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Pharmacotherapy for Attention-Deficit/Hyperactivity Disorder: From Cells to Circuits

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Summary Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent disorder of childhood and adulthood, with a considerable impact on public health. There is a substantial pharmacopoeia available for safe and effective treatment of ADHD, and newly available agents diversify the treatment options. With the burgeoning scientific literature addressing the genetic, neurochemical, and neural systems basis for this condition, increasing attention is directed at establishing the neural basis for the efficacy of existing treatments. ADHD remains the only highly prevalent, nondegenerative neuropsychiatric disorder for which effective medications remediate the principal cognitive disturbances in concert with clinical efficacy. Therefore, deeper insight into the neural mechanisms of cognitive remediation may serve to advance treatment development not only in ADHD, but across a wide range of neuropsychiatric disorders in which cognitive dysfunction is a cardinal feature and a strong predictor of clinical outcome. To date, all effective medications for ADHD act on 1 or both of the major catecholamine neurotransmitter systems in the brain. These 2 systems, which arise from subcortical nuclei and use norepinephrine (NE) or dopamine (DA) as transmitters, exert strong modulatory effects on widely distributed cortical–subcortical neural circuits, with important effects on cognition, mood, and behavior, in both health and illness. The present review outlines the actions of ADHD medications from subcellular effects to effects on neural systems and cognition in ADHD patients. This is a very active area of investigation at all phases of the translational cycle, and near-term work is poised to firmly link cellular neuropharmacology to large-scale effects, and point the way toward advances in treatment.

Keywords Attention-deficit/hyperactivity disorder · Psychostimulants · Neuropharmacology · Norepinephrine · Dopamine · Cognition

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Overview of Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset disorder defined by clinically evident disturbances in attention, often with hyperactivity and impulsive behavior, and other important clinical features, including mood and interpersonal disturbances [1]. In the most recent edition of the standard Diagnostic and Statistical Manual, 4th edition (text revision), individuals with this disorder are categorized predominantly by inattentive, hyperactive/impulsive, or combined types. ADHD is the most prevalent psychiatric disorder of childhood, affecting 8 to 12 % of children globally, with important consequences for educational attainment and social relationships in adolescence. Males and children of relatively lower socioeconomic status are relatively at a higher risk for developing ADHD [2]. This is also increasingly recognized as persisting into adulthood, and the estimate of 1-year ADHD prevalence of approximately 4.4 % in the community [3] suggests that it is 1 of the most prevalent adult psychiatric disorders. Adults with persisting ADHD are at increased risk for employment problems, divorce, antisocial behavior, serious accidents (such as motor vehicle accidents), and comorbid mood, anxiety, substance use and personality disorders that confer additional subjective distress and functional impairment.

The neural basis of ADHD and the symptom domains that characterize the disorder have been increasingly studied on the genetic and cellular neural systems and cognitive levels. ADHD is 1 of the most heritable of psychiatric disorders, with estimates of heritability (from twin studies and other studies) consistently ranging at or greater than 0.6 to 0.7. Candidate gene studies have implicated several elements of monoamine neurotransmitter systems, including genes encoding the dopamine D_4 and D_5 receptors, dopamine transporter (DAT), dopamine beta-hydroxylase, which synthesizes norepinephrine (NE) from dopamine (DA), serotonin (5-hydroxytryptamine) transporter, and serotonin receptor (for more detail see Biederman and Faraone [1]). An elevated pooled odds-ratio in ADHD has also been found for the gene encoding synaptosomal-associated protein of 25 KDa (SNAP25), and genome-wide association studies have identified several genes encoding proteins involved in cellular processes, such as cell division, cell adhesion, neuronal migration, spine formation and plasticity, and inflammatory mediators [4, 5]. There are also environmental risk factors identified in ADHD, which include lead exposure, pregnancy complications (including maternal use of alcohol or tobacco during pregnancy and low birth weight), psychosocial adversity, including socioeconomic factors, familial conflict, and parental psychopathology. These observations suggest that ADHD, as with most important psychiatric conditions, arises from the combination of a genetic predisposition and environmental pressures.

Animal models have been developed and evaluated for ADHD. The most well-developed of these is the spontaneously hypertensive rat, which exhibits various behavioral measures of deficits in sustained attention, impulsivity, and hyperactivity, including some laboratory measures analogous to those for which ADHD children show deficits. The spontaneously hypertensive rat also shows alterations in DAT gene expression with a duration of time, DA, NE, and second messenger function, and altered neural/behavioral responses to an amphetamine [6]. Other animal models of ADHD exist, and these can support not only potential treatment development but also the improved specification of cognitive/clinical constructs, such as impulsivity, which does not appear to represent a unitary construct [7].

A number of treatments are available for ADHD that remediate the symptoms and cognitive dysfunction associated with the disorder. Because ADHD is defined as a disorder of cognition, considerable investigation has been directed at the characterization of these cognitive deficits and their neural basis; therefore, measures of cognitive and neural dysfunction also serve as important treatment targets and biomarkers of drug action. Among neuropsychological approaches, executive functions have been most widely studied in ADHD, with consistent deficits found in sustained and control-dependent aspects of attention, working memory, inhibitory processes, set-shifting, and fluency [8–12]. Perspectives derived from a cognitive neuroscience framework have emphasized a fundamental underlying disturbance in cognitive control as the basis for these various deficits [13]. However, cognitive domains that are distinct from (and interacting with) control processes have been increasingly addressed, including social cognition [14]. Particularly important, incentive/reward processes appear to be altered in ADHD and related disorders, and recent models of the pathophysiology of cognition in ADHD now emphasize the disrupted integration of executive control processes with motivational/reward processes, as the basis of ADHD phenomenology [15–17]. Accordingly, the neural systems investigated to evaluate the neural basis of these cognitive processes have focused first on disturbances in dorsal/lateral fronto-striato-thalamic and fronto-cerebellar circuits, with evidence derived from both structural [18–20] and functional [13, 21] neuroimaging; and more recently, the ventral emotion/reward circuitry that includes the amygdala, ventral striatum, and orbitofrontal cortex [17]. Recent meta-analyses of structural neuroimaging studies have found children with ADHD, relative to matched healthy comparison groups, to exhibit smaller volumes of the basal ganglia (including the right putamen, caudate, and globus pallidus) [22, 23], and importantly, increasing age and stimulant treatment were independently associated with relative normalization of these volume deficits. Among adults with ADHD, 1 of these meta-analytic studies found evidence for reduced volume of the anterior cingulate cortex [22]. Overall, as with the genes/environment dichotomy, this emerging "dorsal/ventral" (i.e., fronto-limbic) systems model may be characteristic of serious mental illness in general, with substantial evidence supporting this type of model in mood, anxiety, and personality disorders, substance-related disorders and schizophrenia.

One critical link between these 2 large-scale systems in the brain is the strong modulatory influence of monoamine systems, especially NE and DA. Importantly for ADHD, there is evidence for DA dysfunction in these circuits. Initial findings from positron-emission tomography (PET) studies using selective ligands for the DAT indicated elevated binding in the brains of ADHD patients (e.g., for more detail see Dougherty et al. [24]), and a recent meta-analysis of 9 studies using either single photon emission tomography or PET found an average increase of 14 % in striatal DAT density among ADHD groups compared to healthy comparison groups, with higher density among ADHD patients without medication exposure [25]. In addition, recent studies, including those that control for potentially confounding effects (such as medication exposure) have typically found either no significant change or a reduction in DAT binding (e.g., for more detail see Volkow et al. [26, 27], and for more detail see Swanson et al. [28] for review of findings and

controversies). The specific binding at D_2/D_3 receptors may also be reduced, particularly in subcortical regions, including the striatum and midbrain (nucleus accumbens and hypothalamus) [28], and these regions appear to have impaired dihydroxyphenylalanine (DOPA) utilization as well [29, 30]. Although the evaluation of the central NE system in psychiatric disorders is hampered by the lack of available ligands for norepinephrine transporter (NET) or adrenergic receptors for use in humans, genetic and pharmacological evidence also strongly implicates this system in the pathophysiology of ADHD [31]. The present review summarizes the effects of ADHD medications on the cellular processes, and in ADHD patients, on the neural systems operation and cognition as a potential basis for therapeutic effects. The extensive empirical literature on the behavioral pharmacology *per se* of stimulants is reviewed in detail elsewhere [32, 33]. Interestingly, much of that work, investigating the overt behavioral (activating) effects of stimulants, involves drug doses that are considerably higher than those which confer benefits for cognition [34], and may therefore have more clinical relevance for stimulant use disorders rather than the treatment of ADHD. Clinical considerations in the use of these medications (such as pharmacokinetics, efficacy, adverse events, guidelines for use, and so forth) are also reviewed in numerous publications elsewhere [35–41].

