

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

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Published online: 21 June 2012

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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

## 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.

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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<sub>4</sub> and D<sub>5</sub> 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<sub>2</sub>/D<sub>3</sub> 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 bupropion 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 effect 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 [<sup>11</sup>C]raclopride found that while AMP increases extracellular DA approximately four-fold higher than MPH, the resulting DA concentrations at D<sub>2</sub>/D<sub>3</sub> 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<sub>2</sub> 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  $\leq 3$  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  $\alpha_2$  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  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [89]. In this latter study, intramygdalar 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  $\alpha_2$  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  $\alpha_2$  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 [<sup>11</sup>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 fronto-subcortical 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; ↑Temp/Occ Cx, rSupTemp /InfOcc Cx	↑OFC/ 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, IACC, bPreCentG, bCaud, bSupraMargG, bMOG	Within-Grp Rx N/A; ADHD-Rx vs HC ↓Caud, 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 rAng, rMOG; ↑ Eff Conn rAng-LatPFC (BA47)	↓ rAng act (= HC); ↓ rAng-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, rIFL, ACC, bCaud	Youths: ↑ lMFG, lIFG, rIFL, ACC, rCaud, lCerebellum; Adults: ↑ lCaud; ↓ lMFG, rIFL
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 ↑ activity; 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, bIFL/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; ↑ rdIFG, 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	No diff vs HC Simon effect on PLC; No	↓ rIFG/rIFL, 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
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	Simon Task with Oddball condition DMTS	Rx effect on performance ↑ acc on Rx	rSMA/ACC/PCC, ISTG/MTG N/A	Occipital, ISTG/IPL/precuneus Whole-brain: ↓ PFC and precuneus during encoding; ROI: ↓ rMFG 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 ↓ perf vs HC on PLC; ↑ perf on Rx	↓ 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	Stemberg 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)	[ <sup>15</sup> 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; VMPPFC = 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  $\alpha_2$  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  $\alpha_2$  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.

**Acknowledgments** This work was supported by a Clinical Scientist Development Award from the Doris Duke Charitable Foundation (to MJM).

**Required Author Forms** Disclosure forms provided by the authors are available with the online version of this article.

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