

The Roles of Dopamine and Noradrenaline in the Pathophysiology and Treatment of Attention-Deficit/Hyperactivity Disorder

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Through neuromodulatory influences over fronto-striato-cerebellar circuits, dopamine and noradrenaline play important roles in high-level executive functions often reported to be impaired in attention-deficit/hyperactivity disorder (ADHD). Medications used in the treatment of ADHD (including methylphenidate, dextroamphetamine and atomoxetine) act to increase brain catecholamine levels. However, the precise prefrontal cortical and subcortical mechanisms by which these agents exert their therapeutic effects remain to be fully specified. Herein, we review and discuss the present state of knowledge regarding the roles of dopamine (DA) and noradrenaline in the regulation of cortico-striatal circuits, with a focus on the molecular neuroimaging literature (both in ADHD patients and in healthy subjects). Recent positron emission tomography evidence has highlighted the utility of quantifying DA markers, at baseline or following drug administration, in striatal subregions governed by differential cortical connectivity. This approach opens the possibility of characterizing the neurobiological underpinnings of ADHD (and associated cognitive dysfunction) and its treatment by targeting specific neural circuits. It is anticipated that the application of refined and novel positron emission tomography methodology will help to disentangle the overlapping and dissociable contributions of DA and noradrenaline in the prefrontal cortex, thereby aiding our understanding of ADHD and facilitating new treatments.

Key Words: Attention-deficit/hyperactivity disorder, dopamine, frontostriatal circuits, nigrostriatal projections, noradrenaline, positron emission tomography

Attention deficit/hyperactivity disorder (ADHD) is an early-onset neurobehavioral disorder characterized by symptoms of inattention, impulsivity, and/or hyperactivity (1). It is the most prevalent pediatric disorder, with conservative estimates indicating prevalence rates of 3% to 5% in children worldwide (2). Prospective follow-up studies estimate that in about 50% of children with ADHD, symptoms carry on into adulthood and are associated with substance abuse, depression, unemployment, and criminal offenses when left untreated (3,4). Without necessary or sufficient behavioral deficits, ADHD is a highly heterogeneous disorder.

Dysregulated dopaminergic and noradrenergic neurotransmission has been widely implicated in the pathophysiology of ADHD (1,5). Dopamine (DA) and noradrenaline (NA) are intrinsically linked via chemical pathways, in that hydroxylation of the former yields the latter (6). Through neuromodulation of fronto-striato-cerebellar circuits, both catecholamines play a critical role in prefrontal-dependent executive functions often reported to be suboptimal in ADHD patients, representing a key target for pharmacotherapy in ADHD. Yet, the precise neurobiological mechanisms underlying the disorder and its treatment are poorly understood.

Using radioactively labeled tracers that bind to or are metabolized by specific molecules, positron emission tomography (PET) and single photon emission computed tomography (SPECT) allow the direct assessment of neurotransmitters *in vivo*, at baseline or in response to pharmacological challenges. Here, we review and discuss the present state of knowledge regarding the involvement of

DA and NA in the pathophysiology of ADHD, with a focus on the molecular neuroimaging literature.

Molecular Imaging of the DA System in ADHD

As the DA transporter (DAT) is the main target for ADHD stimulant medication, molecular imaging studies in ADHD initially focused on the role of this marker, leading to the well-replicated finding that ADHD patients have increased DAT density (7). Based on the data obtained in this field at the time, Madras *et al.* (8) were awarded a US patent for "Methods for diagnosing and monitoring treatment ADHD by assessing the dopamine transporter level." They stated that "(increased) DAT levels can complement, and in some cases, supplant, traditional ADHD diagnostic techniques."

This idea was recently challenged by a set of well-powered case-control PET studies in adult medication-naïve ADHD patients, which found ADHD to be associated with reduced DAT and D₂/D₃ receptor availability in subcortical regions of the left hemisphere, including the nucleus accumbens, caudate nucleus, and midbrain (9–11). A possible interpretation proffered by Volkow *et al.* (9–11) regarding the discrepancies in DAT findings is the medication history of the patients. It has also been argued that the levels of DAT (and associated downstream effects) are determined by a polymorphism of the DAT1 gene and that genetic differences across study samples might explain conflicting results (12,13). However, in this regard, the literature has again been inconsistent (14–16).

Studies investigating D₂/D₃ receptor status in ADHD have largely been restricted to brain areas with relatively high D₂/D₃ receptor density such as the striatum because of the use of radiotracers with low affinity (for example, [¹¹C]raclopride). A low D₂/D₃ receptor density area where inadequate catecholamine transmission is thought to play a key role in ADHD is the prefrontal cortex (17). The application of high-affinity tracers such as [¹⁸F]fallypride or [¹¹C]FLB 457 in future studies might help to shed light in this respect.

