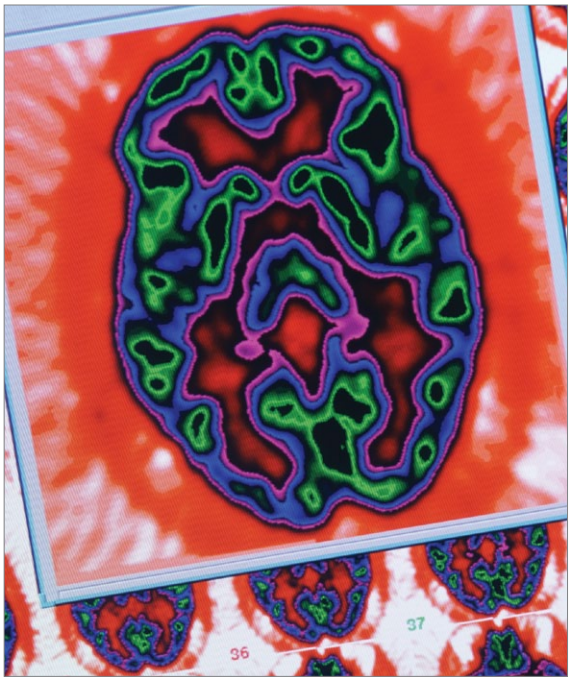
Current PSYCHIATRY

What does molecular imaging reveal about the causes of ADHD and the potential for better management?



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Dysfunction of dopaminergic-frontostriatal neural circuits appears central in ADHD

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common pediatric psychiatric disorders, occurring in approximately 5% of children.[1] The disorder persists into adulthood in about one-half of those who are affected in childhood.[2] In adults and children, diagnosis continues to be based on the examiner's subjective assessment. (See this article on CurrentPsychiatry.com for ***Box 1***[3-9] that describes how ADHD presents a complicated, moving target for the diagnostician.)

Patients who have ADHD are rarely studied with imaging; there are no established imaging findings associated with an ADHD diagnosis. Over the past 20 years, however, significant research has shown that molecular alterations along the dopaminergic–frontostriatal pathways occur in association with the behavioral constellation of ADHD symptoms—suggesting a pathophysiologic mechanism for this disorder.

In this article, we describe molecular findings from nuclear medicine imaging in ADHD. We also summarize imaging evidence for dysfunction of the dopaminergic-frontostriatal neural circuits as central in the pathophysiology of ADHD, with special focus on the dopamine reuptake transporter (DaT). See this article on CurrentPsychiatry.com for ***Box 2***[10,11] that reviews our key observations and looks at the future of imaging in the management of ADHD.

Disclosures

Dr. Thacker reports no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

Dr. Binkovitz received 4 doses of ioflupane I123I (DaTscan) from General Electric for investigator-initiated research, used for animal imaging in 2012.

Dopaminergic theory of ADHD

The executive functions that are disordered in ADHD (impulse control, judgment, maintaining attention) are thought to be centered in the infraorbital, dorsolateral, and medial frontal lobes. Neurotransmitters that have been implicated in the pathophysiology of ADHD include norepinephrine[12] and dopamine[13]; medications that selectively block reuptake of these neurotransmitters are used to treat ADHD.[14,15] Only the dopamine system has been extensively evaluated with molecular imaging techniques.

Because methylphenidate, a potent selective dopamine reuptake inhibitor, has been shown to reduce disordered executive functional behaviors in ADHD, considerable imaging research has focused on the dopaminergic neural circuits in the frontostriatal regions of the brain. The dopaminergic theory of ADHD is based on the hypothesis that alterations in the density or function of these circuits are responsible for behaviors that constitute ADHD.

Despite decades of efforts to delineate the underlying pathophysiology and neurochemistry of ADHD, no single unifying theory accounts for all imaging findings in all patients. This might be in part because of imprecision inherent in psychiatric diagnoses that are based on subjective observations. The behavioral criteria for ADHD can manifest in several disorders. For example, anxiety-related symptoms seen in posttraumatic stress disorder, social anxiety disorder, and panic disorder also present as behaviors similar to those in ADHD diagnostic criteria.

Molecular imaging might provide a window into the underlying pathophysiology of ADHD and, by identifying objective findings, (1) allow for patient stratification based on underlying physiologic subtypes, (2) refine diagnostic criteria, and (3) predict treatment response.