The Cellular Effects of ADHD Medications in Animal Models

With few exceptions, medications with clinical efficacy for ADHD exert potent inhibition of the NET and DAT. The 2 most widely prescribed ADHD medications (methylphenidate [MPH] and amphetamine [AMP]) both have nanomolar range affinity for NET and DAT (for more detail see Madras et al. [42]), and at clinically effective doses, they exert significant occupation of these 2 transporters in humans (determined by PET) [43]. Atomoxetine (ATM) similarly shows potent (and highly selective) NET binding, and other, less commonly used ADHD medications, such as modafinil, desipramine, and buproprion all exert variable but significant levels of inhibition of NET and/or DAT. At higher concentrations, the 5-hydroxytryptamine transporter is inhibited by MPH [44], AMP [45], and ATM [46], although it remains unclear whether this contributes significantly to clinical efficacy in ADHD. One characteristic consequence of NET/DAT inhibition is a significant elevation of extracellular concentrations of NE and DA (measurable by intracranial microdialysis) in widespread regions of the brain [47]. This includes DA elevation in the nucleus accumbens [48–50]. However, each medication (including ATM, desipramine, and modafinil) tends to raise both NE and DA levels most strongly in frontal cortex, probably due to the role of the NET in clearing extracellular DA in this region [51–54]. However, it is unclear whether these neurotransmitter elevations persist with sustained stimulant treatment [55]. Stimulant effects on catecholamine levels in the prefrontal cortex (PFC) also appear to be state-dependent, as MPH effects are greater in animals that are restrained *versus* those able to freely move [56]. Both MPH and AMP lead to increased expression of the immediate early gene c-Fos after acute administration [57], although this affect attenuates (after MPH at least) with repeated administration [58, 59]. In contrast, chronic MPH administration leads to decreased DAT density, particularly in the striatum [60, 61]; this also increases vesicular DA transport by the vesicular monoamine transporter-2 [62].

AMP, however, has a number of additional actions in catecholamine neurons that indirectly affect neurotransmission. AMP competes with DA for transport by the DAT [63], yet it can also enter the cell by diffusion across the plasma membrane [64]; AMP promotes internalization of the DAT [65, 66], and it is sequestered by the vesicular monoamine transporter into vesicles. AMP promotes DA release into the cytoplasm by this mechanism, as well as by acting as a weak base to abolish the vesicular pH gradient [67]. AMP also inhibits monoamine oxidase, which also increases cytoplasmic DA levels [68]. These increases in cytoplasmic DA tend to lead to increased DA release by reversal of DAT transport [69], which may involve channel-like activity of the DAT [70, 71], and it is regulated via phosphorylation by protein kinase C - Beta [72]. However, a study that used both intracranial microdialysis and separately PET with [^{11}C]raclopride found that while AMP increases extracellular DA approximately four-fold higher than MPH, the resulting DA concentrations at D_2/D_3 receptors in the striatum are comparable [73]. AMP can also stimulate NE efflux, probably also by reversing the action of the NET, but this only occurs at considerably higher doses [74]. AMP also increases transmembrane currents that increase DA cell excitability [75], thereby increasing DA release [76, 77], although it may also attenuate exocytotic DA release via terminal D_2 autoreceptor activation, resulting from reverse transport of DA [78]. Finally, AMP also stimulates cAMP formation mediated by the trace amine receptor 1 subtype [79], an effect not seen with MPH [42]. There is recent evidence for interactions between the trace amine receptor 1 and both DA neuron activity [80] and DAT activity [81–83], suggesting that this may represent yet another indirect effect on DA neurotransmission.

Stimulants used in ADHD also exhibit robust effects on the discharge of NE and DA neurons and activity in target neurons in terminal fields such as the PFC. Devilbiss and Berridge [84] have conducted an elegant series of experiments to characterize the effects of low-dose stimulants on the discharge of NE single units in the LC, as the potential

basis of efficacy for PFC-dependent cognition. Low doses of MPH, for instance, are typically defined in the experimental literature as ≤3 mg/kg orally, and aim to achieve bioavailability which compares with that targeted in clinical practice. These investigators found that low-dose MPH modestly suppresses both tonic and phasic LC-NE discharge in rats anesthetized with halothane [84], while preserving the signal-to-noise ratio of phasic LC-NE responses to salient environmental events. Interestingly, they [84] also found that MPH dose dependently increased the inhibitory component of phasic Locus Coeruleus (LC) activity, which has been proposed to form the basis for the attentional blink (transient suppression of attention) observed in performance of attention tasks in which the stimuli occur at very short time intervals [85]. These low doses of MPH, which are known to enhance working memory, also increase the responsivity (both excitatory and inhibitory) of individual PFC neurons and altered neuronal ensemble responses preferentially within the PFC, without affecting spontaneous PFC neuronal discharge rates [86]. MPH increases in cortical excitability depend on α_2 receptor activation [87], and MPH can both amplify long-term plasticity in the hippocampus [88] and facilitate learning-related strengthening of cortical amygdala synapses via postsynaptic increases in currents linked to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [89]. In this latter study, intra-amygdalar MPH enhanced cue-reward associations in a D_1-receptor dependent manner, and suppressed task irrelevant behavior via D_2 receptors. Plasticity effects may also be mediated by structural changes in neurons, as sustained low-dose MPH treatment increases the length and complexity of dendrites in cortical areas, such as the anterior cingulate [90]. MPH and AMP in low doses also modulate the oscillatory pattern of postsynaptic membrane potentials, accelerating oscillatory frequencies of neurons in the substantia nigra (pars compacta) and globus pallidus from approximately 0.03 Hz to 0.10 to 0.20 Hz [91]. ATM (at low doses) also enhances the activity of neurons in the monkey PFC, with enhanced firing for preferred directions during spatial working memory performance, which is dependent on α_2 receptors, and suppression of firing for nonpreferred directions (dependent on D_1 receptor activation) [92]. In contrast, higher doses of MPH suppress evoked responses in PFC neurons [86] and other cortical regions (e.g., the hippocampus) also show attenuated responses to high-dose stimulants [93]. High doses of stimulants and other NET inhibitors (e.g., antidepressants, cocaine) also profoundly suppress LC-NE discharge, as increased NE activates somatodendritic α_2 autoreceptors [94–99] which hyperpolarize LC cells via an inward rectifier K^+ current on LC neurons [100]. There is some evidence, however, that the suppression of firing in LC-NE cells habituates in a span of time with sustained MPH treatment [101].

