral prefrontal cortex in young adult monkeys. *Behav Neural Biol* **62**: 134–139.

Ma C-L, Arnsten AFT, Li B-M (2005). Locomotor hyperactivity induced by blockade of prefrontal cortical alpha-2-adrenoceptors in monkeys. *Biol Psychiatry* **57**: 192–195.

Ma C-L, Qi X-L, Peng J-Y, Li B-M (2003). Selective deficit in no-go performance induced by blockade of prefrontal cortical alpha2-adrenoceptors in monkeys. *NeuroReport* **14**: 1013–1016.

Malmo RB (1942). Interference factors in delayed response in monkeys after removal of frontal lobes. *Neurophysics* **5**: 295–308.

Manes F, Sahakian BJ, Clark L, Rogers R, Antoun N, Aitken M *et al* (2002). Decision-making processes following damage to the prefrontal cortex. *Brain* **125**: 624–639.

Manji HK, Lenox RH (1999). Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic-depressive illness. *Biol Psychiatry* **46**: 1328–1351.

Mao Z-M, Arnsten AFT, Li B-M (1999). Local infusion of alpha-1 adrenergic agonist into the prefrontal cortex impairs spatial working memory performance in monkeys. *Biol Psychiatry* **46**: 1259–1265.

McLean A, Dowson J, Toone B, Young S, Bazanis E, Robbins TW *et al* (2004). Characteristic neurocognitive profile associated with adult attention-deficit/hyperactivity disorder. *Psychol Med* **34**: 681–692.

Mehta MA, Goodyer IM, Sahakian BJ (2004). Methylphenidate improves working memory and set-shifting in AD/HD: relationships to baseline memory capacity. *J Child Psychol Psychiatry* **45**: 293–305.

Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD, Robbins TW (2000). Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. *J Neurosci* **20**: RC651–RC656.

Miller EK, Li L, Desimone R (1993). Activity of neurons in anterior inferior temporal cortex during a short-term memory task. *J Neurosci* **13**: 1460–1478.

Morita M, Nakahara K, Hayashi T (2004). A rapid presentation event-related functional magnetic resonance imaging study of response inhibition in macaque monkeys. *Neurosci Lett* **356**: 203–206.

Muir JL, Everitt BJ, Robbins TW (1996). The cerebral cortex of the rat and visual attentional function: dissociable effects of mediofrontal, cingulate, anterior dorsolateral, and parietal cortex lesions on a five-choice serial reaction time task. *Cerebral Cortex* **6**: 470–481.

Muller U, Clark L, Lam ML, Moore RM, Murphy CL, Richmond NK *et al* (2005). Lack of effects of guanfacine on executive and memory functions in healthy male volunteers. *Psychopharmacology* **182**: 205–213.

Muller U, von Cramon DY, Pollmann S (1998). D1- *versus* D2-receptor modulation of visuospatial working memory in humans. *J Neurosci* **18**: 2720–2728.

Park L, Nigg JT, Waldman ID, Nummy KA, Huang-Pollock C, Rappley M *et al* (2005). Association and linkage of alpha-2A adrenergic receptor gene polymorphisms with childhood ADHD. *Mol Psychiatry* **10**: 572–580.

Petrides M (1986). The effect of periarcuate lesions in the monkey on the performance of symmetrically and asymmetrically reinforced visual and auditory go, no-go tasks. *J Neurosci* **6**: 2054–2063.

Ramos B, Colgan L, Nou E, Ovadia S, Wilson SR, Arnsten AFT (2005). The beta-1 adrenergic antagonist, betaxolol, improves working memory performance in rats and monkeys. *Biol Psychiatry* **58**: 894–900.

Ramos B, Stark D, Verduzco L, Arnsten AFT (2006). Guanfacine improves prefrontal cortical reulation of behavior through inhibition of cAMP/PKA signaling. (in submission).

Rapoport JL, Inoff-Germain G (2002). Responses to methylphenidate in attention-deficit/hyperactivity disorder and normal children: update 2002. *J Atten Disord* **6**: S57–S60.

Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson C *et al* (2003). Prazosin reduces nightmares and other PTSD symptoms in combat veterans: a placebo-controlled study. *Am J Psychiatry* **160**: 371–373.

Roman T, Schmitz M, Polanczyk GV, Eizirik M, Rohde LA, Hutz MH (2003). Is the alpha-2A adrenergic receptor gene (ADRA2A) associated with attention-deficit/hyperactivity disorder? *Am J Med Genet B Neuropsychiat Genet* **120**: 116–120.

Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SCR, Simmons A *et al* (1999). Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. *Am J Psychiatry* **156**: 891–896.

Rubia K, Smith AB, Brammer MJ, Taylor E (2003). Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage* **20**: 351–358.

Sawaguchi T (1998). Attenuation of delay-period activity of monkey prefrontal cortical neurons by an alpha-2 adrenergic antagonist during an oculomotor delayed-response task. *J Neurophysiol* **80**: 2200–2205.

Schoechlin C, Engel RR (2005). Neuropsychological performance in adult attention-deficit hyperactivity disorder: meta-analysis of empirical data. *Arch Clin Neuropsychol* **20**: 727–744.