A different DA marker that has been examined in prefrontal cortex in ADHD is 3,4-dihydroxyphenylalanine decarboxylase activity, an indicator of DA synthesis capacity. Using [¹⁸F]fluorodopa, one study found reduced metabolism in the prefrontal cortex of adult ADHD patients compared with control subjects (18). However, a subsequent study by the same research group failed to

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replicate this cortical finding in adolescent ADHD, reporting instead increased [^{18}F]fluorodopa utilization in patients in the right mid-brain (19). More recent evidence has associated ADHD with decreased 3,4-dihydroxyphenylalanine metabolism in subcortical regions, including midbrain and striatum (20,21). Given that the low level of dopaminergic signaling in the prefrontal cortex weakens the power to detect significant differences between groups in that region, there is a need to replicate these findings in larger samples.

Table 1 summarizes PET and SPECT studies examining different components of the DA system in ADHD. The aim of this table is to both illustrate key findings across studies and highlight some of the methodological and experimental factors that should be acknowledged when trying to reconcile disparate findings. Not only can the choice of imaging technique (PET vs. SPECT) and radiotracer have an impact on DA marker estimates (7), factors such as age (22), previous drug or nicotine exposure (23,24), and regular psychostimulant treatment (25) have a known influence on the expression of dopaminergic markers and yet have not always been controlled for. Furthermore, the application of state-of-the-art PET tools in psychiatric research has increasingly highlighted the need to quantify PET parameters (for example, ligand-receptor binding potential) at the subregional level, particularly within the striatum (26). One important shortcoming of the existing PET literature in ADHD is that studies have often averaged data across the entire striatum or used different landmarks to define caudate and putamen, complicating between-study comparisons and potentially masking highly localized group effects.

Psychostimulant Treatment: Neuropsychological Evidence

With a history of use spanning five decades, methylphenidate (MPH) and dextroamphetamine (D-AMPH) constitute the two main first-line ADHD therapies (45). Methylphenidate increases extrasynaptic DA and NA levels by blocking their reuptake (46). Dextroamphetamine also robustly raises extracellular levels of both DA and NA, albeit via more complicated mechanisms: D-AMPH not only inhibits the reuptake of DA and NA but also increases release of these neurotransmitters into extraneuronal space and inhibits the catabolic activity of monoamine oxidase (47).

The effectiveness of stimulant medication in the treatment of ADHD has always been of great theoretical interest in behavioral pharmacology (48). Initially, the calming effect of stimulants on hyperactive children was considered paradoxical and thought to be explained by an underlying neurological or biochemical deficit. However, accumulating evidence suggests that stimulant effects can be better understood in terms of their often similar actions in normal, healthy individuals. Indeed, while small-scale single-dose studies suggest, overall, that therapeutic doses of MPH ameliorate fronto-executive functions in children and adults diagnosed with ADHD (49–51), analogous findings in healthy subjects reveal that these effects are not pathognomonic for ADHD (52–54). Moreover, studies reporting mixed or negative results suggest that only specific neurocognitive processes in domains such as impulse control, working memory, and attention are affected by MPH and that these interact with the drug in a baseline performance-dependent manner (51,55–57). Further studies reported no cognitive-enhancing effects of MPH on executive functions in children with ADHD (58) and thus more data are needed to allow formal conclusions regarding acute MPH effects across all cognitive processes. With regard to D-AMPH, there is supporting evidence that this drug exerts its therapeutic effects via normalizing actions, much like MPH (59,60).

The complex relationship between performance and psychostimulant medication has been interpreted in accordance with a

hypothesized inverted U-shaped function, whereby optimal catecholamine levels determine optimal performance and catecholamine levels along the curve at either side of the optimum are associated with impaired performance (61–63). This hypothesis was originally formulated with respect to the chemical neuromodulation of the prefrontal cortex (61) but it probably also applies to other structures within the same circuitry, including the striatum (56,64). Consequently, cognitive and behavioral effects of stimulant drugs might be best predicted by baseline catecholamine levels, with these drugs acting as cognitive enhancers only in those individuals with hypocatecholaminergic states. Regardless of the underlying mechanisms, a likely implication of these findings for ADHD is that stimulant therapy corrects the hypodopaminergic condition underlying the disorder, thereby remediating cognitive and behavioral deficits.

PET Imaging of the Effects of MPH and D-AMPH

The binding competition between D_2/D_3 radioligands and endogenous DA provides an imaging paradigm with which to measure DA transmission following an acute drug challenge. A large body of [^{11}C]raclopride PET-based evidence has helped to characterize the distribution and cellular actions of MPH in the human striatum. Therapeutic doses of MPH were found to block more than 50% of DAT in healthy volunteers (65), leading to an increase in extracellular DA levels in the striatum (66). Importantly, increases in DA levels were not correlated with MPH-induced DAT blockade, suggesting that other factors such as rate of DA release or baseline differences in DA tone may be implicated in the individual differences in MPH-induced DA increases (67). The ability to increase DA levels in striatum has also been well established for D-AMPH (26,68–70).

Microdialysis studies in rodents and nonhuman primates have shown that stimulants increase DA levels also in extrastriatal areas, including the frontal cortex (71), and it has generally been assumed that this same phenomenon occurs in humans. Increased DA levels observed in the cortex following stimulant administration are thought to be largely mediated by the NA transporter (NAT); whereas in the striatum DAT density is high and NAT density low, the opposite is true in the frontal cortex (72). Dopamine has a higher affinity for NAT than for DAT, and thus, it is the NA system (via NAT) that controls the termination of DA transmission in the frontal cortex (73).