The Cognitive Effects of Medications in ADHD Patients

There is an extensive empirical literature that evaluates the effects of ADHD medications on cognitive performance in ADHD patients (both children/adolescents and adults) in both experimental and clinical settings. This literature has been comprehensively reviewed in several available articles [28, 33, 102–105], and due to both space considerations and the present emphasis on neural effects of these medications, the literature is briefly summarized here. Pietrzak et al. [102] reviewed 40 placebo-controlled MPH treatment studies of ADHD children reported since 1993, which indicated that 25 (62.5 %) of these studies found significant improvements in 1 or more cognitive processes with MPH treatment. Improvements on saccadic eye movement, planning and cognitive flexibility, attention/vigilance, and inhibitory control were each found in at least 70 % of the original reports that assessed these particular cognitive functions. Long-term memory and working memory/divided attention improvements were noted in 58 % and 50 % of the studies, respectively. Among these reports, higher doses of MPH (when compared in individual studies to lower doses) generally conferred greater improvements on tasks of attention/vigilance, and working and long-term memory, but not in planning/cognitive flexibility, inhibitory control, or motor speed. The authors of the review addressed sources of variability in the set of primary reports, including measurement issues and other methodological concerns, variability within and between patients in medication response, and the complexities of stimulant dose-response relationships in general. The long-term effects of stimulant treatment on cognition in ADHD patients are comparatively more complex and inconsistent. The largest, most rigorous clinical trial of ADHD treatment to date (the Multimodal Treatment study of ADHD) found that stimulant treatment was associated with immediate post-treatment improvements in reading and mathematics achievement test scores, along with clinical improvement [106]. However, the academic gains were lost at the 3-year naturalistic follow-up [107], and importantly, only 32.5 % of the original 579 patients enrolled in the study were still in treatment with stimulants at the 8-year follow-up [108].

Other studies have found that with a period of time, those ADHD patients who remain on stimulant medications may show improved sustained attention and verbal learning [109], and advantages in academic achievement [110]. However, these are relatively smaller studies with self-selected patients in naturalistic longitudinal treatment designs, and therefore the conclusions from these findings must be tempered. Some observers have concluded that while ADHD medications improve short-term academic performance of children with ADHD, they may not have lasting effects on long-term academic achievement, as

measured with standardized achievement tests or rates of grade failure [104]. It is also important to note that there may be a divergence of goals with clinical *versus* cognitive improvement, as the doses used by clinicians to manage the classroom behavior of a child may be suboptimal (or even deleterious) for cognition (for more detail see Gadow [111] and Swanson et al. [112]). An important, relatively recent, innovation in clinical study design that can rigorously address this issue involves the use of analog classroom paradigms as experimental settings to study ADHD treatment effects. These studies permit controlled observation periods for up to 12 to 14 h, and have shown clear dose-dependent benefits for concurrent overt behavior and mathematics performance with 1-to-5-week treatment courses with mixed amphetamine salts [113], methylphenidate [114] or lisdexamphetamine (a d-amphetamine pro-drug that is activated with intestinal and/or hepatic biotransformation) [115]. Among adults with ADHD, a naturalistic study of young adults found that stimulants improve sustained attention and verbal learning [109]; otherwise, the evidence that stimulant treatment improves cognition and/or academic achievement in college students or adults with ADHD is inconsistent (for more detail see Advokat [104]). The potential for ADHD medications to improve cognition and academic achievement in adults with ADHD remains understudied. In particular, whether these medications can positively impact academic outcome (given the high school failure rates in ADHD) or improve cognition among adults who experience persisting ADHD in the face of a ubiquitous age-related cognitive decline throughout the adult years, there pose important questions deserving further rigorous research. The use of novel measures of cognitive task performance is gaining favor as an important methodological innovation in evaluating drug effects on cognition. This includes the use of ex-Gaussian analyses to evaluate reaction times (RTs) that are not normally distributed, and Fourier transformation of RT data to evaluate periodicity in task performance. These types of analyses have shown that MPH may have selective effects on an ex-Gaussian RT component in ADHD patient performance (i.e., RTs found at the tail of a distribution) [116], and that MPH can normalize a baseline group difference in which the ADHD group exhibits a stronger oscillatory pattern of RT [117, 118].

Despite the uncertainty of the long-term effects of stimulant medications on cognitive function and academic achievement, there is promising evidence that these medications have positive effects on brain structure in ADHD. Medicated ADHD patients, compared to well-matched unmedicated ADHD patient groups, have significantly larger (i.e., more normal) volumes of the basal ganglia [119], right anterior cingulate gyrus [120], posterior inferior vermis of the cerebellum [121] and total white matter [122], and increased cortical thickness [123, 124]. In addition, recent meta-analyses support the notion that stimulant treatment is associated with normalization of basal ganglia volumes [22, 23]. Although these studies are cross-sectional in design, they are strongly suggestive that stimulant medication treatment can remediate the gross structural brain abnormalities found in this condition.

Effects of ADHD Medications on Brain Function in ADHD: Neuroimaging Studies

The expanding literature is emerging, which reports the neural effects of these medications in ADHD patients with functional neuroimaging (see Table 1 for summary). MPH increases blood flow in the cerebellum of adults with ADHD [125], and moderate and high doses of MPH alter T2 relaxation time (a functional magnetic resonance imaging proxy for blood flow) in the cerebellum of children with ADHD in a manner associated with the baseline activity levels of the child, with increases in the most active children and opposite effects in the children lacking clinical hyperactivity [126]. MPH effects on striatal [^{11}C]raclopride displacement also correlate with measures of impairment in continuous performance test performance in unmedicated adolescents with ADHD [127]. Functional magnetic resonance imaging studies that evaluate drug effects on regional brain activation while the ADHD patient performs cognitive tasks have primarily included children and adolescents, and have targeted complex cognitive processes, such as those that are highly dependent on PFC-based networks. In studies of MPH effects on attention in these patients, MPH is found to normalize activation in the parietotemporal cortical regions, and frontal connectivity with both the striatum and the cerebellum under high sustained attention demands, and normalized orbitofrontal cortex (OFC) activity in these subjects in response to reward [128]; and remediated the hypoactivity observed in the inferior aspect of the left dorsal striatum during a divided attention condition [129]. In working memory paradigms, stimulant treatment increased activity in 3 brain networks (identified via independent components analysis of task-related activation during Sternberg task performance), strengthened the connectivity in frontoparietal regions, and led to task-related recruitment of brain regions not previously engaged [130], although another study found no effects of MPH treatment on cortical network activity during the Sternberg performance [131]. In addition, 1 study found PFC activation and frontosubcortical connectivity decreased with drug treatment in ADHD adolescents [132], and other studies have found improved in-scanner working memory performance on MPH without associated changes in task-related brain activation, in children [133] and adults with ADHD [134]. Cognitive processes that are more explicitly control-

Table 1 Summary of functional neuroimaging studies investigating pharmacological treatment effects on cognition in attention-deficit/hyperactivity disorder