Nuclear medicine findings

In general, nuclear medicine investigations of ADHD can be divided into studies of changes in regional cerebral blood flow (rCBF) or glucose metabolism (rCGM) and those that have assessed the concentration of synaptic structures, using highly specific radiolabeled ligands. Both kinds of studies provide limited anatomic resolution, unless co-registered with MRI or CT scans and either single photon emission computed tomography (SPECT) or positron emission tomography (PET).

Synaptic imaging using radiolabeled ligands with high biologic specificity for synaptic structures has high molecular resolution—that is, radiolabeled ligands used for selective imaging of the dopamine transporter or receptor do not identify serotonin transporters or receptors, and vice versa. (Details of SPECT and PET techniques are beyond the scope of this article but can be found in standard nuclear medicine textbooks.)

SPECT and PET of rCBF

Early investigations of rCBF in ADHD were performed using inhaled radioactive xenon-133 gas.[16] Later, rCBF was assessed using fat-soluble radiolabeled ligands that rapidly distribute in the brain in proportion to blood flow by crossing the blood–brain barrier. Labeled with radioactive 99m-technetium, these ligands cross rapidly into brain cells after IV injection. Once intracellular, covalent bonds within the ligands cleave into 2 charged particles that do not easily recross the cell membrane. There is little redistribution of tracer after initial uptake.

The imaging data set that results can be reconstructed as (1) surface images, on which defects indicate areas of reduced rCBF, or (2) tomographic slices on which color scales indicate relative rCBF values (***Figure 1, page 36***). Because of the minimal redistribution of the tracer, SPECT images obtained 1 or 2 hours after injection provide a snapshot of rCBF at the time tracer is injected. Patients can be injected under various conditions, such as at rest with eyes and ears open in a dimly lit, quiet room, and then under cognitive stress (***Figure 2, page 37***), such as performing a computer-based attention and impulse control task, or during stimulant treatment.

Numerous investigators have found reduced frontal or striatal rCBF, or both, in patients with ADHD, unilaterally on the right[17] or left,[18,19] or bilaterally.[20] Additionally,

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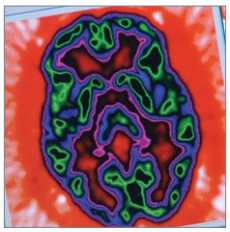
Clinical Point

Molecular imaging might give clinicians the ability to refine diagnostic criteria for ADHD, stratify patients, and predict treatment response



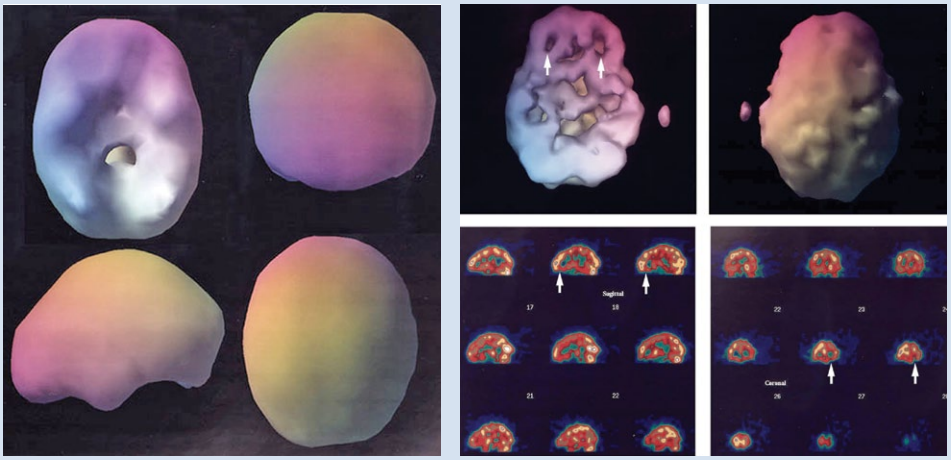
Molecular imaging of ADHD

Clinical Point

Imaging of ADHD examines changes in cerebral blood flow and glucose metabolism and concentrations of synaptic structures

Figure 1

Surface-rendered 3-dimensional cerebral blood flow images in children



Left: Images from a healthy child (age 7), who was imaged for a nonpsychiatric indication. Images were obtained 1 hour after injection of 99m-technetium HMPAO following SPECT acquisition and post-processing (threshold, 55%). Color shading indicates anatomic orientation (light blue, right posterior and inferior; pink, left anterior and lateral; white, left posterior and inferior). The cerebellum is excluded from the reconstructed image. Note the lack of fine anatomic detail, with smoothing of the cortical surface. The smooth outer surface indicates relatively uniform cerebral blood flow (above the 55% threshold value)