The PET studies using tracers suitable to examine regions with low D_2/D_3 receptor density (e.g., [^{11}C]FLB 457 and [^{18}F]fallypride) have addressed whether stimulants increase extrastriatal DA levels in humans (68–70,74). However, the regional specificity, magnitude, and levels of significance of these effects were highly variable across studies. Intriguingly, one recent study using [^{18}C]FLB 457 showed that D-AMPH did not induce marked changes in measures of extrastriatal D_2/D_3 receptor availability. A further observation that future research needs to resolve is the lack of sensitivity of [^{18}F]fallypride to DA depletion reported by Cropley *et al.* (69).

ADHD-Specific Stimulant Actions

To date, only one published study examined stimulant-induced increases in endogenous DA in adult ADHD patients compared with age-matched control subjects, using [^{11}C]raclopride PET (10). Following intravenous MPH treatment (.5 mg/kg), ADHD patients showed smaller increases in DA levels in the caudate. Moreover, a voxel-wise analysis revealed that the volumes of the regions where MPH significantly reduced tracer binding were significantly smaller in ADHD patients compared with control subjects in bilateral cau-

Table 1. Positron Emission Tomography and Single Photon Emission Computed Tomography Imaging of Dopamine Markers in Attention-Deficit/Hyperactivity Disorder

Authors (reference)	Radiotracer	Dysregulation in ADHD	Age	Sample Size (Patients-Controls)	Treatment History	Comorbid Neurological/ Axis-I Psychiatric Disorders	Drug Challenge	Drug Administration	Regions Examined	Behavioral Correlates	Key Findings
D₂/D₃ Receptors											
Volkow <i>et al.</i> 2010 (27)	[¹¹ C]raclopride	<	A	45-41	Naïve	None			Accumbens, midbrain	MPQ (Achievement scale)	Significant correlation between trait motivation and D ₂ /D ₃ in accumbens and midbrain in ADHD patients but not control subjects.
Volkow <i>et al.</i> 2009 (11)	[¹¹ C]raclopride	<	A	53-44	Naïve	None			Whole brain analysis followed by confirmatory template ROI analysis	SWAN	Decreased D ₂ /D ₃ in L accumbens, L CAUL midbrain and L hypothalamic region. Negative correlation between SWAN inattention scores and D ₂ /D ₃ in L accumbens, L CAU, and L hypothalamic regions.
Volkow <i>et al.</i> 2007 (10) ^a	[¹¹ C]raclopride	<	A	19-24	Naïve	None	MPH (single dose)	IV	Whole brain analysis and L/R CAU and PUT	CAARS	Reduced baseline D ₂ /D ₃ in L CAU. No significant correlations with CAARS, in either patients or control subjects.
Rosa-Neto <i>et al.</i> 2005 (28) ^a	[¹¹ C]raclopride	NA	T	9-NA	Naïve	None	Placebo	Oral	L/R striatum	TOVA	Correlations between TOVA performance and baseline D ₂ /D ₃ were not calculated.
Jucaite <i>et al.</i> 2005 (29)	[¹¹ C]raclopride	φ	T	12-10 (not age matched)	<i>n</i> = 3 (MPH), but exclusion of these subjects from analysis did not change conclusions.	None			L/R CAU and PUT	DSM-IV scores, CPT, <i>r</i> measurements	No difference in striatal D ₂ /D ₃ . Positive correlation between head movement and D ₂ /D ₃ in R CAU. No significant correlations with omission/commission errors, inattention, or impulsivity.
Lou <i>et al.</i> 2004 (30)	[¹¹ C]raclopride	>	T	6-NA	Naïve	Preterm birth (<i>n</i> = 6), right hemiplegia (<i>n</i> = 1), leukomalacia (<i>n</i> = 3)			L/R striatum	TOVA	High D ₂ /D ₃ , associated with poor TOVA reaction time. Low neonatal cerebral blood flow predicted high D ₂ /D ₃ .
Rosa-Neto <i>et al.</i> 2002 (31) ^a	[¹¹ C]raclopride	NA	T	6-NA	No current stimulant treatment	Birth trauma and/or low birth weight	Placebo	Oral	L/R striatum	TOVA	No significant correlations with performance

