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The Cognition-Enhancing Effects of Psychostimulants Involve Direct Action in the Prefrontal Cortex

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Abstract

Psychostimulants are highly effective in the treatment of attention deficit hyperactivity disorder (ADHD). The clinical efficacy of these drugs is strongly linked to their ability to improve cognition dependent on the prefrontal cortex (PFC) and extended frontostriatal circuit. The procognitive actions of psychostimulants are only associated with low doses. Surprisingly, despite nearly 80 years of clinical use, the neurobiology of the procognitive actions of psychostimulants has only recently been systematically investigated. Findings from this research unambiguously demonstrate that the cognition-enhancing effects of psychostimulants involve the preferential elevation of catecholamines in the PFC and the subsequent activation of norepinephrine α 2- and dopamine D1 receptors. In contrast, while the striatum is a critical participant in 'PFC-dependent' cognition, where examined, psychostimulant action within the striatum is not sufficient to enhance cognition. At doses that moderately exceed the clinical range, psychostimulants appear to improve PFC-dependent attentional processes at the expense of other PFC-dependent processes (e.g. working memory, response inhibition). This differential modulation of PFC-dependent processes across dose appears to be associated with the differential involvement of noradrenergic α 2 vs. α 1 receptors. Collectively, this evidence indicates that at low, clinically-relevant doses, psychostimulants are devoid of the behavioral and neurochemical actions that define this class of drugs and instead act largely as cognitive enhancers (improving PFC-dependent function). This information has potentially important clinical implications as well as relevance for public health policy regarding the widespread clinical use of psychostimulants and for the development of novel pharmacological treatments for ADHD and other conditions associated with PFC dysregulation.

Keywords

ADHD; Prefrontal Cortex; Cognition; Norepinephrine; Dopamine; Stimulants

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Psychostimulants elicit potent arousing, behaviorally-activating and reinforcing actions that are associated with significant potential for abuse (1–6). Nonetheless, these drugs are highly effective in treating hyperactivity, impulsivity and inattention associated with attention deficit hyperactivity disorder (ADHD; 7–10). Given these apparently contradictory actions, it was initially proposed that psychostimulants acted ‘paradoxically’ in individuals with ADHD: calming, rather than activating behavior. This ‘paradoxical hypothesis’ strongly influenced clinical and basic science research into the neurobiology and pharmacology of ADHD.

A major breakthrough in our understanding of psychostimulant action was the demonstration in 1980 that the cognition-enhancing and behavioral-calming actions of psychostimulants are not unique to ADHD, with similar effects seen in healthy human subjects (11). This and subsequent studies unambiguously demonstrate that when used at low and clinically-relevant doses, psychostimulants improve prefrontal cortex (PFC)-dependent behavioral/cognitive processes in human subjects with and without ADHD (11–15). This ability of psychostimulants to act as cognitive enhancers drives the recent growth in use of these drugs by the general population to improve academic and work-related performance (16–18). Low-dose psychostimulant improvement in PFC-dependent function is consistent with evidence indicating ADHD involves dysregulation of the PFC and extended frontostriatal circuitry (19–22). Moreover, the procognitive actions of psychostimulants are also observed in ‘normal’ animal subjects (see Figure 1; 5,6,23,24), indicating an animal model of ADHD is not required to study the neural mechanisms underlying the cognition-enhancing/therapeutic effects of psychostimulants. This is an important advantage given there are no animal models known to definitively mimic the neurobiology of ADHD.

Collectively these observations indicate that the neural mechanisms responsible for the therapeutic/cognition-enhancing effects of low-dose psychostimulants cannot be extrapolated from actions of higher doses that exert opposing behavioral and cognitive effects. Over the past 10 years, correlative evidence has suggested the hypothesis that the PFC is a key site in the cognition-enhancing actions of psychostimulants (for review, 25,26). More recent work provides critical, causal evidence for a role of the PFC in the cognition-enhancing effects of psychostimulants. In the following sections we review the collective body of research on the neurobiology of clinically-relevant and procognitive doses of psychostimulants.

Clinically-Relevant Doses of Psychostimulants Elevate Catecholamine Signaling Preferentially in the PFC

The two most commonly used psychostimulants in the treatment of ADHD are methylphenidate (MPH; e.g. Ritalin®) and amphetamine (e.g. Adderall®). At behaviorally-activating doses, these drugs potently increase extracellular levels of norepinephrine (NE) and dopamine (DA) throughout the brain, largely by blocking NE and DA reuptake (27,28). Some psychostimulants, particularly amphetamine, actively stimulate DA efflux through the DA transporter (29). Although amphetamine can also stimulate NE efflux and block

serotonin reuptake, these actions only occur at high and clinically-inappropriate doses (30). In contrast, MPH acts only to block NE and DA reuptake, neither inhibiting serotonin reuptake nor stimulating NE or DA efflux (31).

Early animal studies demonstrated a central role of DA acting in the striatal subregion, the nucleus accumbens (NAcc), in the motor activating and reinforcing effects of higher doses of psychostimulants. Based on this, the early clinical literature emphasized the potential role of NAcc DA in the therapeutic effects of psychostimulants. However, given low, clinically-relevant doses of psychostimulants exert qualitatively different behavioral effects vs. higher, behaviorally-activating doses, the neurobiology of higher doses may not have strong translational relevance. However, in order to study the *clinically-relevant actions* of psychostimulants in animals, it is essential to identify doses that model clinical use. Pharmacokinetic studies identified doses of MPH in animals that elicit plasma concentrations associated with clinical efficacy in humans (~10–40 ng/ml; 23,24,32,33). In rats, clinically-relevant plasma levels are seen following 1.0–3.0 mg/kg MPH given orally and 0.25–1.0 mg/kg MPH administered intraperitoneally (24,32,33). At these doses, MPH is largely devoid of behaviorally-activating or arousing actions (Figure 1; 24,32,33). Moreover, under conditions associated with elevated locomotor activity, these clinically-relevant doses of MPH suppress motor activity, similar to that seen in ADHD (Figure 1; 33). Finally, these doses of MPH improve PFC-dependent cognition (working memory, sustained attention), similar to that seen in humans (Figure 1; 5,24,34). The behavioral/cognitive effects of low and clinically-relevant doses contrast with the motor activating, arousal-promoting, and cognition-impairing actions associated with abuse-related doses of psychostimulants.

Microdialysis studies demonstrate that clinically relevant doses of MPH elicit prominent increases in extracellular NE and DA within the PFC (100–250%; Figure 2). In contrast, substantially smaller effects are observed on DA levels in the NAcc and NE levels in the medial septum, regions associated with psychostimulant-induced motor activation and arousal, respectively (see Figure 2; 24,32,33,35–39). As with the cognitive effects of MPH (6,24), the preferential targeting of PFC catecholamines is not dependent on route of administration, as long as dose is adjusted to yield similar plasma concentrations (24). These doses of MPH increase hippocampal and somatosensory cortical NE levels similar to that seen in the medial septal area (32,33,40), indicating the greater sensitivity of PFC catecholamines reflects a relatively unique aspect of PFC physiology (32,33,40).