Right: Images obtained in a 15-year-old child with attention-deficit/hyperactivity disorder, 1 hour after injection of 99m-technetium HMPAO following SPECT acquisition and post-processing (threshold, 55%). Undersurface image of brain (top frames) demonstrates bilateral infraorbital prefrontal "defects," a result of broad areas of relative cortical hypoperfusion (arrows). Coronal SPECT reconstructions (bottom frames) demonstrate markedly reduced left prefrontal cortical perfusion (arrows). The step 10-color scale indicates a reduction in left infraorbital frontal perfusion of approximately 20% to 30%, compared with other cortical regions

HMPAO: hexamethylpropyleneamine oxime; SPECT: single photon emission computed tomography

with stimulant therapy, normalization of striatal and frontal rCBF has been demonstrated[14,19]—changes that correlate with resolution of behavioral symptoms of ADHD with stimulant treatment.[21]

SPECT of 32 boys with previously untreated ADHD. Kim et al[21] found that the presence of reduced right or left, or both, frontal rCBF, which normalized with 8 weeks of stimulant therapy, predicted symptom improvement in 85% of patients. Absence of improvement of reduced frontal rCBF had a 75% negative predictive value for treatment response. (Additionally, hyperperfusion of the somatosensory cortex has been demonstrated in children with ADHD,[16,22] suggesting increased responsiveness to extraneous environmental input.)

SPECT of 40 untreated pediatric patients compared with 17 age-matched controls. Using SPECT, Lee et al[23] reported rCBF reductions in the orbitofrontal cortex and the medial temporal gyrus of participants; reductions corresponded to areas of motor and impulsivity control. The researchers also demonstrated increased rCBF in the somatosensory area.

After methylphenidate treatment, blood flow to these areas normalized, and rCBF to higher visual and superior prefrontal areas decreased. Substantial clinical improvement occurred in 64% of patients—suggesting methylphenidate treatment of ADHD works by (1) increasing function of areas of the brain that control impulses, motor activity, and attention, and (2) reducing function to sensory areas that lead to distraction by extraneous environmental sensory input.

See this article at CurrentPsychiatry.com for additional discussion of the difficulty of diagnosing ADHD and a summary of how imaging might help make that diagnosis

O-15-labeled water PET of 10 adults with ADHD. Schweitzer et al[24] found that participants who demonstrated improvement in behavioral symptoms with chronic stimulant therapy had reduced rCBF in the striata at baseline—again, suggesting that baseline hypometabolism in the striata is associated with ADHD.

PET of regional cerebral glucose metabolism

Cerebral metabolism requires a constant supply of glucose; regional differences in cerebral glucose metabolism can be assessed directly with positron-emitting F-18-fluoro-2-deoxyglucose. Although metabolically inert, this agent is transported intracellularly similar to glucose; once phosphorylated within brain cells, however, it can no longer undergo further metabolism or redistribution.

Studies using PET to assess rCGM were some of the earliest molecular imaging applications in ADHD. Zametkin et al[25] reported low global cerebral glucose utilization in adults, but not adolescents,[26] with ADHD. However, further study, with normalization of the PET data, confirmed reduced rCGM in the left prefrontal cortex in both adolescents[26] and adults,[27] indicating hypometabolism of cortical areas associated with impulse control and attention in ADHD. In adolescents, symptom severity was inversely related to rCBF in the left anterior frontal cortex.

Synaptic imaging

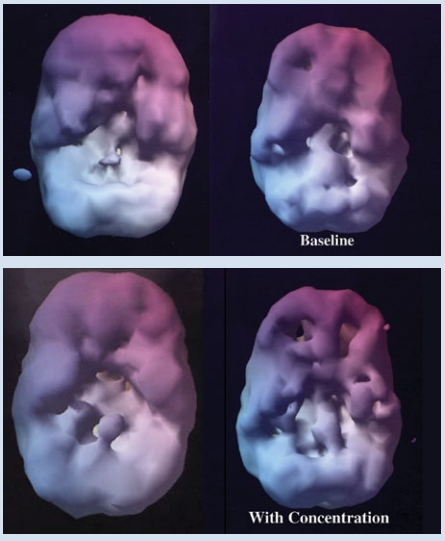
Nuclear imaging has been used to study several components of the striatal dopaminergic synapse, including:

- dopamine substrates, using fluorine-18-labeled dopa or carbon-11-labeled dopa
- dopamine receptors, using carbon-11-labeled raclopride or iodine-123 iodobenzamide
- the tDaT, using iodine-123 ioflupane, 99m-technetium TRODAT, or carbon-11 cocaine (***Figure 3, page 38***).