Study (year)	Imaging method	ADHD Sample	Rx	Cognitive task/ process	ADHD Task performance	ADHD *vs* HC on placebo	ADHD Drug *vs* PLC
Rubia (2009) [143]	fMRI Whole-brain	12 Males (10-15 years old; mean, 13) Comb type; all medication-naive	MPH (0.3 mg/kg orally)	Interval time discrim.	ADHD grp errors ns diff from HC on PLC or MPH	↓ bOFC, caud, ACC; ↑lTemp/Occ Cx, rSupTemp /InfOcc Cx	↑lOFC/ IFG ↓rMFG/ SFG, rMTL/Hpc/lentiform
Prehn-Kristensen (2011)	fMRI Whole-brain	*12 Patients (11-16.5 years old; mean, 13) 10 Comb, 2 Inatt ICD-10, all on MPH	MPH mean 16.7 mg (0.4 mg/kg)	DMTS ± distractors	Rx ↑ acc: ADHD-rx not diff from HC, without distract only	↓ bIFG, lMedFG, lACC, bPreCentG, bCaud, bSupraMargG, bMOG	Within-Grp Rx N/A; ADHD-Rx *vs* HC↓lCaud, lMOG
Posner (2011)	fMRI Whole-brain and Eff Conn (DCM)	15 ADHD (13 males), (13.5±1.2 years old), 13 Comb, 2 Inatt, all on Stim Rx	N/A; counterbal withdrawal	Passive Resp to Sublim Fear Faces; Recog of Supralim Neutral Faces	ADHD acc = HC	↑ act rAmg, rMOG; ↑ Eff Conn rAmg-LatPFC (BA47)	↓ rAmg act (= HC); ↓ rAmg-LatPFC (BA47) Eff Conn (=HC)
Bush (2008)	fMRI, whole-brain and dACC ROI	21 adults (MPH grp: 7/4 M/F, (29.5±5.9 years old), off meds	RCT MPH grp 86.7±21.8 mg/d x 6 wk	Multi-Source Interf Task	No Rx effect on performance	N/A	MPH grp > PLC grp dACC ROI activity (task-related); MPH grp > PLC grp Frontal-Parietal-Caudate-Thal-Cerebellum activity
Epstein (2007)	fMRI Whole-Brain with multiple ROIs	20 youth (7-9 years old), Comb type/parent dyads; 13 for Rx effects (in MTA Study)	MPH 20 mg	Go/No-Go	↑ d-prime youths and adults on Rx	↓ bMFG, rIFG, rIPL, ACC, bCaud	Youths: ↑ lMFG, lIFG, rIPL, ACC, rCaud, lCerebellum; Adults: ↑ lCaud; ↓ lMFG, rIPL
Kobel (2009)	fMRI Whole-Brain	14 Males (10.4±1.3 years old), 9 Comb, 1 Inatt, on MPH≥ 3 mo.	MPH (10-20 mg/d IR, or 36-40 mg/d ER), counterbal withdrawal	N-Back verbal (0, 2, 3-Back)	↓ acc 2-back, 3-back on PLC; no diff on Rx *vs* HC	↓ 2/3-back lPreCentG, bSPL, lIPL, rCerebellum	No Rx effects
Konrad (2007)	fMRI, Whole-Brain	9 males (11.1±1.3 years old), 5 Comb, 4 Inatt, on MPH≥ 1 year	MPH mean 30 mg/d; open withdrawal	Attention-Network Test	↓ perf with Conflict on PLC; No Rx effect on performance	↓ TPJ in re-orienting, ↓ ACC with conflict	No Rx effects to ↑ acticity; Rx ↓ activity in rInsula/Putamen
Lee (2010)	fMRI, Whole-Brain	8 Males (10.3 ±1.3 years old), past MPH-responders	MPH (5 on Concerta 27-45 mg/d, 3 on Metadate 30-40 mg/d); open withdrawal	Flanker	↑ perform in Conflict condition on Rx	N/A	No Rx effects
Liddle (2011)	fMRI, Whole-Brain with DMN ROI analysis	18 (9-15 years old), MPH-responders	MPH 1.01±0.45 mg/kg, counterbal withdrawal	Go/No-Go with incentives	↓ d-prime *vs* HC on PLC; no diff on Rx *vs* HC	↓ DMN deact in low-incentive, but ↑ modulation of DMN with incentive	On Rx, no DMN deact diff *vs* HC, any condition
Rubia (2009) [128]	fMRI, Whole-Brain	13 Males (12.5±1.3 years old), all Comb	MPH 0.3 mg/kg	CPT with incentive	↑omission errors on PLC; no diff on Rx *vs* HC	Activity ↓ rmedOFC, rIFG, rPremotor, bIPL/STG, bCerebellum, bStriatum/ Thal/Hpc. Connectivity ↓ bet. bIFG and striatal/ thalamic/cerebellar, and ↓ bet. Cerebellar and IPL/ striatal/ACC	On Rx *vs* HC, activity ↓ rmedOFC, rIFG, rPremotor, bCerebellum, bStriatum/Thal/Hpc; ↑ rdlIFG, vermis Cerebellum/Occipital Cx. Connectivity on Rx, no diffs *vs* HC except bCerebellar-parietal
Rubia (2011)	fMRI, Whole-Brain	12 Males (13± 1 year old)	MPH 0.3 mg/kg		No diff *vs* HC Simon effect on PLC; No	↓ rIFG/rIPL, lVMPFC,/ striatum/thalamus,	On Rx *vs* HC, ↓ rSMA, /ACC/PCC, lMTG/

Table 1 (continued)

Study (year)	Imaging method	ADHD Sample	Rx	Cognitive task/ process	ADHD Task performance	ADHD *vs* HC on placebo	ADHD Drug *vs* PLC
				Simon Task with Oddball condition	Rx effect on performance	rSMA/ACC/PCC, lSTG/MTG	Occipital, lSTG/IPL/ precuneus
Sheridan (2010)	fMRI, Whole-Brain and ROI	5 females (14.8±2.4 years old), 4 on MPH, 1 on AMP	Pt's regular stim meds, with counterbal withdrawal	DMTS	↑ acc on Rx	N/A	Whole-brain: ↓ PFC and precuneus during encoding; ROI: ↓ bMFG during encoding' ↓ connectivity MFG-striatum; ↑ connectivity MFG-cerebellum
Shafritz (2004)	fMRI Whole-Brain	15 adolescents (M/F 11/4; 15.1±0.3 years old), all Comb, 8 on MPH, 4 past MPH	MPH (<30 mg/30-60 kg/> 60 kg: 15/20/25 mg)	Selective attention, divided attention	↓ perf *vs* HC select/divid attention; no Rx effects on performance	↓ l dorsal striatum, bMTG	On Rx *vs* HC, ↓ bMTG; no diff *vs* HC l dorsal striatum
Vaidya (1998)	fMRI Whole-Brain	10 males (10.5±1.4 years old), 8 Comb, 2 Inatt, all on MPH	Pt's regular MPH dose (7.5-30 mg); HC admin 10 mg MPH	Go/No-Go	↓ perf *vs* HC on PLC; ↑ perf on Rx	↓ striatum	On Rx *vs* PLC, ↑ PFC; On Rx *vs* HC, ↑ striatum (> HC)
Wong (2012)	fMRI Whole-Brain with ICA	18 (15/3 M/F, 14.6 years old), all Comb, all on MPH or AMP	Pt's regular Rx dose, counterbal withdrawal	Sternberg with letters	↓ RT for targets/foils on Rx	N/A	On Rx *vs* PLC, ↑ activity in Indep Components during encoding/ maintenance and retrieval; including various PFC-parietal-temporal-caudate-cerebellar regions
Schweitzer (2004)	[^{15}O] PET with ROI	10 males (31.5±8.2 years old), all Comb; 4 past MPH	MPH 1.0 mg/kg/d by 3rd week, x 3 weeks (mean 19 mg/d)	PASAT	↑ acc on Rx, no diff *vs* HC on Rx	↓ IFG, STG, vACC; ↑ lMFG, midbrain, pons, rCaud, vermis Cerebellum	On Rx *vs* PLC, ↓ rMFG/rMedFG; ↑ rThal, r PrecentG; On Rx *vs* HC, ↓ ACC/OFC, MTG/ITG; ↑ rMFG, lIFG, l Inf Occipital Cx, r Insula, parietal Cx (BA3), vermis cerebellum, b Striatum

Note: If information is missing from summary (e.g. Rx history for patients) this indicates that it was not reported in the original article