The modest actions of low-dose psychostimulants on extracellular catecholamines in subcortical regions associated with motor activation (e.g. accumbens) and arousal (e.g. medial septum) appears to explain why, clinically, psychostimulants are devoid of the prototypical behavioral-activating and arousal-enhancing effects of psychostimulants. Moreover, the fact that low-dose psychostimulants do not increase, and may reduce, drug abuse in ADHD patients (41,42) is consistent with a relatively modest impact of clinically-relevant doses on neural circuitry posited to underlie drug abuse (e.g. NAcc DA; 39).

Potential Mechanisms Underlying the Preferential Sensitivity of PFC Catecholamines

The above-described studies fail to identify the circuit mechanisms associated with the preferential sensitivity of PFC catecholamines. Recent studies using reverse microdialysis demonstrate that when infused in low concentrations, MPH elicits significantly larger increases in extracellular NE and DA in the PFC relative to the medial septum or NAcc (Figure 3; 43). This selectivity for the PFC disappeared with higher concentrations of MPH, similar to that seen with systemic administration (24,31). These observations demonstrate that the enhanced sensitivity of PFC catecholamines reflects, at least in part, an intrinsic property of the PFC.

The mechanisms within the PFC responsible for the increased sensitivity of PFC catecholamines are less clear. However, this may involve the fact that the density of DA transporters (DAT) is sparse in the PFC relative to the striatum (44,45), largely consistent with the reduced density of DA innervation of the PFC relative to the striatum (except see, 45). Moreover, the NE transporter (NET) displays a high affinity for DA and plays a prominent role in PFC DA clearance (46–48). Consistent with this, selective NET inhibitors effective in ADHD increase both NE *and* DA in the PFC without altering striatal DA (Figure 4; 49,50). It is important to note that ‘limited’ DAT density in the PFC (relative to the striatum) does not indicate an absence of functional DAT. Indeed, evidence demonstrates measurable DAT in the medial PFC of rats (44,45). Further, DAT inhibitors are known to elevate extracellular DA levels in this region (43,51,52). Moreover, recent studies demonstrate that when administered at a cognition-enhancing dose, a selective DAT inhibitor increases both extracellular DA *and* NE in the PFC similar to cognition-enhancing doses of psychostimulants (Figure 4; 53). The elevation in NE is posited to result indirectly from drug-induced increases in extracellular DA that compete with NE at the NET, resulting in an increase in extracellular NE.

Collectively, these observations suggest that, in the PFC, NE and DA competitively bind to the NET, with elevations in one transmitter increasing extracellular levels of the other. We posit that this ‘feed-forward’ mechanism contributes to the preferential sensitivity of PFC catecholamines to clinically-relevant doses of psychostimulants. These observations further indicate a close relationship between drug-induced increases in PFC catecholamines and the cognition-enhancing effects of a variety of drug classes, including psychostimulants, NET inhibitors and DAT inhibitors. Specifically, at cognition-enhancing doses all of these drugs elicit moderate elevations in PFC NE and DA of ~100%–250%. In contrast, the effects of these drugs on striatal DA fail to predict their cognition-enhancing effects (a range of 0%–200%; see Figures 2 and 4).

Do the Cognition-Enhancing Effects of Psychostimulants Involve Direct Action Within the PFC?

Though correlative in nature, the neurochemical effects of low-dose psychostimulants reviewed above suggest the hypothesis that the PFC is an important site of action in the

cognition-enhancing properties of these drugs. As in primates, the rat medial PFC is functionally and anatomically heterogeneous, with the dorsomedial PFC (dmPFC; i.e. dorsal anterior cingulate, dorsal prelimbic PFC) associated with flexible cognitive function and the ventromedial PFC (vmPFC; i.e. infralimbic PFC, ventral prelimbic PFC) associated with affective/motivation-related processes (54–57). Recent studies demonstrate that when infused directly into the rat dmPFC, but not vmPFC, MPH facilitates working memory in an inverted-U shaped manner, comparable to systemic administration (Figure 5; 58). Thus, MPH action in the dmPFC is *sufficient* to elicit cognitive improvement.

In contrast to the cognition-enhancing effects of systemically administered clinically-relevant doses of MPH, 4–8-fold higher doses impair working memory (Figure 1). Thus, it is surprising that intra-PFC MPH fails to impair performance, even at concentrations 16-fold and 32-fold higher than a performance-improving concentration (Figure 5; 58). These observations indicate: 1) there is a mechanism within the PFC that drives *the descending limb* of the inverted-U curve (to zero) and 2) the cognition-*impairing* actions of systemically administered psychostimulants involve drug action outside the PFC. A possible candidate system for the cognition-impairing effects of psychostimulants is the hypothalamo-pituitary-adrenal (HPA) axis. Thus, behaviorally-activating doses of psychostimulants activate the HPA axis, elevating circulating glucocorticoids (59) and impair spatial working memory through glucocorticoid receptor activation within the PFC (60). Clinically, it would likely be beneficial to extend the effective dose range of psychostimulants, particularly in patients that do not respond optimally to lower doses. Understanding the neural mechanisms responsible for the cognition-impairing actions of psychostimulants is a translationally important area for future research.

Psychostimulant Action Outside the PFC: Striatum

The above reviewed information unambiguously demonstrates the PFC is a key region for the cognition-enhancing/therapeutic effects of psychostimulants. Nonetheless, the PFC does not act in isolation to support higher cognitive function, representing one node in a broader corticothalamocortical circuit. As part of this, the PFC extends topographically organized projections to the striatum (61,62), a region that plays a prominent role in cognitive processes historically associated with the PFC and dysregulation of frontostriatal circuitry is implicated in ADHD (20). Thus, it is of interest that clinically-relevant doses of MPH increase striatal DA signaling in both humans and animals (24,63,64), albeit to a lesser degree than in the PFC (Figure 2; 24). Furthermore, in humans, cognition-enhancing actions of MPH are associated with changes in DA signaling in both the dorsal and ventral striatum (63,65). However, an important caveat to these imaging studies is that catecholamine signaling in the PFC was not measured. Based on the observations reviewed above (Figure 2) it is likely that a similar, if not stronger, relationship exists between drug-induced changes in cognition and catecholamine signaling in the PFC. Nonetheless, collectively, these observations suggest that psychostimulant-induced increases in DA in the striatum could contribute to the cognition-enhancing effects of psychostimulants.

In rats, the dorsomedial and ventromedial striatum receive direct projections from the dmPFC (57,58,66), a region associated with the cognition-enhancing actions of MPH (see

above). Inactivation or lesion of either the dorsomedial or ventromedial striatum significantly impairs working memory (Figure S1; 58,67). Nonetheless, MPH infusion into either of these striatal regions (Figure S1; 58) has no effect on working memory performance. Thus, unlike the dmPFC, psychostimulant action within the striatum is *not sufficient* for the working memory enhancing effects of MPH. Nonetheless, drug-induced alterations in PFC neuronal function are likely relayed to downstream targets, altering the overall function/activity of frontostriatal-thalamocortical networks. Additionally, it remains possible that although action in the striatum is not sufficient for the procognitive effects of psychostimulants, combined actions in the PFC and striatum may contribute to the maximal therapeutic effects of these drugs.