All of these synaptic imaging agents were used mainly as research tools until 2011, when the FDA approved the SPECT imaging agent iodine-123 ioflupane (DaTscan) for clinical use in assessment of Parkinson's disease.[28] This commercially available agent has high specificity for the DaT, with little background activity noted on SPECT imaging (***Figure 4, page 39***).

Figure 2

Paired surface-rendered 3-dimensional cerebral blood flow images in adults



Images from a healthy adult subject (top) and in an adult patient with ADHD (bottom), both obtained 1 hour after injection of 99m-technetium HMPAO after SPECT acquisition and post-processing (1) without cognitive stress and (2) again 24 hours later during cognitive stress. Note the relative fullness of the infraorbital prefrontal cortices and lack of change in the healthy subject. At baseline, images from the ADHD patient's scan demonstrate only mild reduced blood flow in these regions as well as in the right inferior temporal lobule at baseline; reduced flow becomes markedly worse, however, upon cognitive stress, with new bilateral frontal and temporal defects developing

ADHD: attention-deficit/hyperactivity disorder; HMPAO: hexamethylpropyleneamine oxime; SPECT: single photon-emission computed tomography

Dopamine transporter imaging

Because the site of action of methylphenidate is the DaT, imaging this component of the striatal dopaminergic synapse has been an area of intense investigation in ADHD. Located almost exclusively in the striata,

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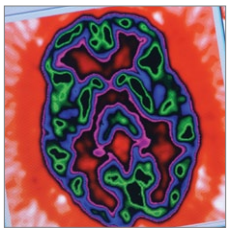
Hyperperfusion of the somatosensory cortex in ADHD suggests increased responsiveness to extraneous environmental input



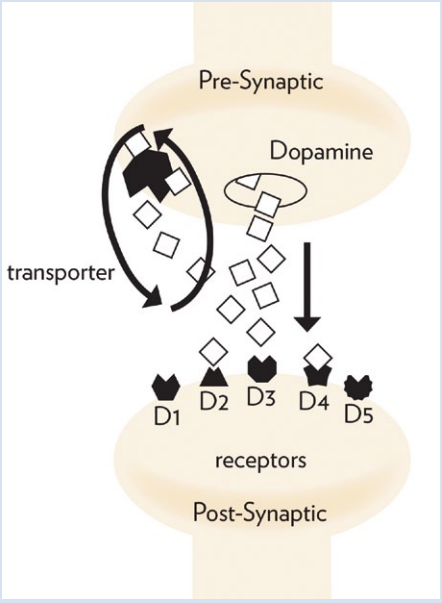
Molecular imaging of ADHD

Clinical Point

SPECT imaging reveals that methylphenidate increases blood flow in the orbitofrontal cortex and medial temporal gyrus

Figure 3

A dopamine synapse, demonstrating dopamine-containing vesicles in the presynaptic neuron



Upon neuronal activation, dopamine is released into the synapse and diffuses across the synaptic cleft, where it might bind to available dopamine receptors (D1–D5; not all types of dopamine receptors are on each dopamine neuron). The transporter carries free synaptic dopamine back into the presynaptic neuron to be reused

DaT reduces synaptic concentrations of dopamine by means of reuptake channels in the cell membrane.[29] By reversibly binding to, and occupying sites on, the DaT, methylphenidate impedes dopamine reuptake, which results in increased availability of dopamine at the synapse.[30]

By demonstrating an increase in striatal DaT density in patients with ADHD—first reported by Dougherty et al[31] using iodine-123 altropane (a dopaminergic uptake inhibitor) in 6 adults with ADHD—investigators have hypothesized that excessive expression of the DaT protein in the striata, which may result from genetic or environmental factors, is a central causative agent of ADHD.[32] Subsequent studies, however, have yielded contradictory findings: Hesse et al,[33] using SPECT imaging, and Volkow et al,[34] using carbon-11 cocaine PET imaging, found reduced DaT density in, respectively, 9 and 26 patients with ADHD.