ACC = anterior cingulate gyrus; ADHD = attention-deficit/hyperactivity disorder; AMP = amphetamine; b = bilateral; Caud = caudate nucleus; Comb = Combined; Cx = cortex; d = dorsal; diff = different; discrim. = discrimination; dl = dorsolateral; DMN = default-mode network; DMTS = delayed match-to-sample; fMRI = functional magnetic resonance imaging; grp = group; Hc = healthy control; Hpc = hippocampus; l = left hemisphere; ICA = independent components analysis; IFG = inferior frontal gyrus; IPL = inferior parietal lobule; med = medial; MedFG = medial frontal gyrus; meds = medications; MFG = middle frontal gyrus; MOG = middle occipital gyrus; MPH = methylphenidate; MTA study = Multimodal Treatment study of ADHD; MTG = middle temporal gyrus; MTL = medial temporal lobe; N/A = not available (e.g., no healthy control group in study); PASAT = paced auditory serial addition task; ns = not significant; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; perf = performance; PET = positron-emission tomography; PLC = placebo; PreCentG = precentral gyrus; r=right hemisphere; ROI = region-of-interest; Rx = treatment; SFG = superior frontal gyrus; SMA = supplementary motor area; SPL = superior parietal lobule; STG = superior temporal gyrus; Thal = thalamus; VMPFC = ventromedial prefrontal cortex

*Gender not specified

dependent have been studied as well for MPH effects in ADHD patients. Brain activation measured during go/no-go task performance is associated with varied responses to MPH, including increases in frontal and striatal areas in children with ADHD [135], increased fronto-striatal and cerebellar activation in children with ADHD (whereas ADHD adults showed striatal and cerebellar responses without frontal changes among parent-child ADHD dyads) [136], and normalized task-related default-mode deactivation that was attenuated in ADHD children at baseline [137]. A few conflict-processing tasks have been used to interrogate PFC-based networks in response to MPH treatment in ADHD. These studies have found that MPH treatment modulates the brain regions that mediate suppression of interference, including the dorsal anterior midcingulate cortex [138], lateral PFC [139], and normalizes inhibition-related activity in fronto-parietal and thalamic areas [140], error-related activity in parietotemporal cortex and cerebellum [140], and conflict-related activation in right inferior PFC and striato-thalamic regions [141], although not all studies have found MPH effects on PFC in conflict monitoring in ADHD [142]. Other studies have investigated diverse processes, finding MPH to partly remediate altered patterns of activity in frontal and temporal cortical regions during interval time discrimination [143], and stimulant treatment to normalize both amygdala activity and amygdala-lateral PFC connectivity in response to subliminal exposure to facial expressions of fear [144]. Overall, this literature suggests that distributed cortical-subcortical circuits (which include important nodes in the frontal and parietal cortex, dorsal striatum, thalamus and cerebellum, and mediate complex, and control-dependent cognitive processes that are disturbed in ADHD) are responsive to ADHD drug treatment and probably serve as important mediators of cognitive and clinical efficacy. Conclusions at this point in time should be tempered by the acknowledgment of numerous methodological issues in the existing literature. These include the near-ubiquity of prior stimulant treatment among ADHD patients at study, which is likely associated with sustained changes in the structure and function of neurons in the brain, relatively small (and heterogeneous) samples that limit the replicability of findings, and a frequent lack of concordance between the neural and task performance effects of drug treatment, which may leave the significance of drug-related changes uncertain in the brain. In addition, there may not be any simple relationship of regional brain effects of treatment to changes in cognitive function. These may have complex multiphasic dose-response relationships (established in animal studies of both physiology and cognition, and in clinical trials with ADHD patients), and drug effects could be dependent on cellular changes that emerge in time, mediated by transcriptional and plasticity processes.

Conclusion/Future Directions

The current pharmacopoeia for ADHD is large and diverse. Nonetheless, all effective medications for ADHD share modulatory actions on catecholaminergic neurons in the brain. This is consistent with the multiple lines of evidence implicating the central DA and NE systems in the pathophysiology of ADHD. These neurochemical systems strongly modulate all the cognitive processes that are important in this disorder. Classic psychostimulants share several key actions on these cells and systems; however, there are potentially important differences in the cellular effects of methylphenidate *versus* amphetamine, the clinical implications of which are not yet understood. The clinical efficacy of agents, such as the α_2 receptor agonists guanfacine and clonidine suggest that catecholamine transport inhibition is not the only route to efficacy. In addition, the observation that drugs without significant direct DA effects, such as the α_2 receptor agonists, as well as atomoxetine and desipramine all remediate ADHD symptoms, indicates that action on the central LC-NE system (probably targeting both NE and DA signaling in the PFC) is a key mediator of effective drug action for ADHD. Although the functional role of catecholamine systems in the modulation of distributed neural circuits is a topic of intensive research, the effects of these drugs on those modulatory processes is still emerging. This is a rich and important area of research that stands to inform not only the basic science of neural network operation, but also to support advances in the treatment of this high-impact disorder.

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References

1. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet 2005;366:237-248.
2. Scahill L, Schwab-Stone M. Epidemiology of ADHD in school-age children. Child Adolesc Psychiatr Clin N Am 2000;9:541-555.
3. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry 2006;163:716-723.
4. Franke B, Neale BM, Faraone SV. Genome-wide association studies in ADHD. Hum Genet 2009;126:13-50.
5. Lesch KP, Timmesfeld N, Renner TJ, et al. Molecular genetics of adult ADHD: converging evidence from genome-wide association and extended pedigree linkage studies. J Neural Transm 2008;115:1573-1585.
6. Sagvolden T, Russell VA, Aase H, Johansen EB, Farshbaf M. Rodent models of attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:1239-1247.