Table 1. Continued

Authors (reference)	Radiotracer	Dysregulation in ADHD	Age	Sample Size (Patients-Controls)	Treatment History	Comorbid Neurological/Axis-I Psychiatric Disorders	Drug Challenge	Drug Administration	Regions Examined	Behavioral Correlates	Key Findings
Ilgin <i>et al.</i> 2001 (32) ^a	[¹²³ I] IBZM	>	C	9-published control data	Naïve	Screened for psychosis and neurological conditions			L/R CAU and PUT	CTRS, DSM-IV scores	D ₂ at baseline was increased compared with previously published control data. No significant correlations with CTRS. Greater baseline D ₂ was associated with greater reduction in hyperactivity (not inattention) and CTRS scores following a 3 month MPH treatment.
Endogenous DA Levels ^a											
Volkow <i>et al.</i> 2007 (10)	[¹¹ C]raclopride	<	A	19-24	Naïve	None	MPH (single dose)	IV (0.5 mg/kg)	Whole brain analysis and L/R CAU and PUT	CAARS	Reduced MPH-induced change in D ₂ /D ₃ in L and R CAU, amygdala, and hippocampus. Correlation between CAARS inattention and MPH-induced changes in L/R CAU and PUT.
Rosa-Neto <i>et al.</i> 2005 (28)	[¹¹ C]raclopride	>	T	9-NA	Naïve	None	MPH (single dose)	Oral (.3 mg/kg)	L/R striatum	TOVA	MPH decreased D ₂ /D ₃ in L and R striatum. Greater changes in D ₂ /D ₃ availability in the R striatum were associated with greater inattention and impulsivity as measured by TOVA (omission and commission errors, reaction time, variability).
Rosa-Neto <i>et al.</i> 2002 (31)	[¹¹ C]raclopride	>	T	6-NA	No current stimulant treatment	Birth trauma and/or low birth weight	MPH (single dose)	Oral (.3 mg/kg)	L/R striatum	TOVA	MPH decreased D ₂ /D ₃ availability. Positive correlation between commission errors and MPH-induced change in D ₂ /D ₃ availability.
Ilgin <i>et al.</i> 2001 (32)	[¹²³ I] IBZM	>	C	9-NA	Naïve	Screened for psychosis and neurological conditions	MPH (3-month therapy)	Oral (.5 to 1.5 mg/kg.day)	L/R CAU and PUT	CTRS	Three-month MPH treatment significantly reduced baseline D ₂ in all regions. Higher baseline levels were associated with greater MPH-induced reductions in D ₂ .
FDOPA (Brain Decarboxylase Activity, i.e. DA Synthesis)											
Ludolph <i>et al.</i> 2008 (20)	[¹⁸ F]F-DOPA	<	A	20-18	n = 12 (MPH)	History of drug/nicotine consumption (n = 9)-matched with control subjects			Whole brain analysis, with small volume correction in midbrain, R/L CAU and PUT, and amygdala	NA	Decreased [¹⁸ F]DOPA in patients in bilateral PUT, amygdala and dorsal midbrain. [¹⁸ F]DOPA was lower in untreated patients compared with subjects with controls in L PUT, R amygdala and R dorsal midbrain and increased in L amygdala and R anterior cingulate cortex.

Table 1. Continued

Authors (reference)	Radiotracer	Dysregulation in ADHD	Age	Sample Size (Patients-Controls)	Treatment History	Comorbid Neurological/Axis-I Psychiatric Disorders	Drug Challenge	Drug Administration	Regions Examined	Behavioral Correlates	Key Findings
Forsberg <i>et al.</i> 2006 (21)	L-[¹¹ C]DOPA	<	T	8-6	<i>n</i> = 8 (MPH)	Dyslexia (<i>n</i> = 1) and Tourette's syndrome (<i>n</i> = 1)			28 manually adjusted template ROIs, including midbrain, CAU, and PUT	DSM-IV scores	Decreased L-DOPA utilization particularly in subcortical regions. Pattern correlated with symptoms of inattention.
Ernst <i>et al.</i> 1999 (19)	[¹⁸ F]F-DOPA	>	T	10-10 (healthy siblings)	<i>n</i> = 6 (stimulants), medication-free at least 2 weeks before PET scanning.	None			L and R PFC, CAU, PUT, and midbrain	DSM-III-R scores, Child Behavior Checklist, CPRS, CTRS, CPT	48% increased [¹⁸ F]DOPA in R midbrain. [¹⁸ F]DOPA in R midbrain positively correlated with DSM-III-R criteria for ADHD and Conners' hyperactivity subscale.
Ernst <i>et al.</i> 1998 (18)	[¹⁸ F]F-DOPA	<	A	17-23	<i>n</i> = 4 history of stimulant treatment	None			L and R PFC, CAU, PUT, and midbrain	DSM-III-R, CTRS (abbreviated version), Utah criteria of childhood ADHD	Decreased [¹⁸ F]DOPA in medial and L prefrontal areas, no differences in midbrain or striatum. Negative correlation between [¹⁸ F]DOPA in L PFC and Utah criteria of childhood ADHD.
Dopamine Transporter											
Volkow <i>et al.</i> 2010 (27)	[¹¹ C]cocaine	<	A	45-41	Naïve	None			Accumbens, midbrain	MPQ (Achievement scale)	Significant correlation between trait motivation and DAT in accumbens and midbrain in ADHD patients but not control subjects.
Volkow <i>et al.</i> 2009 (11)	[¹¹ C]cocaine	<	A	53-44	Naïve	None			Whole brain analysis and template ROIs from the Talairach Daemon database	SWAN	Decreased DAT in L accumbens, midbrain, CAU and in hypothalamic region. Negative correlation between SWAN inattention scores and DAT in L midbrain.
Hesse <i>et al.</i> 2009 (33)	[¹²³ I]FP-CIT	<	A	17-14	Naïve	Depression in remission (<i>n</i> = 2), multiple sclerosis (<i>n</i> = 1)			Striatum, head of CAU, PUT, thalamus, midbrain	ASRS, WURS, BDI	Decreased DAT in striatum but not in thalamus/midbrain. No correlations with clinical measures.
Szobot <i>et al.</i> 2008 (34)	[⁹⁹ Tc]TRODAT-1	NA	T	17-NA	Naïve	Comorbid drug abuse (cannabis and cocaine)	MPH (3 weeks)	week1: .3 mg/kg/day, week2: .7 mg/kg/day, week3: 1.2 mg/kg/day	L and R CAU and PUT	SNAP-IV	52% reductions of DAT binding in CAU and PUT following 3 weeks of treatment with MPH. No correlations with clinical improvement.