Segal DS, Kuczenski R (1987). Individual differences in responsiveness to single and repeated amphetamine administration: behavioral characteristics and neurochemical correlates. *J Pharmacol Exp Ther* **242**: 917–926.

Segal DS, Kuczenski R (1997a). Repeated binge exposures to amphetamine and methamphetamine: behavioral and neurochemical characterization. *J Pharmacol Exp Ther* **282**: 561–573.

Segal DS, Kuczenski R (1997b). An escalating dose 'binge' model of amphetamine psychosis: behavioral and neurochemical characteristics. *J Neurosci* **17**: 2551–2566.

Segal DS, Kuczenski R (1999). Escalating dose-binge treatment with methylphenidate: role of serotonin in the emergent behavioral profile. *J Pharmacol Exp Ther* **291**: 19–30.

Seidman LJ, Valera EM, Makris N (2005). Structural brain imaging of attention-deficit/hyperactivity disorder. *Biol Psychiatry* **57**: 1263–1272.

Sowell ER, Thompson PM, Welcome SE, Henkenius AL, Toga AW, Peterson BS (2003). Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. *Lancet* **362**: 1699–1707.

Steere JC, Arnsten AFT (1997). The alpha-2A noradrenergic agonist, guanfacine, improves visual object discrimination reversal performance in rhesus monkeys. *Behav Neurosci* **111**: 1–9.

Tanila H, Rama P, Carlson S (1996). The effects of prefrontal intracortical microinjections of an alpha-2 agonist, alpha-2 antagonist and lidocaine on the delayed alternation performance of aged rats. *Brain Res Bull* **40**: 117–119.

Thompson-Schill SL, Jonides J, Marshuetz C, Smith EE, D'Esposito M, Kan IP *et al* (2002). Effects of frontal lobe damage on interference effects in working memory. *Cogn Affect Behav Neurosci* **2**: 109–120.

Turner DC, Blackwell AD, Dowson JH, McLean A, Sahakian BJ (2005). Neurocognitive effects of methylphenidate in adult attention-deficit/hyperactivity disorder. *Psychopharmacology* **178**: 286–295.

van Mourik R, Oosterlaan J, Sergeant JA (2005). The Stroop revisited: a meta-analysis of interference control in AD/HD. *J Child Psychol Psychiatry* **46**: 150–165.

Van Tol HHM, Bunzow JR, Guan H-C, Sunahara RK, Seeman P, Niznik HB *et al* (1991). Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. *Nature* **350**: 610–614.

Vijayraghavan S, Wang M, Birnbaum SG, Bruce CJ, Williams GV, Arnsten AFT (2006). Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nat Neurosci* (in submission).

Volkow ND, Fowler JS, Wang GJ, Ding YS, Gatley SJ (2002a). Role of dopamine in the therapeutic and reinforcing effects of methylphenidate in humans: results from imaging studies. *Eur Neuropsychopharmacol* **12**: 557–566.

Volkow ND, Wang GJ, Fowler JS, Thanos PP, Logan J, Gatley SJ *et al* (2002b). Brain DA D2 receptors predict reinforcing effects of stimulants in humans: replication study. *Synapse* **46**: 79–82.

Wallis JD, Anderson KC, Miller EK (2001). Single neurons in prefrontal cortex encode abstract rules. *Nature* **411**: 953–956.

Wang M, Ramos B, Paspalas C, Duque A, Vijayraghavan S, Brennan A *et al* (2006). 2A-Adrenoceptor stimulation enhances working memory by closing Ih channels and strengthening functional connectivity of prefrontal cortical microcircuitry (in preparation).

Wang M, Tang ZX, Li BM (2004). Enhanced visuomotor associative learning following stimulation of alpha 2A-adrenoceptors in the ventral prefrontal cortex in monkeys. *Brain Res* **1024**: 176–182.

Watanabe M (1986). Prefrontal unit activity during delayed conditional go/no-go discrimination in the monkey I. Relation to the stimulus. *Brain Res Rev* **382**: 1–14.

Wilkins AJ, Shallice T, McCarthy R (1987). Frontal lesions and sustained attention. *Neuropsychologia* **25**: 359–365.

Williams GV, Goldman-Rakic PS (1995). Blockade of dopamine D1 receptors enhances memory fields of prefrontal neurons in primate cerebral cortex. *Nature* **376**: 572–575.

Woods DL, Knight RT (1986). Electrophysiological evidence of increased distractability after dorsolateral prefrontal lesions. *Neurology* **36**: 212–216.

Yamaguchi S, Knight RT (1990). Gating of somatosensory input by human prefrontal cortex. *Brain Res* **521**: 281–288.

Yeo RA, Hill D, Campbell R, Vigil J, Brooks WM (2000). Developmental instability and working memory ability in children: a magnetic resonance spectroscopy investigation. *Dev Neuropsychol* **17**: 143–159.

Zahrt J, Taylor JR, Mathew RG, Arnsten AFT (1997). Supranormal stimulation of dopamine D1 receptors in the rodent prefrontal cortex impairs spatial working memory performance. *J Neurosci* **17**: 8528–8535.