7. Winstanley CA, Eagle DM, Robbins TW. Behavioral models of impulsivity in relation to ADHD: translation between clinical and preclinical studies. Clin Psychol Rev 2006;26:379-395.
8. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 1997;121:65-94.
9. Boonstra AM, Oosterlaan J, Sergeant JA, Buitelaar JK. Executive functioning in adult ADHD: a meta-analytic review. Psychol Med 2005;35:1097-1108.
10. Hervey AS, Epstein JN, Curry JF. Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review. Neuropsychology 2004;18:485-503.
11. Alderson RM, Rapport MD, Kofler MJ. Attention-deficit/hyperactivity disorder and behavioral inhibition: a meta-analytic review of the stop-signal paradigm. J Abnorm Child Psychol 2007;35:745-758.
12. Kenemans JL, Bekker EM, Lijffijt M, Overtoom CC, Jonkman LM, Verbaten MN. Attention deficit and impulsivity: selecting, shifting, and stopping. Int J Psychophysiol 2005;58:59-70.
13. Nigg JT, Casey BJ. An integrative theory of attention-deficit/hyperactivity disorder based on the cognitive and affective neurosciences. Dev Psychopathol 2005;17:785-806.
14. Uekermann J, Kraemer M, Abdel-Hamid M, et al. Social cognition in attention-deficit hyperactivity disorder (ADHD). Neurosci Biobehav Rev 2010;34:734-743.
15. Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci 2002;3:617-628.
16. Castellanos FX, Sonuga-Barke EJ, Milham MP, Tannock R. Characterizing cognition in ADHD: beyond executive dysfunction. Trends Cogn Sci 2006;10:117-123.
17. Sonuga-Barke EJ. Psychological heterogeneity in AD/HD — a dual pathway model of behavior and cognition. Behav Brain Res 2002;130:29-36.
18. Castellanos FX, Lee PP, Sharp W, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 2002;288:1740-1748.
19. Proal E, Reisds PT, Klein RG, et al. Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. Arch Gen Psychiatry 2011;68:1122-1134.
20. Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. Biol Psychiatry 2007;61:1361-1369.
21. Durston S. Imaging genetics in ADHD. Neuroimage 2010;53:832-838.
22. Frodl T, Skokauskas N. Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. Acta Psychiatr Scand 2012;125:114-126.
23. Nakao T, Radua J, Rubia K, Mataix-Cols D. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. Am J Psychiatry 2011;168:1154-1163.
24. Dougherty DD, Bonab AA, Spencer TJ, Rauch SL, Madras BK, Fischman AJ. Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet 1999;354:2132-2133.
25. Fusar-Poli P, Rubia K, Rossi G, Sartori G, Balottin U. Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? A meta-analysis. Am J Psychiatry 2012;169:264-272.
26. Volkow ND, Wang GJ, Newcorn J, et al. Brain dopamine transporter levels in treatment and drug naive adults with ADHD. Neuroimage 2007;34:1182-1190.
27. Volkow ND, Wang GJ, Kollins SH, et al. Evaluating dopamine reward pathway in ADHD: clinical implications. JAMA 2009;302:1084-1091.
28. Swanson J, Baler RD, Volkow ND. Understanding the effects of stimulant medications on cognition in individuals with attention-deficit hyperactivity disorder: a decade of progress. Neuropsychopharmacology 2011;36:207-226.
29. Forssberg H, Fernell E, Waters S, Waters N, Tedroff J. Altered pattern of brain dopamine synthesis in male adolescents with attention deficit hyperactivity disorder. Behav Brain Funct 2006;2:40.
30. Ludolph AG, Kassubek J, Schmeck K, et al. Dopaminergic dysfunction in attention deficit hyperactivity disorder (ADHD), differences between pharmacologically treated and never treated young adults: a 3,4-dihdroxy-6-[18 F]fluorophenyl-l-alanine PET study. Neuroimage 2008;41:718-727.
31. Biederman J, Spencer T. Attention-deficit/hyperactivity disorder (ADHD) as a noradrenergic disorder. Biol Psychiatry 1999;46:1234-1242.
32. Tzschentke TM. Pharmacology and behavioral pharmacology of the mesocortical dopamine system. Prog Neurobiol 2001;63:241-320.
33. Solanto MV. Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. Behav Brain Res 1998;94:127-152.
34. Berridge CW, Devilbiss DM. Psychostimulants as cognitive enhancers: the prefrontal cortex, catecholamines, and attention-deficit/hyperactivity disorder. Biol Psychiatry 2011;69:e101-e111.
35. Wolraich M, Brown L, Brown RT, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics 2011;128:1007-1022.
36. Kaplan G, Newcorn JH. Pharmacotherapy for child and adolescent attention-deficit hyperactivity disorder. Pediatr Clin North Am 2011;58:99-120.
37. Kooij SJ, Bejerot S, Blackwell A, et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC Psychiatry 2010;10:67.
38. Nutt DJ, Fone K, Asherson P, et al. Evidence-based guidelines for management of attention-deficit/hyperactivity disorder in adolescents in transition to adult services and in adults: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2007;21:10-41.
39. Pliszka SR, Crismon ML, Hughes CW, et al. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2006;45:642-657.
40. Wilens TE, Morrison NR, Prince J. An update on the pharmacotherapy of attention-deficit/hyperactivity disorder in adults. Expert Rev Neurother 2011;11:1443-1465.
41. Pliszka SR. Pharmacologic treatment of attention-deficit/hyperactivity disorder: efficacy, safety and mechanisms of action. Neuropsychol Rev 2007;17:61-72.
42. Madras BK, Miller GM, Fischman AJ. The dopamine transporter and attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:1397-1409.
43. Volkow ND, Fowler JS, Wang G, Ding Y, Gatley SJ. Mechanism of action of methylphenidate: insights from PET imaging studies. J Atten Disord 2002;6(suppl b1):S31-S43.
44. Eshleman AJ, Carmolli M, Cumbay M, Martens CR, Neve KA, Janowsky A. Characteristics of drug interactions with recombinant biogenic amine transporters expressed in the same cell type. J Pharmacol Exp Ther 1999;289:877-885.
45. Kuczenski R, Segal DS, Cho AK, Melega W. Hippocampus norepinephrine, caudate dopamine and serotonin, and behavioral

responses to the stereoisomers of amphetamine and methamphetamine. J Neurosci 1995;15:1308-1317.
46. Gehlert DR, Schober DA, Hemrick-Luecke SK, et al. Novel halogenated analogs of tomoxetine that are potent and selective inhibitors of norepinephrine uptake in brain. Neurochem Int 1995;26:47-52.
47. Kuczenski R, Segal DS. Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. J Neurochem 1997;68:2032-2037.
48. Kuczenski R, Segal D. Concomitant characterization of behavioral and striatal neurotransmitter response to amphetamine using in vivo microdialysis. J Neurosci 1989;9:2051-2065.
49. Hernandez L, Hoebel BG. Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. Life Sci 1988;42:1705-1712.
50. Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 1988;85:5274-5278.
51. Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology 2002;27:699-711.
52. Carboni E, Tanda GL, Frau R, Di Chiara G. Blockade of the noradrenaline carrier increases extracellular dopamine concentrations in the prefrontal cortex: evidence that dopamine is taken up in vivo by noradrenergic terminals. J Neurochem 1990;55:1067-1070.
53. Moron JA, Brockington A, Wise RA, Rocha BA, Hope BT. Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines. J Neurosci 2002;22:389-395.
54. Berridge CW, Devilbiss DM, Andrzejewski ME, et al. Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. Biol Psychiatry 2006;60:1111-1120.
55. Koda K, Ago Y, Cong Y, Kita Y, Takuma K, Matsuda T. Effects of acute and chronic administration of atomoxetine and methylphenidate on extracellular levels of noradrenaline, dopamine and serotonin in the prefrontal cortex and striatum of mice. J Neurochem 2010;114:259-270.
56. Marsteller DA, Gerasimov MR, Schiffer WK, et al. Acute handling stress modulates methylphenidate-induced catecholamine overflow in the medial prefrontal cortex. Neuropsychopharmacology 2002;27:163-170.
57. Yatin SM, Miller GM, Norton C, Madras BK. Dopamine transporter-dependent induction of C-Fos in HEK cells. Synapse 2002;45:52-65.
58. Brandon CL, Steiner H. Repeated methylphenidate treatment in adolescent rats alters gene regulation in the striatum. Eur J Neurosci 2003;18:1584-1592.
59. Chase TD, Brown RE, Carrey N, Wilkinson M. Daily methylphenidate administration attenuates c-fos expression in the striatum of prepubertal rats. Neuroreport 2003;14:769-772.
60. Izenwasser S, Coy AE, Ladenheim B, Loeloff RJ, Cadet JL, French D. Chronic methylphenidate alters locomotor activity and dopamine transporters differently from cocaine. Eur J Pharmacol 1999;373:187-193.
61. Moll GH, Hause S, Ruther E, Rothenberger A, Huether G. Early methylphenidate administration to young rats causes a persistent reduction in the density of striatal dopamine transporters. J Child Adolesc Psychopharmacol 2001;11:15-24.
62. Sandoval V, Riddle EL, Hanson GR, Fleckenstein AE. Methylphenidate redistributes vesicular monoamine transporter-2: role of dopamine receptors. J Neurosci 2002;22:8705-8710.
63. Heikkila RE, Orlansky H, Mytilineou C, Cohen G. Amphetamine: evaluation of d- and l-isomers as releasing agents and uptake inhibitors for 3 H-dopamine and 3 H-norepinephrine in slices of rat neostriatum and cerebral cortex. J Pharmacol Exp Ther 1975;194:47-56.
64. Amara SG, Sonders MS, Zahniser NR, Povlock SL, Daniels GM. Molecular physiology and regulation of catecholamine transporters. Adv Pharmacol 1998;42:164-168.
65. Fleckenstein AE, Haughey HM, Metzger RR, et al. Differential effects of psychostimulants and related agents on dopaminergic and serotonergic transporter function. Eur J Pharmacol 1999;382:45-49.
66. Saunders C, Ferrer JV, Shi L, et al. Amphetamine-induced loss of human dopamine transporter activity: an internalization-dependent and cocaine-sensitive mechanism. Proc Natl Acad Sci U S A 2000;97:6850-6855.
67. Sulzer D, Rayport S. Amphetamine and other psychostimulants reduce pH gradients in midbrain dopaminergic neurons and chromaffin granules: a mechanism of action. Neuron 1990;5:797-808.
68. Green AL, el Hait MA. Inhibition of mouse brain monoamine oxidase by (+)-amphetamine in vivo. J Pharm Pharmacol 1978;30:262-263.
69. Raiteri M, Cerrito F, Cervoni AM, Levi G. Dopamine can be released by two mechanisms differentially affected by the dopamine transport inhibitor nomifensine. J Pharmacol Exp Ther 1979;208:195-202.
70. Sitte HH, Huck S, Reither H, Boehm S, Singer EA, Pifl C. Carrier-mediated release, transport rates, and charge transfer induced by amphetamine, tyramine, and dopamine in mammalian cells transfected with the human dopamine transporter. J Neurochem 1998;71:1289-1297.
71. Kahlig KM, Binda F, Khoshbouei H, et al. Amphetamine induces dopamine efflux through a dopamine transporter channel. Proc Natl Acad Sci U S A 2005;102:3495-3500.
72. Johnson LA, Guptaroy B, Lund D, Shamban S, Gnegy ME. Regulation of amphetamine-stimulated dopamine efflux by protein kinase C beta. J Biol Chem 2005;280:10914-10919.
73. Schiffer WK, Volkow ND, Fowler JS, Alexoff DL, Logan J, Dewey SL. Therapeutic doses of amphetamine or methylphenidate differentially increase synaptic and extracellular dopamine. Synapse 2006;59:243-251.
74. Florin SM, Kuczenski R, Segal DS. Regional extracellular norepinephrine responses to amphetamine and cocaine and effects of clonidine pretreatment. Brain Res 1994;654:53-62.
75. Shi WX, Pun CL, Zhang XX, Jones MD, Bunney BS. Dual effects of D-amphetamine on dopamine neurons mediated by dopamine and nondopamine receptors. J Neurosci 2000;20:3504-3511.
76. Gnegy ME, Khoshbouei H, Berg KA, et al. Intracellular Ca2+ regulates amphetamine-induced dopamine efflux and currents mediated by the human dopamine transporter. Mol Pharmacol 2004;66:137-143.
77. Ingram SL, Prasad BM, Amara SG. Dopamine transporter-mediated conductances increase excitability of midbrain dopamine neurons. Nat Neurosci 2002;5:971-978.
78. Schmitz Y, Lee CJ, Schmauss C, Gonon F, Sulzer D. Amphetamine distorts stimulation-dependent dopamine overflow: effects on D2 autoreceptors, transporters, and synaptic vesicle stores. J Neurosci 2001;21:5916-5924.
79. Bunzow JR, Sonders MS, Arttamangkul S, et al. Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. Mol Pharmacol 2001;60:1181-1188.
80. Geracitano R, Federici M, Prisco S, Bernardi G, Mercuri NB. Inhibitory effects of trace amines on rat midbrain dopaminergic neurons. Neuropharmacology 2004;46:807-814.