Table 1. Continued

Authors (reference)	Radiotracer	Dysregulation in ADHD	Age	Sample Size (Patients-Controls)	Treatment History	Comorbid Neurological/ Axis-I Psychiatric Disorders	Drug Challenge	Drug Administration	Regions Examined	Behavioral Correlates	Key Findings
Volkow <i>et al.</i> 2007 (9)	[¹¹ C]cocaine	<	A	20-25	Naïve	None			Whole brain analysis and L/R CAU and PUT	CAARS	13% decrease in DAT in L CAU and in L accumbens. No diff in PUT, but positive correlations between DAT in this region and inattention scores both in patients and control subjects.
Spencer <i>et al.</i> 2007 (35)	[¹¹ C]altropane	>	A	21-26	Naïve	None			L/R CAU and PUT	NA	15% increase in R CAU.
Larisch <i>et al.</i> 2006 (36)	[¹²³ I]JFP-CIT	>	A	20-20	Naïve	None			L and R striatum	NA	7% increased striatal DAT in ADHD. Secondary findings: Women > men, age-related decrease of DAT and no influence of nicotine.
La Fougere <i>et al.</i> 2006 (37)	[⁹⁹ Tc]TRODAT-1	>	A	22-14	Naïve	NA	MPH (10 weeks)	5 mg to 60 mg/kg/day	Basal ganglia template ROIs	CGI-I, CGI-S	Increased striatal DAT in 17 out of 22 adult ADHD patients and decreased striatal DAT in further 5 patients who did not respond well to subsequent MPH treatment.
Krause <i>et al.</i> 2006 (14)	[⁹⁹ Tc]TRODAT-1	NA	A	29 patients (10:9/10, 17:10/10, 2:9/9 carriers). NA	Naïve	None			Manually adjusted template ROIs for striatum	NA	DAT1 polymorphism had no influence on striatal DAT.
Krause <i>et al.</i> 2005 (38)	[⁹⁹ Tc]TRODAT-1	NA	A	18	Naïve	None	MPH (10weeks)		Manually adjusted template ROIs for striatum	CGI-S	Patients with high striatal DAT availability responded better to therapy with MPH than those with low DAT availability.
Jucaite <i>et al.</i> 2005 (29)	[¹¹ C]PET2I	<	T	12-10 (not age matched)	<i>n</i> = 3 (MPH), but exclusion of these subjects from analysis did not change conclusions.	None			CAU, PUT and midbrain	CPT, motor measurements	16% lower DAT in midbrain, no difference in striatum. No significant correlations with head movement, omission/commission errors, inattention or impulsivity.
Spencer <i>et al.</i> 2005 (7)	[¹¹ C]altropane	>	A	6-6	<i>n</i> = 1 (stimulant treatment)	Drug abuse history (<i>n</i> = 1)			L/R striatum	NA	34% increased DAT in striatum.
Cheon <i>et al.</i> 2005 (16)	[¹²³ I]IPT	NA	C	11 patients (7: 10/10 DAT allele vs. 4: 9/10 DAT allele)-NA	Naïve	None	MPH (8 weeks)	.3 mg/kg/day to .7 mg/kg/day	L/R basal ganglia	ARS	10/10: 14% increased DAT in striatum; 9/10: 65% decreased DAT in striatum and better response to MPH (opposite to Krause <i>et al.</i> 2005)