Clinically-Relevant Doses of Psychostimulants Strengthen Neuronal Signaling in the PFC

A number of imaging studies indicate that cognition-enhancing doses of psychostimulants normalize ADHD-related hypoactivity within frontostriatal circuitry (12,68–70). However, additional evidence indicates that clinically-relevant doses of psychostimulants exert a more complex pattern of actions on frontostriatal activity that are task, region, and hemisphere-dependent (13,71–74). Currently, there exists only limited information regarding the electrophysiological mechanisms that underlie the cognition-enhancing effects of psychostimulants. In unanesthetized animals, cognition-enhancing doses of MPH increase the responsiveness of PFC neurons to afferent signals while exerting minimal effects on spontaneous discharge rates (Figure S2; 6). Similar to that seen neurochemically (see Figure 2), these doses of MPH do not alter neuronal discharge properties of cortical neurons outside the PFC (e.g. somatosensory cortex; 6,40). A similar improvement in PFC signal processing is observed with cognition-enhancing doses of the NET inhibitor, atomoxetine (34).

Combined, these observations suggest that the procognitive/therapeutic effects of psychostimulants involve strengthening of signal processing within the PFC. This action may bias neuronal activation to salient, task-related information while simultaneously reducing responding to less-salient or irrelevant stimuli. Conversely, the cognition-impairing effects of higher, motorically activating doses of psychostimulants likely involve suppression of neuronal signal processing in the PFC. A similar pattern of low and high dose effects on PFC reactivity has been observed in human imaging studies (75–77). Finally, as reviewed above, psychostimulant action in the PFC is expected to alter signal processing broadly within corticostriatal-thalamocortical loops. Further studies will need to explore how MPH alters signal processing within this broader circuitry involving flexible goal-directed behavior.

Receptor Mechanisms in the PFC: NE α_2 and DA D1 receptors

DA and NE exert an inverted-U shaped facilitation of both PFC dependent working memory and PFC neuronal signaling. In the case of DA, these actions involve inverted-U shaped modulatory actions of D1 receptors (78). For NE, high-affinity postsynaptic α_2 receptors improve, whereas lower affinity α_1 receptors, engaged at higher rates of NE release, impair working memory and PFC neuronal signaling (79). Importantly, α_2 -agonists are efficacious

in the treatment of ADHD and improve PFC-dependent function in healthy animal and human subjects (80–84), similar to that seen with psychostimulants and selective NE reuptake blockers used in ADHD. Moreover, similar to MPH, α 2-agonist infusion into the PFC improves working memory performance and PFC neuronal signaling (85).

This evidence suggests that PFC α 2 and/or D1 receptors play a prominent role in the cognition-enhancing actions of low-dose psychostimulants. Consistent with this, the working memory effects of both low-dose MPH and the selective NET inhibitor, atomoxetine, are prevented with systemically administered α 2 and D1 antagonists (Figure S3; 5,34). Moreover, we recently observed that the cognition-enhancing effects of *intra-PFC infusion* of MPH are blocked by co-infusion of α 2 and D1 antagonists (86).

The neurophysiological actions of clinically-relevant doses of psychostimulants described above likely involve catecholamine-dependent modulation of amino acid signaling. Thus, catecholamines exert receptor-dependent modulation of excitatory and inhibitory amino acid signaling in a variety of brain regions (87–89), including the PFC (90,91). In the PFC, NMDA-receptor mediated excitatory postsynaptic currents (EPSCs) are potentiated by a cognition-enhancing dose of MPH, an action that involves D1 receptors (89–91). Moreover, at least a subset of catecholamine actions in the PFC is linked to the modulation of hyperpolarization-activated cyclic nucleotide (HCN) channels (92). Of particular relevance to the current discussion, stimulation of cognition-enhancing postsynaptic α 2 receptors in the PFC inhibit HCN channels, enhancing neuronal responsiveness to behaviorally salient signals (92). Thus, this mechanism may contribute to the psychostimulant-induced strengthening of PFC neuronal responding. In contrast, suppressive effects of high dose psychostimulant on evoked discharge of PFC neurons (reduced by ~80%; Figure S2; 6) involve D1-mediated activation of HCN channels and/or α 1-mediated activation of SK channels (92). Additionally, psychostimulant-driven reductions in evoked discharge may involve suppression of glutamatergic signaling, as high doses of MPH (8.0 mg/kg) suppress both NMDA and AMPA-receptor mediated EPSCs (89).

Combined, the available evidence indicates that the procognitive and enhanced neuronal signal processing actions of psychostimulants (and selective NE-reuptake blockers and α 2 agonists) involve moderate increases in NE α 2 and/or DA D1 receptor activation in the PFC. Conversely, the cognition-impairing actions of higher doses of psychostimulants likely involve suppression of signal processing in the PFC via high rates of α 1 and D1 receptor activation.

Differing Dose-Response Curves Across Cognitive Tasks Reflect Differing Noradrenergic Receptor Action

In 1977 Sprague and Sleator reported that in ADHD children, MPH elicited a narrow inverted-U shaped facilitation of performance in a ‘cognition/learning’ task, while classroom behavior was improved across a wider dose range (93). However, subsequent studies generally failed to observe differential sensitivity to MPH dose across a range of cognitive tasks vs. overt behavior in ADHD patients (94–96). Importantly, Sprague and Sleator used a memory task that involved short delays (seconds), typical of PFC-dependent working

memory tasks, while subsequent studies examined other forms of cognition (93,94). MPH was also observed to produce a narrow inverted-U shaped improvement in a PFC-dependent test of response inhibition in ADHD patients while eliciting a generally linear dose-dependent improvement in behavioral/motor activity (96).

These observations could suggest that psychostimulants exert differential dose-dependent effects on PFC-dependent vs. PFC-independent processes. However, when the dose-dependent actions of MPH were compared across working memory and sustained attention tasks, two PFC-dependent tasks (Figure S2; 97), a narrower, left-shifted inverted-U curve was observed for working memory vs. sustained attention (Figure 6; 98). A similar shift in dose response curves across these tasks occurs with MPH infusion directly into the dmPFC (99). Prior studies have suggested that PFC NE may differentially regulate flexible vs. focused attention (100,101). Sustained attention requires little cognitive flexibility, relative to working memory. However, when examined in a PFC-dependent attentional set shifting task typically used to measure flexible attention (102,103), MPH elicited dose-dependent improvements in performance identical to sustained attention (Figure 6; 98). Collectively, these observations indicate that differing PFC-dependent cognitive processes display differing dose sensitivity to MPH that are not predicted by the degree to which they are associated with cognitive flexibility.