81. Miller GM, Verrico CD, Jassen A, et al. Primate trace amine receptor 1 modulation by the dopamine transporter. J Pharmacol Exp Ther 2005;313:983-994.
82. Xie Z, Westmoreland SV, Bahn ME, et al. Rhesus monkey trace amine-associated receptor 1 signaling: enhancement by monoamine transporters and attenuation by the D2 autoreceptor in vitro. J Pharmacol Exp Ther 2007;321:116-127.
83. Xie Z, Miller GM. Trace amine-associated receptor 1 is a modulator of the dopamine transporter. J Pharmacol Exp Ther 2007;321:128-136.
84. Devilbiss DM, Berridge CW. Low-dose methylphenidate actions on tonic and phasic locus coeruleus discharge. J Pharmacol Exp Ther 2006;319:1327-1335.
85. Nieuwenhuis S, Gilzenrat MS, Holmes BD, Cohen JD. The role of the locus coeruleus in mediating the attentional blink: a neurocomputational theory. J Exp Psychol Gen 2005;134:291-307.
86. Devilbiss DM, Berridge CW. Cognition-enhancing doses of methylphenidate preferentially increase prefrontal cortex neuronal responsiveness. Biol Psychiatry 2008;64:626-635.
87. Andrews GD, Lavin A. Methylphenidate increases cortical excitability via activation of alpha-2 noradrenergic receptors. Neuropsychopharmacology 2006;31:594-601.
88. Dommett EJ, Henderson EL, Westwell MS, Greenfield SA. Methylphenidate amplifies long-term plasticity in the hippocampus via noradrenergic mechanisms. Learn Mem 2008;15:580-586.
89. Tye KM, Tye LD, Cone JJ, Hekkelman EF, Janak PH, Bonci A. Methylphenidate facilitates learning-induced amygdala plasticity. Nat Neurosci 2010;13:475-481.
90. Zehle S, Bock J, Jezierski G, Gruss M, Braun K. Methylphenidate treatment recovers stress-induced elevated dendritic spine densities in the rodent dorsal anterior cingulate cortex. Dev Neurobiol 2007;67:1891-900.
91. Ruskin DN, Bergstrom DA, Shenker A, Freeman LE, Baek D, Walters JR. Drugs used in the treatment of attention-deficit/hyperactivity disorder affect postsynaptic firing rate and oscillation without preferential dopamine autoreceptor action. Biol Psychiatry 2001;49:340-350.
92. Gamo NJ, Wang M, Arnsten AF. Methylphenidate and atomoxetine enhance prefrontal function through alpha2-adrenergic and dopamine D1 receptors. J Am Acad Child Adolesc Psychiatry 2010;49:1011-1023.
93. Curet O, De Montigny C, Blier P. Effect of desipramine and amphetamine on noradrenergic neurotransmission: electrophysiological studies in the rat brain. Eur J Pharmacol 1992;221:59-70.
94. Graham AW, Aghajanian GK. Effects of amphetamine on single cell activity in a catecholamine nucleus, the locus coeruleus. Nature 1971;234:100-102.
95. Bunney BS, Walters JR, Kuhar MJ, Roth RH, Aghajanian GK. D & L amphetamine stereoisomers: comparative potencies in affecting the firing of central dopaminergic and noradrenergic neurons. Psychopharmacol Commun 1975;1:177-190.
96. Szabo ST, Blier P. Effect of the selective noradrenergic reuptake inhibitor reboxetine on the firing activity of noradrenaline and serotonin neurons. Eur J Neurosci 2001;13:2077-2087.
97. Akaoka H, Roussel B, Lin JS, Chouvet G, Jouvet M. Effect of modafinil and amphetamine on the rat catecholaminergic neuron activity. Neurosci Lett 1991;123:20-22.
98. Pitts DK, Marwah J. Electrophysiological actions of cocaine on noradrenergic neurons in rat locus ceruleus. J Pharmacol Exp Ther 1987;240:345-351.
99. Curtis AL, Conti E, Valentino RJ. Cocaine effects on brain noradrenergic neurons of anesthetized and unanesthetized rats. Neuropharmacology 1993;32:419-428.
100. Ishimatsu M, Kidani Y, Tsuda A, Akasu T. Effects of methylphenidate on the membrane potential and current in neurons of the rat locus coeruleus. J Neurophysiol 2002;87:1206-1212.
101. Lacroix D, Ferron A. Electrophysiological effects of methylphenidate on the coeruleo-cortical noradrenergic system in the rat. Eur J Pharmacol 1988;149:277-285.
102. Pietrzak RH, Mollica CM, Maruff P, Snyder PJ. Cognitive effects of immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. Neurosci Biobehav Rev 2006;30:1225-1245.
103. Bidwell LC, McClernon FJ, Kollins SH. Cognitive enhancers for the treatment of ADHD. Pharmacol Biochem Behav 2011;99:262-274.
104. Advokat C. What are the cognitive effects of stimulant medications? Emphasis on adults with attention-deficit/hyperactivity disorder (ADHD). Neurosci Biobehav Rev 2010;34:1256-1266.
105. Minzenberg MJ, Carter CS. Modafinil: a review of neurochemical actions and effects on cognition. Neuropsychopharmacology 2008;33:1477-1502.
106. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. Arch Gen Psychiatry 1999;56:1073-1086.
107. Jensen PS, Arnold LE, Swanson JM, et al. 3-year follow-up of the NIMH MTA study. J Am Acad Child Adolesc Psychiatry 2007;46:989-1002.
108. Molina BS, Hinshaw SP, Swanson JM, et al. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry 2009;48:484-500.
109. Biederman J, Seidman LJ, Petty CR, et al. Effects of stimulant medication on neuropsychological functioning in young adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry 2008;69:1150-1156.
110. Powers RL, Marks DJ, Miller CJ, Newcorn JH, Halperin JM. Stimulant treatment in children with attention-deficit/hyperactivity disorder moderates adolescent academic outcome. J Child Adolesc Psychopharmacol 2008;18:449-459.
111. Gadow KD. Effects of stimulant drugs on academic performance in hyperactive and learning disabled children. J Learn Disabil 1983;16:290-299.
112. Swanson JM, Cantwell D, Lerner M, McBurnett K, Hanna G. Effects of stimulant medication on learning in children with ADHD. J Learn Disabil 1991;24:219-230.
113. McCracken JT, Biederman J, Greenhill LL, et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SLI381 (Adderall XR), in children with ADHD. J Am Acad Child Adolesc Psychiatry 2003;42:673-683.
114. McGough JJ, Wigal SB, Abikoff H, Turnbow JM, Posner K, Moon E. A randomized, double-blind, placebo-controlled, laboratory classroom assessment of methylphenidate transdermal system in children with ADHD. J Atten Disord 2006;9:476-485.
115. Biederman J, Boellner SW, Childress A, Lopez FA, Krishnan S, Zhang Y. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry 2007;62:970-976.
116. Epstein JN, Conners CK, Hervey AS, et al. Assessing medication effects in the MTA study using neuropsychological outcomes. J Child Psychol Psychiatry 2006;47:446-456.
117. Castellanos FX, Kelly C, Milham MP. The restless brain: attention-deficit hyperactivity disorder, resting-state functional connectivity, and intrasubject variability. Can J Psychiatry 2009;54:665-672.
118. Johnson KA, Barry E, Bellgrove MA, et al. Dissociation in response to methylphenidate on response variability in a group of medication naive children with ADHD. Neuropsychologia 2008;46:1532-1541.
119. Sobel LJ, Bansal R, Maia TV, et al. Basal ganglia surface morphology and the effects of stimulant medications in youth with attention deficit hyperactivity disorder. Am J Psychiatry 2010;167:977-986.