Table 1. Continued

Authors (reference)	Radiotracer	Dysregulation in ADHD	Age	Sample Size (Patients-Controls)	Treatment History	Comorbid Neurological/ Axis-I Psychiatric Disorders	Drug Challenge	Drug Administration	Regions Examined	Behavioral Correlates	Key Findings
Feron <i>et al.</i> 2005 (39)	[¹²³ I]joflupane	NA	C	5-NA	NA	None	MPH (9–20 months)	.25 to .6 mg/kg/day for 9–20 months followed by 4 drug-free weeks.	L/R CAU and PUT	Child Behaviour Checklist, Teachers Report Form, Kaufman Assessment Battery for Children, CPT, Developmental Test of Visual-Motor Integration	MPH does not lead to a permanent downregulation of DAT. All children showed an increase of DAT after withdrawal of MPH, comparable with pretreatment levels.
Cheon <i>et al.</i> 2003 (40)	[¹²³ I]IPT	>	C	9-6	Naïve	None			L/R basal ganglia	ARS	Increased DAT (40% in L striatum, 51% in R striatum). No correlations with symptom severity/type.
Vles <i>et al.</i> 2003 (25)	[¹²³ I]joflupane	NA	C	6-NA	Naïve	None	MPH (3 months)	.25-.6 mg/kg/day	L/R CAU and PUT	Extensive neuropsychological testing battery, but performance not correlated with DAT.	28%-75% reduction of striatal DAT following 3-month therapy with MPH, correlated with improved neuropsychological performance.
van Dyck <i>et al.</i> 2002 (41)	[¹²³ I]β-CIT	φ	A	9-9	<i>n</i> = 1 (stimulant treatment)	None	Postscan MPH treatment	2 × titrated dose starting at 1.0 mg/kg/day	Manually adjusted template ROIs for striatum, diencephalon, brainstem	ARS	No significant difference in baseline DAT and no correlation between DAT and symptom severity or response to treatment.
Krause <i>et al.</i> 2000 (42)	[⁹⁹ Tc]TRODAT-1	>	A	10-10	NA	None	MPH (4weeks)	3 × 5mg/day	Manually adjusted template ROIs for striatum	NA	16% higher DAT in ADHD patients. 30% DAT reduction after MPH treatment.
Dresel <i>et al.</i> 2000 (43)	[⁹⁹ Tc]TRODAT-1	>	A	17-14	NA	Drug abuse (<i>n</i> = 1)	MPH (duration NA)	3 × 5mg/day	Manually adjusted template ROIs for striatum, CAU, and PUT	NA	17% increased DAT in striatum.
Dougherty <i>et al.</i> 1999 (44)	[¹²³ I]altropane	>	A	6-NA (compared with control data on 30 healthy control subjects)	<i>n</i> = 4 (stimulant treatment), discontinuation 1 month before scan	None			Striatum	NA	70% increased DAT in striatum.

A, adults; ADHD, attention-deficit/hyperactivity disorder; ARS, ADHD Rating Scale; ASRS, Adult ADHD Self-Report Scale; BDI, Beck Depression Inventory; C, children; CAARS, Conner's Adult ADHD Rating Scales; CAU, caudate; CGI-I, Clinical Global Improvement Scale; CGI-S, Clinical Global Impression Scale; CPRS, Conner's Parent Rating Scale; CPT, Continuous Performance Task; DA, dopamine; DAT, dopamine transporter; <, decrease; FDOPA, [¹⁸F]fluorodopa; >, increase; IV, intravenous; L, left; L-DOPA, L-3,4-dihydroxyphenylalanine; MPH, methylphenidate; MPQ, Multidimensional Personality Questionnaire; NA, not available; φ, no significant group difference; PET, positron emission tomography; PFC, prefrontal cortex; PUT, putamen; R, right; ROI, region of interest; SNAP-IV, Swanson, Nolan and Pelham scale-IV; SWAN, Strengths and Weaknesses of ADHD Symptoms and Normal Behavior; TOVA, Test of Variables of Attention; WURS, Wender Utah Rating Scale.

^aStudies assessing D₂/D₃ both at baseline and following MPH administration.

date, hippocampus, and left amygdala. These findings contrast with those previously reported in adolescent ADHD patients suggesting that greater oral MPH-induced increases in DA concentrations in the right striatum are associated with greater symptom severity (28) (Table 1). A potential factor explaining this discrepancy is the difference in age of the patients assessed. Whether stimulant effects in the cortex or in other low D₂/D₃ receptor regions differ in ADHD patients and control subjects needs to be explored further.

Understanding the Therapeutic Effects of Psychostimulants

Implication of Frontostriatal Networks

The frontal cortex and the basal ganglia operate together to execute goal-directed behaviors via functionally segregated neural networks. Based on the characterization of neuroanatomical projections in nonhuman primates, inputs to the striatum from limbic, associative, and motor areas of the prefrontal cortex are known to be organized topographically along a ventromedial to dorsolateral gradient, with activity along this gradient modulating limbic, cognitive, and motor processing (75). This framework has served to organize the human striatum into ventral striatum, implicated in emotion, motivation, and reward-guided behaviors; associative striatum, involved in cognition; and sensorimotor striatum, related to motor function (76).

A number of neuroimaging studies have recently attempted to map striatal subregions and associated neural circuits in humans. Accumulating evidence from probabilistic tractography analyses on magnetic resonance diffusion-weighted imaging data have confirmed the topographic segregation of corticostriatal projections (77–79). Moreover, using functional connectivity analyses of resting state functional magnetic resonance imaging data, which allow for the mapping of large-scale functional networks, Di Martino *et al.* (80) demonstrated differential patterns of connectivity in striatal subregions along an affective/cognitive/motor axis predicted by the above model of basal ganglia function.

In vivo evidence for the dopaminergic modulation of distinct corticostriatal networks comes from a study investigating the effects of a DA manipulation on seed-based resting-state functional connectivity in healthy control subjects (81). Acute administration of L-3,4-dihydroxyphenylalanine, a DA precursor, was observed to alter resting state functional connectivity in pathways implicated in motor and cognitive function. Although the above methodologies enabling the mapping of frontostriatal connectivity are yet to be used in conjunction with psychostimulant challenges, abnormal frontostriatal connectivity in unmedicated, but not medicated, children with ADHD was demonstrated (82).