As reviewed above, noradrenergic $\alpha 2$ -receptors improve, while $\alpha 1$ -receptors impair, working memory (104). In contrast, $\alpha 1$ -receptors improve attentional set shifting while $\alpha 2$ -receptors have little impact in this task (100). These observations suggest the hypothesis that the narrow vs. broad inverted-U shaped actions of psychostimulants described above involve differential activation of $\alpha 2$ - vs. $\alpha 1$ -receptors, respectively. Consistent with this, MPH-induced improvement in working memory is dependent on $\alpha 2$ receptors (see above; 104) while MPH-induced improvement in sustained attention is dependent on $\alpha 1$ receptors (98).

Implications for Divergent Dose-Response Curves Across PFC-Dependent Processes

Preclinically, the differential dose sensitivity of PFC-dependent tasks to psychostimulants suggests that not all PFC-dependent tasks are well suited for ADHD-focused drug discovery programs. Extensive evidence demonstrates that the pharmacology of working memory mirrors the pharmacology of ADHD: all approved ADHD-related drugs, including $\alpha 2$ agonists (105), low-dose psychostimulants (5,25) and selective NE reuptake blockers (e.g. atomoxetine; 34) improve working memory. For psychostimulants, their beneficial effects on working memory only occur across a narrow range of doses that produce clinically-relevant plasma concentrations (32,33,37,105,106). Thus, delayed response tests of working memory are a well-suited preclinical tool for identifying potentially efficacious compounds for use in ADHD and possibly other clinical conditions associated with PFC dysfunction.

In contrast, in sustained attention, attentional set shifting, and 5-choice serial reaction time tests, MPH exerts maximal beneficial actions at higher, behaviorally-activating and impulsivity-promoting doses that result in blood concentrations that exceed the clinically-relevant range (Figure 1; 33,37,107,108). Moreover, limited observations indicate that $\alpha 2$ -

agonists lack beneficial effects on attentional set shifting (100) as well as sustained attention (unpublished observations, JL Berkowitz, BD Waterhouse, JS Shumsky). Thus, the potential utility of these tests in an ADHD-focused preclinical program is less clear.

Clinically, as suggested by Sprague and Sleator (93) and Tannock and colleagues (96), differential actions of psychostimulants across cognitive processes raise the question of whether doses that are optimal for controlling classroom behavior impair, or no longer improve, cognitive/behavioral processes important for other functional domains. For example, largely anecdotal evidence suggests that cognitive-constriction or over-focusing can be a side effect of psychostimulant treatment (96). This action may be related to the ability of higher doses of MPH to improve attentional processes while impairing certain forms of cognitive flexibility evinced in tests of working memory and response inhibition (96,98,107). If so, the results reviewed above could suggest the use of $\alpha 1$ -antagonists as an adjunct treatment for ADHD. Given $\alpha 1$ receptors in the PFC are necessary for the motor-activating and reinforcing effects of psychostimulants, $\alpha 1$ antagonists may also lessen certain adverse actions of psychostimulants, including abuse liability. Further studies are needed to better understand the degree to which the dose-dependent actions of psychostimulants across PFC-dependent processes relate to clinical, social, and academic outcomes and role of $\alpha 1$ -receptors in these actions.

Summary and Implications

Low-dose psychostimulants are the first-line treatment for ADHD. At clinically-relevant doses these drugs improve frontostriatal cognitive function in ADHD patients and healthy individuals. The procognitive and behavioral calming actions of psychostimulants are in stark contrast to the behaviorally-activating and cognition-impairing effects seen with higher doses. For much of the history of psychostimulant treatment of ADHD there has been an emphasis on the possible involvement of striatal DA signaling in the therapeutic actions of these drugs. Much of this view was driven by the known neurobiological actions of high and behaviorally-activating doses. However, research over the past ten years has provided significant insight into the neural mechanisms that support the procognitive/therapeutic effects of psychostimulants. In particular, evidence demonstrates that the cognition-enhancing effects of psychostimulants involve an elevation in catecholamine signaling at $\alpha 2$ and D1 receptors preferentially within the PFC. The regionally-selective action of low-dose psychostimulants contrasts with the widespread and uniform actions of higher doses of these drugs. This regional selectivity appears to explain why the clinical use of psychostimulants is not associated with the pronounced arousal, motor activation and abuse liability of higher doses. Evidence also indicates PFC D1 and/or $\alpha 2$ receptors contribute to the the therapeutic actions of the two other FDA approved treatments: selective NE reuptake inhibitors and $\alpha 2$ agonists. Collectively, this indicates a prominent role of PFC catecholamines in the pharmacology of ADHD. In identifying the PFC as a key site of action in the procognitive effects of psychostimulants, this research provides important guiding information for future drug discovery research focused on ADHD. It is hoped further understanding of the neurobiology of the PFC will lead to the identification of novel, non-catecholamine targets for ADHD and other disorders of frontostriatal function.

From a public policy perspective, there has been significant concern about the widespread use of ‘psychostimulants’ in the treatment of ADHD. In the discussion of this issue, the term ‘psychostimulant’ often carries strong negative connotations that are associated with the arousing, activating and abuse liability of these drugs. However, information reviewed above demonstrates that at low and clinically relevant doses, psychostimulants do not exert behavioral and neurochemical actions that define this class of drugs. Instead at these lower doses, these drugs act as ‘cognitive enhancers’ that improve frontostriatal cognitive function while exerting only modest effects in neural circuits associated with psychostimulant-related arousal, motor activation and abuse. While this does not indicate these drugs are devoid of risk, it is important information for policy-based discussions regarding the appropriateness of the clinical use of ‘psychostimulants’. One important caveat to this discussion is that the vast majority of studies on the neural and behavioral actions of clinically relevant doses of psychostimulants in both humans and animals have largely involved males. Extending this work to females is an important area for future research.