To clarify the role of DaT levels in the etiology of ADHD and to explain discrepant results, Fusar-Poli et al[35] performed a meta-analysis of 9 published papers that reported the results of DaT imaging in a total of 169 ADHD patients and 129 controls. They noted that these studies included 6 different imaging agents and protocols. Patients were stimulant therapy-naïve (n = 137) or drug-free (refrained from stimulant therapy for a time [n = 32]). The team found that the degree of elevation of the striatal DaT concentration correlated with a history of stimulant exposure, and that the drug-naïve group had a reduced DaT level.

Fusar-Poli's hypothesis? Elevated DaT levels result from up-regulation in the presence of chronic methylphenidate therapy, which accounts for early reports that demonstrated increased striatal DaT density. Clinically, up-regulation might explain the lack of sustained relief of behavioral symptoms with stimulant therapy in 20% of patients with ADHD who showed clinical improvement initially.[36]

Only limited conclusions can be drawn about the role of DaT levels in ADHD, given the small number of patients studied in published reports. In addition, the Fusar-Poli meta-analysis has come under strong criticism because of methodological errors with improper patient inclusion and characterization of treatment status,[37] calling into question the investigators' conclusions.

Does the DaT level hold promise for practice? Despite a lack of clarity about the significance of DaT level in the etiology of ADHD, knowledge of a patient's level might prove useful in predicting which patients will respond to methylphenidate. Namely, several researchers have found that:

- an elevated baseline level of DaT (before stimulant therapy) correlates with robust clinical response
- absence of an elevated baseline DaT level suggests that symptomatic improvement with stimulant therapy in unlikely.[38-40]

Dresel et al[38] evaluated 17 drug-naïve adults, newly diagnosed with ADHD, using

99m-technetium TRODAT SPECT before and after methylphenidate therapy. They found a 15% increase in specific DaT binding in patients with ADHD, compared with controls, at baseline. After treatment, the researchers observed a 28% reduction in specific DaT binding—a significant change from baseline that correlated with behavioral response.

Study: SPECT in 18 adults with ADHD given methylphenidate. Krause[39] used the same SPECT agent to study 18 adults before they received methylphenidate and 10 weeks after treatment. Participants were categorized as responders or nonresponders based on clinical assessment of ADHD symptoms after those 10 weeks. All 12 responders had an elevated striatal DaT concentration at baseline. Of the 6 nonresponders, 5 had a normal level of striatal DaT compared with age-matched controls.

Study: 22 Adult ADHD patients evaluated with 99m-technetium TRODAT SPECT. The same group of investigators[40] presented imaging findings in 22 additional adult patients. Seventeen had an elevated striatal DaT level, 16 of whom responded to stimulant therapy. The remaining 5 patients had reduced striatal DaT at baseline; none had a good clinical response to methylphenidate.

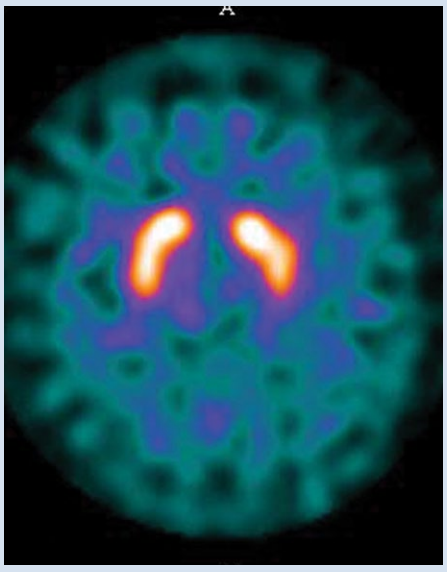
The positive clinical response to methylphenidate in 67%[37] and 77%[40] of patients is in good agreement with results from larger studies, which reported that approximately 75% of patients with ADHD show prompt clinical improvement with stimulants.[41] Improvement might be related to an increase in functioning of the frontostriatal dopaminergic circuit that is seen with stimulant therapy. Increased availability of dopamine at the synapse, resulting from stimulant blockade of the dopamine reuptake transporter, produces increased dopamine neurotransmission and increased activation of frontostriatal circuits.