120. Semrud-Clikeman M, Pliszka SR, Lancaster J, Liotti M. Volumetric MRI differences in treatment-naïve vs chronically treated children with ADHD. Neurology 2006;67:1023-1027. Erratum in: Neurology 2006;67:2091.
121. Bledsoe J, Semrud-Clikeman M, Pliszka SR. A magnetic resonance imaging study of the cerebellar vermis in chronically treated and treatment-naïve children with attention-deficit/hyperactivity disorder combined type. Biol Psychiatry 2009;65:620-624.
122. Castellanos FX, Lee PP, Sharp W, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 2002;288:1740-1748.
123. Shaw P, Lerch J, Greenstein D, et al. Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2006;63:540-549.
124. Shaw P, Eckstrand K, Sharp W, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci USA 2007;104:19649-19654.
125. Schweitzer JB, Lee DO, Hanford RB, et al. A positron emission tomography study of methylphenidate in adults with ADHD: alterations in resting blood flow and predicting treatment response. Neuropsychopharmacology 2003;28:967-973.
126. Anderson CM, Polcari A, Lowen SB, Renshaw PF, Teicher MH. Effects of methylphenidate on functional magnetic resonance relaxometry of the cerebellar vermis in boys with ADHD. Am J Psychiatry 2002;159:1322-1328.
127. Rosa-Neto P, Lou HC, Cumming P, et al. Methylphenidate-evoked changes in striatal dopamine correlate with inattention and impulsivity in adolescents with attention deficit hyperactivity disorder. Neuroimage 2005;25:868-876.
128. Rubia K, Halari R, Cubillo A, Mohammad AM, Brammer M, Taylor E. Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naive children with ADHD during a rewarded continuous performance task. Neuropharmacology 2009;57:640-652.
129. Shafritz KM, Marchione KE, Gore JC, Shaywitz SE, Shaywitz BA. The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder. Am J Psychiatry 2004;161:1990-1997.
130. Wong CG, Stevens MC. The effects of stimulant medication on working memory functional connectivity in attention-deficit/hyperactivity disorder. Biol Psychiatry 2012;71:458-466.
131. Prehn-Kristensen A, Krauel K, Hinrichs H, et al. Methylphenidate does not improve interference control during a working memory task in young patients with attention-deficit hyperactivity disorder. Brain Res. 2011 May 4;1388:56-68.
132. Sheridan MA, Hinshaw S, D'Esposito M. Stimulant medication and prefrontal functional connectivity during working memory in ADHD: a preliminary report. J Atten Disord 2010;14:69-78.
133. Kobel M, Bechtel N, Weber P, et al. Effects of methylphenidate on working memory functioning in children with attention deficit/hyperactivity disorder. Eur J Paediatr Neurol 2009;13:516-523.
134. Schweitzer JB, Lee DO, Hanford RB, et al. Effect of methylphenidate on executive functioning in adults with attention-deficit/hyperactivity disorder: normalization of behavior but not related brain activity. Biol Psychiatry 2004;56:597-606.
135. Vaidya CJ, Austin G, Kirkorian G, et al. Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. Proc Natl Acad Sci U S A 1998;95:14494-14499.
136. Epstein JN, Casey BJ, Tonev ST, et al. ADHD- and medication-related brain activation effects in concordantly affected parent-child dyads with ADHD. J Child Psychol Psychiatry 2007;48:899-913.
137. Liddle EB, Hollis C, Batty MJ, et al. Task-related default mode network modulation and inhibitory control in ADHD: effects of motivation and methylphenidate. J Child Psychol Psychiatry 2011;52:761-771.
138. Bush G, Spencer TJ, Holmes J, et al. Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. Arch Gen Psychiatry 2008;65:102-114.
139. Lee YS, Han DH, Lee JH, Choi TY. The effects of methylphenidate on neural substrates associated with interference suppression in children with ADHD: a Preliminary Study Using Event Related fMRI. Psychiatry Investig 2010;7:49-54.
140. Rubia K, Halari R, Mohammad AM, Taylor E, Brammer M. Methylphenidate normalizes frontocingulate underactivation during error processing in attention-deficit/hyperactivity disorder. Biol Psychiatry 2011;70:255-262.
141. Rubia K, Halari R, Cubillo A, et al. Methylphenidate normalizes fronto-striatal underactivation during interference inhibition in medication-naive boys with attention-deficit hyperactivity disorder. Neuropsychopharmacology 2011;36:1575-1586.
142. Konrad K, Neufang S, Fink GR, Herpertz-Dahlmann B. Long-term effects of methylphenidate on neural networks associated with executive attention in children with ADHD: results from a longitudinal functional MRI study. J Am Acad Child Adolesc Psychiatry 2007;46:1633-1641.
143. Rubia K, Halari R, Christakou A, Taylor E. Impulsiveness as a timing disturbance: neurocognitive abnormalities in attention-deficit hyperactivity disorder during temporal processes and normalization with methylphenidate. Philos Trans R Soc Lond B Biol Sci 2009;364:1919-1931.
144. Posner J, Nagel BJ, Maia TV, et al. Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2011;50:828-837.