Finally, it is now clear that psychostimulants do not exert a uniform facilitation of PFC-dependent processes. In particular, in both animals and humans, lower doses maximally improve performance in tests of working memory whereas maximal suppression of overt behavior and facilitation of attentional processes occurs at higher doses. These differing sensitivities of PFC-dependent processes appear to depend on differential involvement of $\alpha 2$ vs. $\alpha 1$ receptors. These observations raise a number of clinical and preclinical questions regarding the degree to which higher doses that maximally control classroom behavior may exert detrimental actions in other functional domains via activation of $\alpha 1$ receptors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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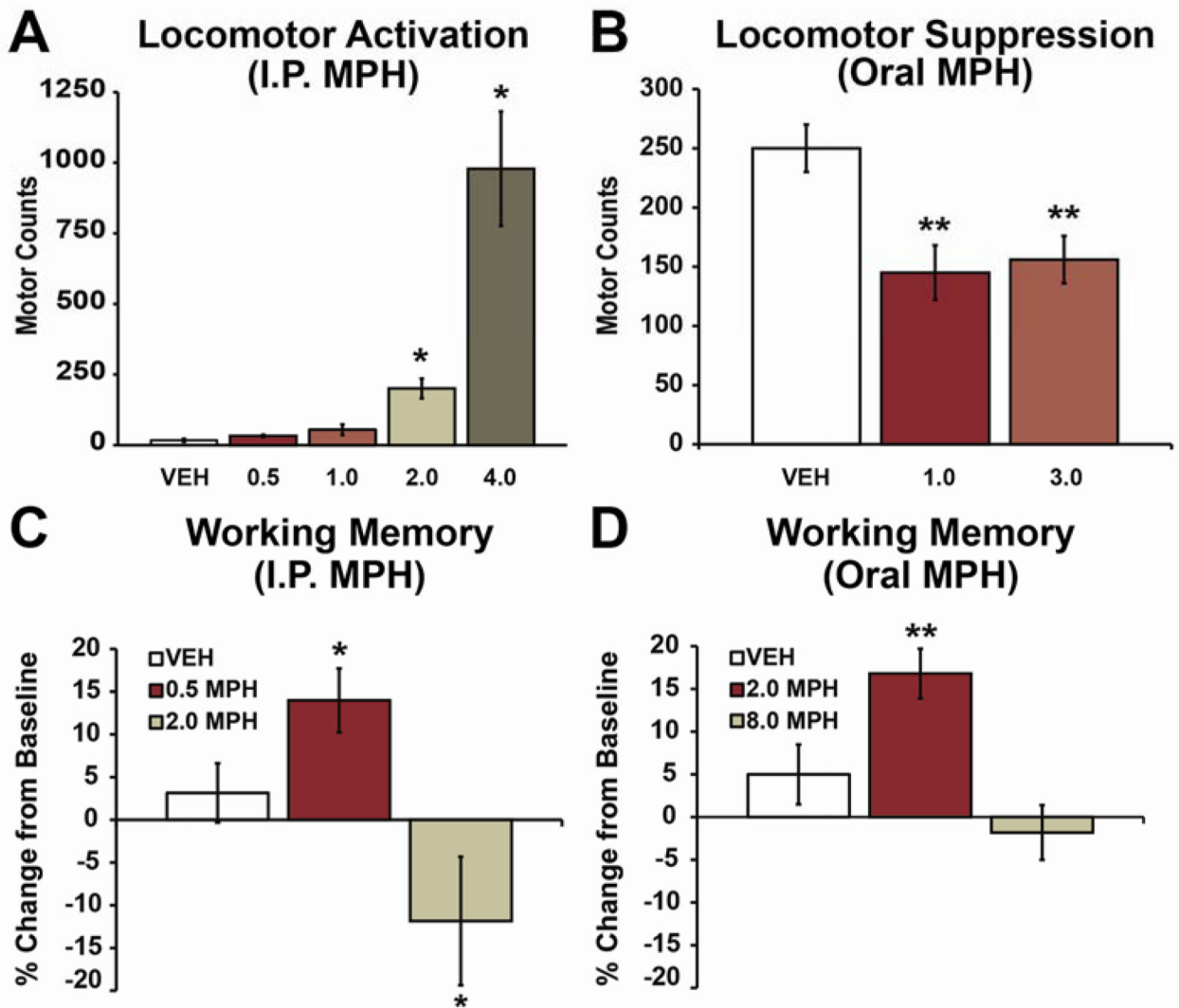


Fig 1. Behavioral-calming and cognition-enhancing actions of clinically-relevant doses of methylphenidate (MPH) in rats

A: Lack of locomotor activation. Bars indicate motor counts (quadrant entries + rears) in the 90-minute period following subcutaneous treatment with vehicle (VEH) or varying doses of MPH (0.5, 1.0, 2.0 and 4.0 mg/kg) during the light (inactive) phase of the circadian cycle in rats (i.e. under low arousal conditions). Doses that produce clinically-relevant plasma concentrations (0.5, 1.0 mg/kg) do not elicit significant locomotor activation. Higher doses elicit dose-dependent increases in locomotor activity. The 4.0 mg/kg dose was peri-threshold for eliciting mild stereotypy. **B: Motoric calming.** When tested under conditions associated with elevated motor activity (during the dark/active phase) clinically relevant doses of oral MPH (1.0, 3.0 mg/kg) suppressed motor activity, similar to that seen in ADHD patients. **C, D: Cognition enhancement.** When administered in doses that elicit clinically relevant plasma concentrations, intraperitoneally (C) or orally (D) administered MPH improves working memory performance as measured by percent change from baseline performance in

a delayed-response test of working memory (T-maze). 4-fold higher doses impair or do not improve performance. All bars indicate mean \pm SEM. * P <0.05, ** P <0.01 compared with vehicle-treated animals. Modified from (6,24,33).

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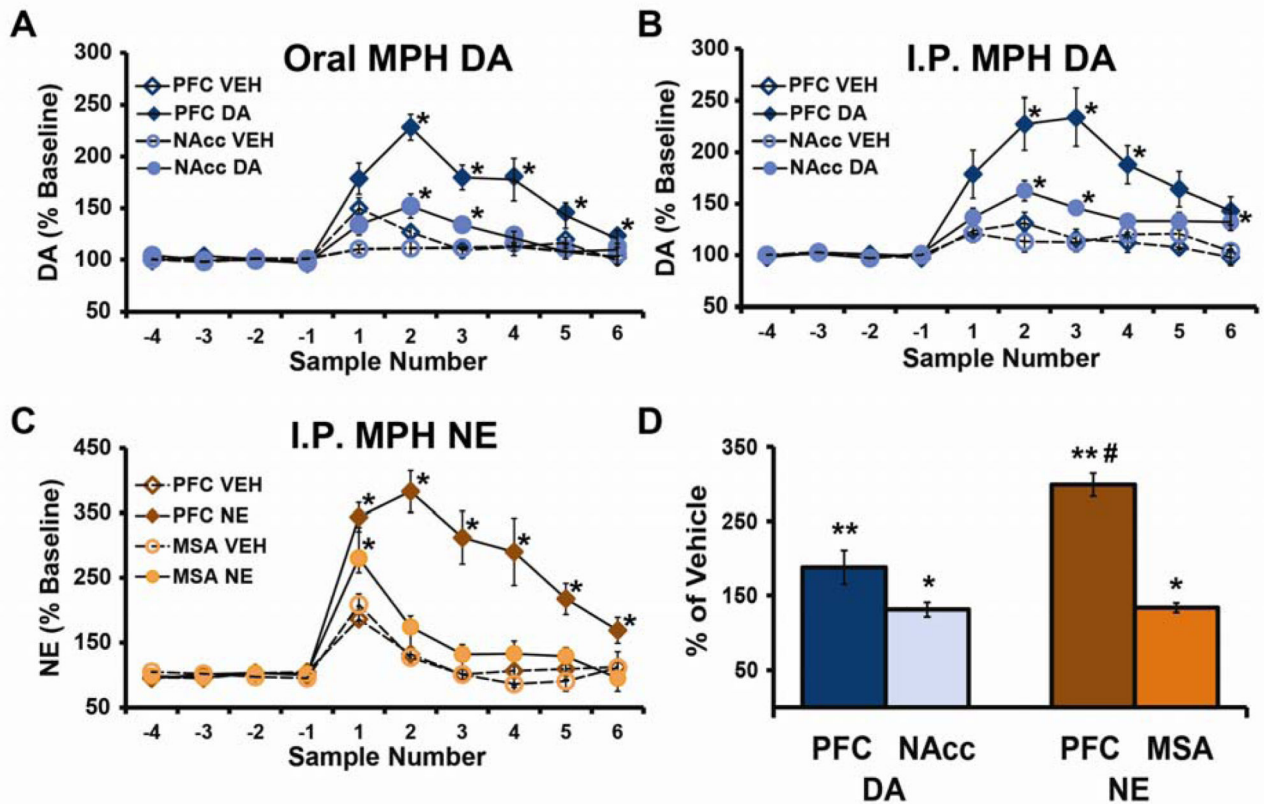