In another study, rCBF in frontostriatal circuits was determined to be inversely proportional to DaT density; rCBF normalized with stimulant therapy.[42]

Will imaging pave the way for therapeutic stratification? Baseline determinations of striatal DaT concentration with SPECT imaging might make it possible to stratify patients with ADHD symptoms into those likely to show significant behavioral symptom response to methylphenidate and those who are not likely to respond. There might be an objective imaging finding—striatal DaT density—that allows clinicians to distinguish stimulant-responsive ADHD from stimulant-unresponsive ADHD.

Figure 4

Normal iodine-123 DaTscan axial SPECT image through the midbrain



The scan demonstrates normal bilateral intense tracer binding to the striatal dopamine transporters. Note extremely low background uptake, which indicate high specificity of the radioligand for the dopamine transporter. This image demonstrates the exquisite neurochemical resolution obtainable with nuclear medicine imaging

Dopamine substrate imaging

Radiolabeled dopa (carbon-11 or fluorine-18) is transported into presynaptic dopaminergic neurons in the striatum, where it is decarboxylated, converted to radio-dopamine, and stored within vesicles until released in response to neuronal excitation. Semiquantitative assessment is achieved with calculation of specific (striatal) to nonspecific (background) uptake ratios. Increased val-

Clinical Point

Excessive expression of DaT in the striata, possibly from genetic or environmental factors, might be a central causative agent of ADHD

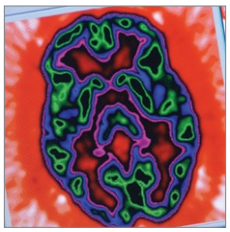
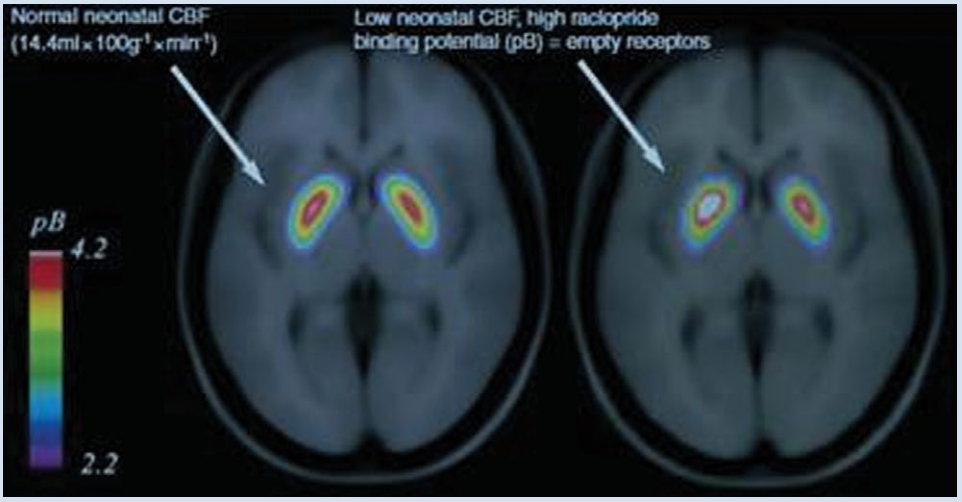


Figure 5

Axial C-11 raclopride SPECT imaging through the midbrain



The scan shows normal D2 receptor binding in a healthy newborn (left), and increased D2 receptor binding in a newborn with history of perinatal hypoxia (right). Increased receptor binding indicates increased D2 availability, which suggests empty receptors due to decreased presynaptic dopaminergic neurons. Decreased neuronal density may be the result of a genetic or environmental cause

SPECT: single photon-emission computed tomography

Source: Reference 50. Reproduced with permission

Clinical Point

Improvement in ADHD seen with stimulant therapy might be related to increased functioning of the dopaminergic–frontostriatal circuit

ues are thought to indicate increased density of dopaminergic neurons.[43]

Ernst et al[44] reported a 50% decrease in specific fluorine-18 dopa uptake in the left prefrontal cortex in 17 drug-naïve adults with ADHD, compared with 23 controls. The same team reported increased midbrain fluorine-18 dopa levels in 10 adolescents with ADHD—48% higher, overall, than what was seen in 10 controls.[43] They hypothesized that these opposite results were the results of a reduction in the dopaminergic neuronal density in adults, which might be part of the natural history of ADHD, or a normal age-related reduction in neuronal density, or both. Increased dopa levels in the team's adolescent group were hypothesized to reflect up-regulation in dopamine synthesis due to low synaptic dopamine concentrations that might result from increased dopamine reuptake.