Recent PET evidence has highlighted the utility of guiding the analysis and interpretation of DA receptor imaging studies by employing a model of functional rather than anatomical subdivisions of the striatum. A well-replicated region-based approach to investigate the distribution of D₂/D₃ receptors within the human striatum across ventral, associative, and sensorimotor striatum is that described by Martinez *et al.* (26). The wide application of this methodology has proved extremely valuable to our understanding of corticostriatal DA neurotransmission, both in health (26,83) and disease (84,85). An important shortcoming of the extant PET literature in ADHD is that studies often averaged data across the entire striatum or used different landmarks to define caudate and putamen.

The differential effects of D-AMPH on the above striatal subregions constitute a well-replicated finding in healthy volunteers (26,68,69). Using [¹¹C]raclopride, oral MPH administered to young healthy subjects was also reported to result in different sized increases in endogenous DA in these subregions. The increment in DA levels in specific subregions predicted performance on particular cognitive tasks (56). Importantly, some of these effects appeared to be modulated by trait impulsivity.

Implication of Nigrostriatal Networks

The midbrain, via its connections with the striatum, provides a continuous feedforward mechanism of information flow across corticostriatal circuits, thereby operating as an interface for the dynamic processing of functionally distinct information (76). One critical aspect that remains particularly unexplored is how stimulants interact with the afferent control of midbrain dopamine neurons to orchestrate their effects on cognition. Somatodendritic D₂/D₃ autoreceptors located on midbrain DA neurons play an important role regulating DA synthesis and release, acting as potent inhibitors in the presence of high DA concentrations (86,87). Mediated by this negative feedback mechanism, stimulant-induced increases in endogenous DA levels inhibit DA neuron firing (88,89).

How this regulatory mechanism modulates therapeutic effects of psychostimulant medication in ADHD remains to be characterized. Volkow *et al.* (66) suggested that increased endogenous DA following DAT blockade by MPH attenuates background firing rates, increasing the signal-to-noise ratio of striatal cells, thereby improving attention and reducing distractibility.

The implication of nigrostriatal dysregulations in the therapeutic effects of stimulants is of particular interest because 1) animal models of ADHD provide evidence for a hypodopaminergic nigrostriatal system in the disorder (90,91), and 2) PET studies document abnormal midbrain dopaminergic markers in ADHD patients. Although initially evidence pointed toward increased dopamine synthesis in ADHD (19), more recent investigations reported reductions in both synthesis (20,21) and midbrain DAT (11,29) (Table 1).

Interactions Between Prefrontal Cortex and Subcortical DA Systems

Alterations in endogenous DA levels are likely to trigger pre- and post-synaptic compensatory changes to restore the balance in the system, including changes in DA synthesis, release, receptor sensitivity, and neuronal responsiveness. To specify better DA dysfunction underlying ADHD, abnormal dopaminergic markers need to be understood in the presence of powerful counteracting regulatory influences. This critical aspect is often overlooked in models of ADHD, primarily because of methodological limitations.

Multiple lines of evidence suggest that D₂/D₃ receptors are differentially expressed across distinct DA-modulated circuits. While there is evidence indicating that different inverted U-shaped functions exist for different forms of behavior (56), it remains to be understood how DA activity in each of the brain regions implicated in the aforementioned functional circuits is associated with different forms of behavior. Microdialysis studies demonstrate that low and clinically relevant MPH doses preferentially increase extracellular catecholamines within the prefrontal cortex relative to subcortical and other cortical regions (92).

So far, progress in our understanding of cortical DA functioning based on PET has been hampered by the lack of D₂/D₃ receptor ligands suited to image receptors in regions with dramatically different receptor densities (as is the case with the

striatum and the cortex). As a consequence, striatal D₂/D₃ binding has been widely treated as a proxy for D₂/D₃ functioning throughout the brain. This extrapolation is based on a simplistic assumption that individual differences in striatal binding are predictive of binding elsewhere in the brain. Inasmuch as [¹⁸F]fallypride allows simultaneous quantification of receptor availability (and changes in endogenous DA) in both striatal and extrastriatal regions from the same scan, this tracer represents a valuable tool to investigate ADHD and its treatment.

Role of Noradrenaline in ADHD

Though DA dysregulation is central to understanding the neurobiology of ADHD and its pharmacological treatment, the potential contribution of NA has also long been implicated in the pathophysiology of ADHD (93,94).

Noradrenaline projections originate primarily from neurons in the locus coeruleus and send projections to multiple regions, including the prefrontal cortices, which play a critical role in high-level cognitive functions that are often impaired in ADHD, such as working memory and inhibitory response control (51,95). However, there is only very sparse innervation of the striatum by NE, and so it is much less implicated in any striatal changes in ADHD or in effects of stimulant effects that are striatally dependent.