Fig 2. Clinically relevant doses of methylphenidate (MPH) preferentially increase extracellular catecholamines within the prefrontal cortex (PFC)

A–C: Shown are the mean \pm SEM catecholamine levels expressed as a percentage of baseline (\pm SEM) values in 16-minute microdialysis samples collected before (negative numbers) and after (positive numbers) injection of vehicle (VEH) or MPH. Clinically-relevant doses of MPH administered orally (**A**; 2.0 mg/kg) or intraperitoneally (**B**; 0.5 mg/kg) elicited large increases in extracellular dopamine (DA) within the PFC relative that that seen in the nucleus accumbens (NAcc). (**C**) Similarly, for norepinephrine (NE), intraperitoneal administration of 0.5 mg/kg MPH elicited a large increase in extracellular NE in the PFC with little change in the medial septal area (MSA). For both DA and NE, although clinically relevant doses of MPH elicit smaller effects outside the PFC, these effects are nonetheless statistically significant relative to both baseline and vehicle-treated animals. **D:** Bars represent effects of 0.5 mg/kg MPH intraperitoneally expressed as a % change from vehicle-treated animals (mean \pm SEM) for DA and NE over a 30-minute period beginning at 15-minutes post-treatment. When measured in this manner, although MPH increases NE and DA outside the PFC by \sim 30% this effect was not significantly significant. * $P < 0.05$, ** $P < 0.01$ compared with vehicle-treated animals. # $P < 0.01$ relative to PFC DA. From (24).

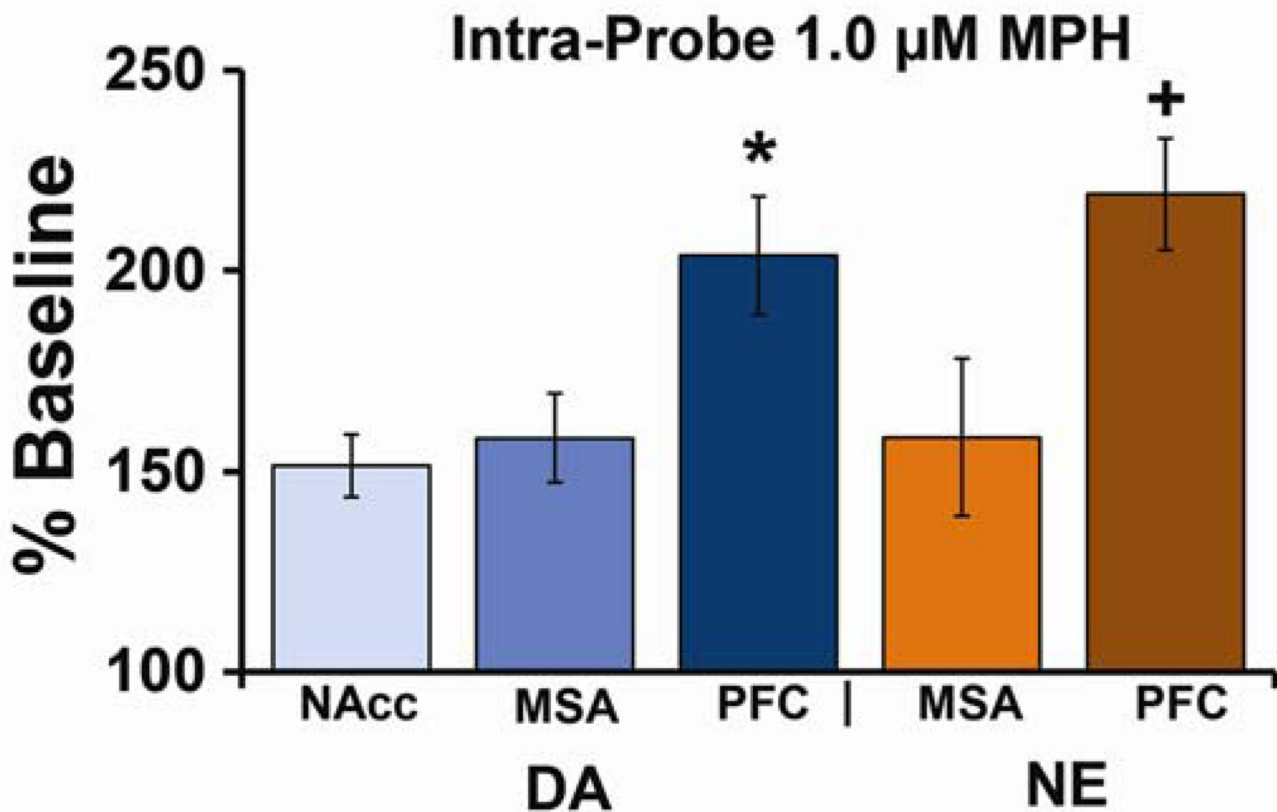


Fig 3. Preferential sensitivity of PFC catecholamines involves local mechanisms

Locally administered methylphenidate (MPH) increases dopamine (DA) and norepinephrine (NE) preferentially within the prefrontal cortex (PFC). Shown are the effects of local application of 1.0 μM MPH on extracellular levels of DA and NE within the PFC, nucleus accumbens (NAcc), and medial septal area (MSA). Data are an average (\pm SEM) of three 30-min samples following MPH application and are expressed as percent above baseline. At this concentration, MPH produced only modest increases in DA and NE levels (\sim 50–60%) in subcortical regions (NAcc and MSA), while eliciting significantly larger increases in DA and NE levels (\sim 100–120%) within the PFC. A similar pattern of effects is seen with systemic administration of clinically-relevant doses of MPH (see Figure 2). * $P < 0.05$ relative to NAcc DA and ⁺ $P < 0.05$ relative to MSA NE. From 43.