Dopamine-receptor imaging

The 5 distinct dopamine receptors (D1, D2, D3, D4, and D5) can be grouped into 2 subtypes, based on their coupling with G proteins. D1 and D5 constitute a group; D2, D3, and D4, a second group.

The D1 receptor is the most common dopamine receptor in the brain and is widely distributed in the striatum and prefrontal cerebral cortex. D1 receptor knockout mice demonstrate hyperactivity and poorer performance on learning tasks and are used as an animal model for ADHD.[45] D1 has been imaged using C-11 SCH 23390 PET[46] in rats, but its role in ADHD has yet to be evaluated. D5 is the most recently cloned and most widely distributed of the known dopamine receptors; however, there are no imaging studies of the D5 receptor.[13]

D2 receptors are present in presynaptic and postsynaptic neurons[47] in the neocortex, substantia nigra, nucleus accumbens, and olfactory tubercle, as well as in other structures.[48] Presynaptic D2 receptors act as autoregulators, inhibiting dopaminergic synthesis, firing rate, and release.[49]

continued on page 41

continued from page 40

Using C-11 raclopride PET imaging, Lou et al[50] reported high D2/3 receptor availability in adolescents who had a history of perinatal cerebral ischemia. They found that this availability is associated with an increase in the severity of ADHD symptoms. They proposed that the increase in "empty" receptor density might have been caused by perinatal ischemia-induced presynaptic dopaminergic neuronal loss or an increase in presynaptic dopamine reuptake (***Figure 5, page 40***[50]). Either mechanism could result in upregulation in postsynaptic D2/3 receptors.

Volkow et al[51] reported that D2 receptor density correlated with methylphenidate-induced changes in rCBF in frontal and temporal lobes in humans. They postulated that the variable therapeutic effects of methylphenidate seen in ADHD patients might be related to variations in baseline D2 receptor availability.

Lou et al[50] reported elevated D2 receptor density, demonstrated using carbon-11 raclopride, in children with ADHD, compared with normal adults.

Further support for a relationship between D2-receptor density and symptomatic improvement with methylphenidate in ADHD was presented by Ilgin et al[52] using iodine-123 iodobenzamide SPECT. They found elevated D2 receptor levels in 9 drug-naïve children with ADHD, which is 20% to 60% above what is seen in unaffected children. They noted that these patients showed improvement in hyperactivity when treated with methylphenidate.

In a similar study of 20 drug-naïve adults, Volkow et al[53] found that durable symptomatic improvement with methylphenidate therapy was associated with increased D2 receptor availability.

Summing up

Striatal DaT is the most likely synaptic target for stratifying patients with ADHD, now that a dopamine transporter imaging agent is available commercially. Stratification might allow for refinement in the diagnostic categorization of ADHD, with introduction of stimulant-responsive and stimulant-unresponsive subtypes that are based on DaT imaging findings.

Related Resources

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Drug Brand Names

Iodine-123 ioflupane • DaTscan
Methylphenidate • Ritalin

Acknowledgment

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Bottom Line

Given recent advances showing molecular alterations in the dopaminergic-frontostriatal pathway as central to attention-deficit/hyperactivity disorder, molecular imaging might be useful as an objective study for diagnosis.

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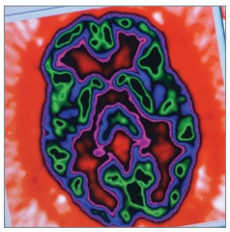
Striatal dopamine reuptake transporter density might be able to distinguish stimulant-responsive ADHD from stimulant-unresponsive ADHD



Molecular imaging of ADHD

Clinical Point

The variable therapeutic effects of methylphenidate seen in ADHD patients might be related to variations in baseline D2 receptor availability

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Box 1

ADHD is a complicated, moving target for the diagnostician

As with all psychiatric disorders, diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) have been defined on the basis of (1) decades of clinical observation of patient behaviors and (2) consensus within the American Psychiatric Association. Diagnostic criteria for ADHD are enumerated in the DSM-5, which defines the disorder as:

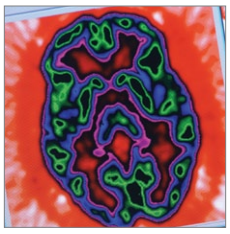
"a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development" characterized by 6 or more inattentive symptoms (ADHD-predominantly inattentive presentation), 6 or more hyperactivity/impulsivity symptoms (ADHD-predominantly hyperactive/impulse presentation), or both (ADHD-combined presentation) that "have persisted for at least 6 months to a degree that is inconsistent with developmental level and has a direct negative impact on social and academic/occupational activities."[3]

Some common behavioral symptoms of ADHD include:

- easy distractability
- forgetfulness
- poor ability to organize
- excessive fidgeting or talking
- difficulty waiting one's turn to answer questions or speak in conversation.