Reuptake of NA by NAT is the principal mechanism for terminating NA neurotransmission in the central nervous system (96), with rapid termination of NA actions before diffusion of NA molecules away from the synapse. Of the pharmacological treatment options available for ADHD, it is noteworthy that the overwhelming majority of drugs shown to be effective have important effects on NA transmission, including MPH and D-AMPH. By contrast, selective serotonin reuptake inhibitors are generally regarded as ineffective in treating the cardinal symptoms of ADHD and its cognitive sequelae (97). The indirect DA/NA agonist bupropion has been shown to be effective in ADHD (98), as have tricyclic drugs with potent noradrenergic properties, such as desipramine (99), and specific alpha-2 receptor agonists such as guanfacine (100).

Modafinil, though not currently approved by the Food and Drug Administration for ADHD, appears to be effective in its treatment (101). Certain of the behavioral and cognitive effects of modafinil are contingent on the integrity of NA transmission (102). The alpha-1 receptor antagonist prazosin antagonizes the prolocomotor effects of modafinil seen in mice (103), while co-administration of prazosin in healthy volunteers blocks the beneficial effects of modafinil seen on the more difficult levels of the Tower of London test of frontal lobe function (104). Furthermore, functional magnetic resonance imaging data suggest that modafinil may modulate the noradrenergic locus coeruleus system that potentially affects prefrontal cortical functioning (105,106).

Another line of evidence implicating brain NA pathways in the treatment of ADHD symptoms is the development of the relatively selective NA reuptake inhibitor atomoxetine and its approval for the treatment of ADHD by the Food and Drug Administration (107). In animals, atomoxetine has been shown to increase cortical NA and DA levels several-fold when given systemically, without putative effects on the subcortical DA system (108). It is these subcortical DA effects that are thought to be responsible for the abuse potential of psychostimulant treatments (109). As such, NA targeting agents such as atomoxetine may offer clinical advantages by virtue of their limited effects on subcortical DA.

The effects of NA-modulating pharmacotherapies on ADHD symptomatology are thought to stem, in part, from intermediary

beneficial effects on cognition (110). Translational studies have dissociated cognitive effects of NA at subreceptors: moderate levels of NA improve cognition (including impulse control) via effects at alpha-2a receptors, while higher levels, such as during extreme stress, impair cognition by engaging alpha-1-adrenoceptors (17). The stop-signal task (SST), which measures impulsivity and is sensitive to ADHD, depends on the integrity of the right inferior frontal gyrus (111–114). On this test, participants make speeded motor responses to go stimuli and attempt to inhibit responses when stop stimuli occur. Impaired response inhibition on the SST is one of the most robust cognitive findings in ADHD (115). Single doses of MPH, modafinil, and atomoxetine have been found to improve response inhibition in humans and in rats (116–118). By contrast, serotonin manipulations appear to have no behavioral effects on the SST (119). In a healthy volunteer study, atomoxetine was found to augment right frontal lobe activation during SST inhibitory control, linking together NA reuptake blockade with cognition and prefrontal cortex blood oxygenation level-dependent response (120). It remains to be seen in humans whether the benefits of ADHD medications on response inhibition can be convincingly dissociated with respect to cortical NA as opposed to DA.

Molecular Imaging of the NA System

For many years, there has been a paucity of suitable NA tracers, because of nonspecific binding of putative ligands and other factors (121). The recent successful deployment of NAT radioligands in humans (122–124) represents an important step forward in the field. Using (S,S)-[¹¹C]methylreboxetine PET in healthy volunteers, clinically relevant doses of MPH were found to significantly reduce NAT availability in a dose-dependent manner in NAT-rich regions, including locus coeruleus, raphé, hypothalamus, and thalamus (122).

The questions of whether there is a difference in NAT density in stimulant-naïve ADHD patients and whether current first-line pharmacotherapies such as MPH and atomoxetine induce similar changes in NAT availability in ADHD patients and healthy control subjects remain to be addressed.

Conclusions

Overall, the previously discussed findings are consistent with a dual role of DA and NA in the pathophysiology of ADHD and its treatment. It is via the close interplay of both the DA and NA systems in corticostriatal circuitry that pharmacotherapies for ADHD operate on different cognitive processes. A growing body of evidence suggests that psychostimulants exert their therapeutic effects in a baseline-dependent manner, according to a hypothesized inverted U-shaped function (48,50). The neurochemical mechanisms underlying this functional effect remain to be fully specified, although they presumably depend on a mixture of dopaminergic and noradrenergic actions at the level of the cortex (especially the prefrontal cortex [95]) and of dopaminergic effects subcortically, e.g., within the basal ganglia. These actions may well be responsible for different therapeutic effects of methylphenidate, whereas more selective agents such as atomoxetine, which is presumably devoid of significant striatal activity, may not exert such a range of effects.

Recent PET findings suggest that DA activity in adult ADHD is depressed (9–11,18,20,21), confirming the catecholamine-agonist theory of stimulant drugs. However, these recent findings are not universally accepted, and references to the old and long-accepted theories regarding ADHD (e.g., increased DAT) still permeate the

literature. There is a need to replicate and expand the molecular neuroimaging literature in ADHD, controlling for potential confounding variables, including examination of DA markers in striatal subregions implicated differentially in limbic, associative, and motor circuits governed by cortical influences.

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