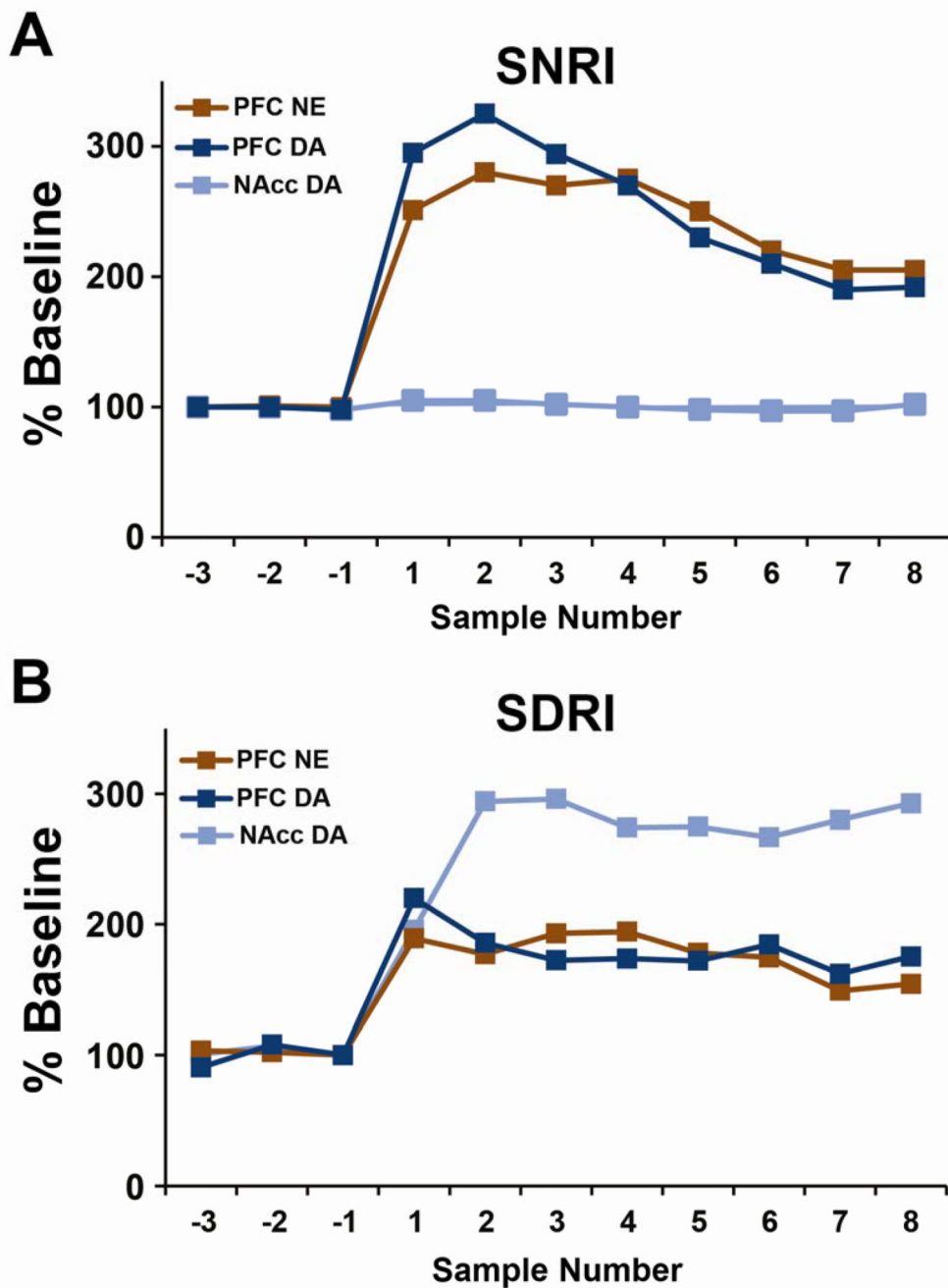


Fig 4. Similar neurochemical actions in the prefrontal cortex (PFC) of a selective norepinephrine reuptake inhibitor (SNRI) and a selective dopamine reuptake inhibitor (SDRI)

Shown are the mean (\pm SEM) change in extracellular norepinephrine (NE) in the PFC and extracellular dopamine (DA) in the PFC and nucleus accumbens (NAcc) expressed as a percent change from baseline. Data are shown for 30-min samples collected prior to (negative numbers) and following (positive numbers) systemic treatment with either (A) the selective NE inhibitor (SNRI), atomoxetine (3 mg/kg) or (B) the selective DA inhibitor (SDRI), AHN 2005 (10 m/kg). At these doses, these drugs exert cognition-enhancing

effects. **A:** The SNRI elicited similar increases in extracellular levels of *both* NE and DA (~150% above baseline) while having no effect on DA within the NAcc. **B:** The SDRI also elicited significant increases in *both* extracellular DA and NE in the PFC that were comparable in magnitude (~100% above baseline). However, in contrast to the SNRI, the SDRI elicited a relatively large increase in extracellular DA levels in the NAcc (~200% above baseline). Panel A adapted from 49. Panel B adapted from 53. Error bars removed for clarity. * $P < 0.05$, compared to vehicle-treated animals.