However, these signs and symptoms are based on subjective observations that are fraught with observer error and bias.[4-6]

The lack of objective criteria for diagnosing ADHD has resulted in both overdiagnosis and underdiagnosis,[1,6] and there is considerable public debate about nearly every aspect of this disorder.[7] Additionally, because the mainstays of psychiatric treatment for ADHD are stimulants such as methylphenidate and amphetamines, problems of prescription abuse[8] and medication shortages have arisen.[9]



Box 2

Key points to consider for the future of imaging in ADHD management

In this article, we touch on several important areas of the use of nuclear imaging to both investigate the etiology of attention-deficit/hyperactivity disorder (ADHD) and create a better path to managing the disorder:

- **The underlying pathophysiology of ADHD remains incompletely elucidated** despite multiple lines of inquiry and decades of research. The constellation of executive function symptoms used to define ADHD—ie, inattention and impulsivity—implicate dysfunction of the infraorbital prefrontal cortex.
- **The effectiveness of stimulant blockade of dopamine reuptake in the amelioration of symptoms further suggests involvement of the striatal infraorbital prefrontal dopaminergic neural circuits.** Molecular imaging opens a window into these circuits by assessing (1) regional cerebral blood flow (rCBF) and regional glucose metabolism (rCGM) and (2) underlying synaptic structures, with determination of the relative concentrations of dopamine substrate, receptors, and reuptake proteins.
- **Early molecular imaging studies identified a reduction in rCBF and rCGM in frontal lobes**; later studies demonstrated that stimulant-induced normalization of these findings is associated with symptomatic improvement. The robustness of the therapeutic response correlated with the dopamine transporter density (DaT) concentration and the availability of the dopamine D2 receptor. Genetic and environmental variables have been identified that affect the synaptic density of these structures; these findings might account for the variability seen in the therapeutic response within subpopulations of ADHD patients.
- **Several challenges need to be overcome** before (1) the dopaminergic theory of ADHD can be considered validated with molecular imaging and (2) these imaging findings can be incorporated into strategies for diagnosing and treating the disorder:
  - the number of children and adult subjects whose imaging findings have been reported is small; larger, prospective studies with standardized protocols are needed to validate early findings
  - 2 variables—first, the extent of up-regulation and down-regulation of the dopamine receptors and reuptake proteins as a result of chronic stimulant use and, second, the natural history of ADHD—remain unknown, and their impact on imaging findings in ADHD needs to be clarified; these variables might account for disparate findings about molecular imaging of ADHD that have been reported in the literature
  - correlation of molecular imaging findings with imaging findings from functional magnetic resonance imaging is needed, and might help strengthen, refine, and clarify the dopaminergic theory of ADHD.[10,11]
- **The definitional nature of psychiatric diagnosis presents a fundamental challenge to elucidating molecular causes of ADHD**. The diagnosis of ADHD is based on subjective assessment of behavioral findings. Certain behaviors, such as "fidgeting often," are key to the diagnosis, but are left undefined: What is a "fidget"? How frequent is "often"? More important, these behaviors can have alternative etiologic explanations. For example, a child with anxiety-related symptoms resulting from neglect or abuse can have behaviors that are interpreted as ADHD and treated as such—leading to inappropriate interventions, including stimulant treatment.
- **Identification of an objective imaging finding that accurately predicts response to stimulant treatment response would permit stratification** of patients who are given a diagnosis of ADHD: those in whom a stimulant is indicated and those who require a different intervention and, perhaps, a different diagnosis.
- **Striatal DaT is the most likely synaptic target for stratifying patients**, now that a dopamine transporter imaging agent is available commercially. Stratification might also allow for refinement in the diagnostic categorization of ADHD, with introduction of stimulant-responsive and stimulant-unresponsive subtypes that are based on DaT imaging findings.