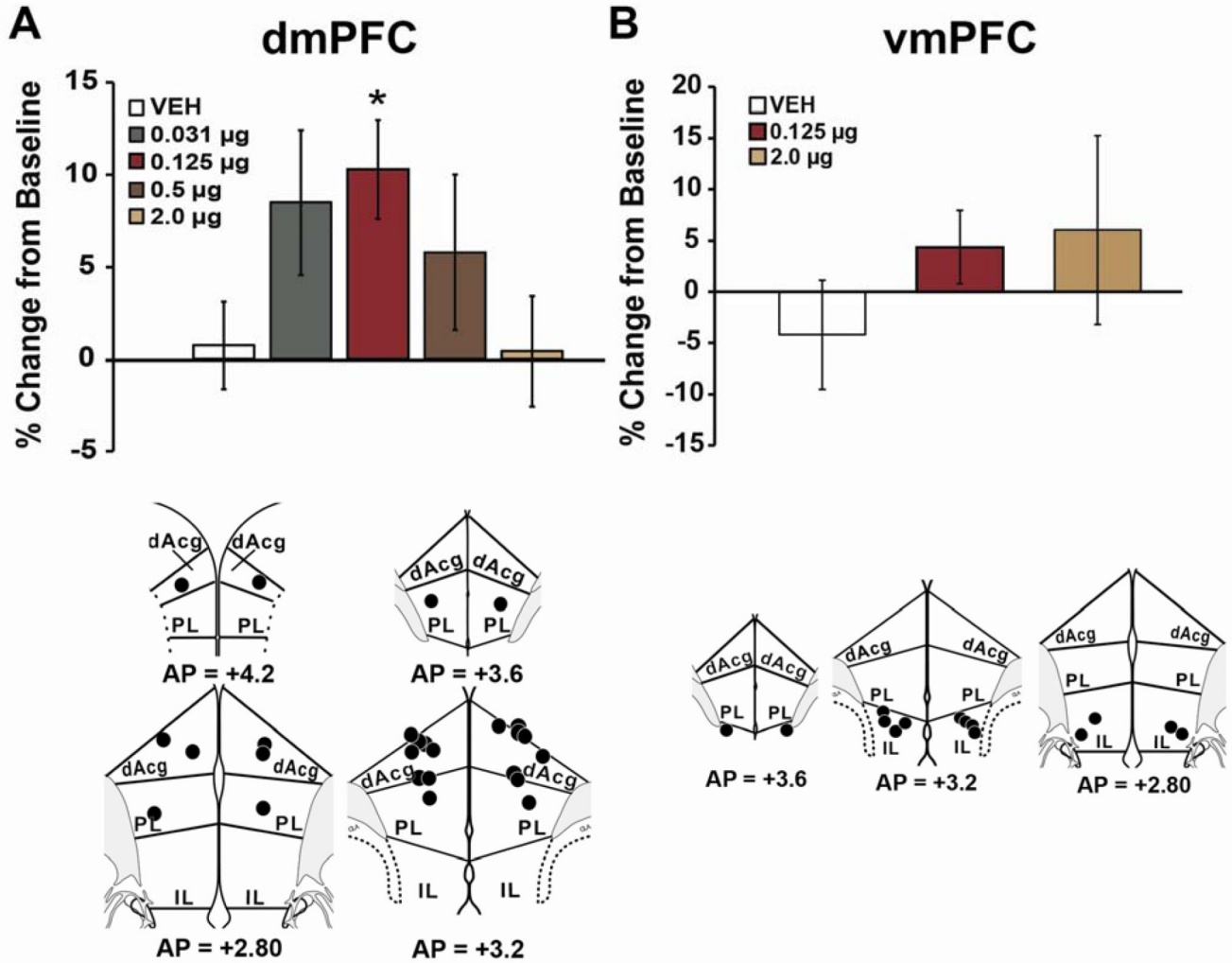


Fig 5. Cognition-enhancing effects of methylphenidate (MPH) involve actions within the prefrontal cortex (PFC)
 Shown are the effects of *intra-PFC* infusion of MPH on performance in a test of working memory expressed as percent change from baseline (mean ± SEM). **Top Panels:** Infusion of methylphenidate into the dmPFC (A) but not vmPFC (B) improved working memory in an inverted-U dose-dependent manner, with 0.125 µg/hemisphere producing maximal improvement. The magnitude of MPH-induced improvement in performance was comparable to that seen with systemic administration of clinically relevant doses (see Figure 1). Note that doses 4 and 16-fold higher than an optimal dose infused into the dmPFC do not impair performance as seen with systemic administration. **Bottom Panels:** Schematic diagram indicating all 0.125 µg infusion sites into the dmPFC (A) and vmPFC (B). Numbers represent anterior-posterior (AP) level (data from [Swanson]). **P*<0.05 relative to vehicle treatment. dAcg, dorsal anterior cingulate; IL, infralimbic; PL, prelimbic.

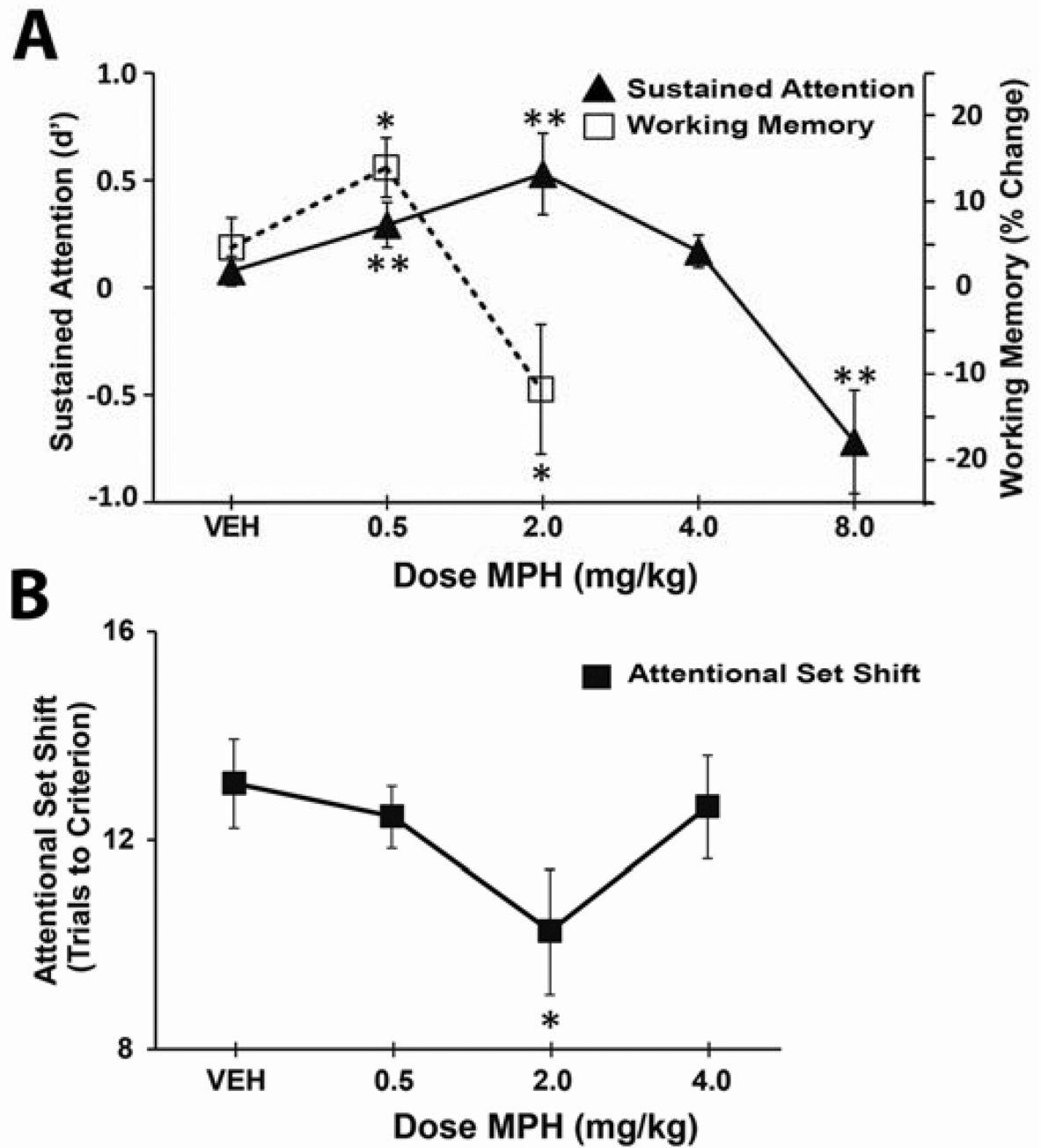


Fig 6. Different PFC-dependent cognitive tasks show differential sensitivity to methylphenidate
 Methylphenidate (MPH) exerts a relatively narrow inverted-U shaped facilitation of working memory performance (A), with maximal improvement seen following 0.5 mg/kg I.P. In contrast, MPH exerts a right shifted dose-dependent facilitation of sustained attention (A) and attentional set shifting (B). Importantly, doses that improve sustained attention and attentional set shifting impair performance in working memory (2.0 mg/kg). ** $P < 0.01$ compared to vehicle treatment. Data from (98).