Evaluating Dopamine Reward Pathway in ADHD
Clinical Implications

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Attention-deficit/hyperactivity disorder (ADHD)—characterized by symptoms of inattention, hyperactivity, or impulsivity that produce impairment across cognitive, behavioral, and interpersonal domains—has been recognized to also occur in adulthood. It is now recognized that ADHD affects 3% to 5% of the US adult population, which makes it one of the most prevalent of all psychiatric disorders.

Genetic and environmental etiologies that implicate the neurotransmitter dopamine have been proposed for ADHD. Genetic studies have identified a few genes with polymorphisms associated with ADHD, with the most replicated being 2 dopamine genes (e.g., DRD4 and DAT 1 genes), and environmental studies have identified important non-genetic risk factors (e.g., maternal smoking during pregnancy and lead levels) that also may affect the dopamine systems of the brain. Evidence from brain imaging studies have shown that brain dopamine neurotransmission is disrupted in ADHD and that these deficits may underlie core symptoms of inattention and impulsivity.

There is also increased awareness that patients with ADHD may have reward and motivation deficits. Although defined in different ways across studies, this reward-motivation deficit is typically characterized by abnormal behavior change following conditions of reward and punishment. For example, compared with controls, ratings of the reward value of food in ADHD were lower in ADHD than in controls (threshold for significance set at \( P < .005 \) in regions of the dopamine reward pathway in the left side of the brain). Region-of-interest analyses corroborated these findings. The mean (95% confidence interval [CI] of mean difference) for DAT in the nucleus accumbens for controls was 0.71 vs 0.63 for those with ADHD (95% CI, 0.03-0.13, \( P = .004 \)) and in the midbrain for controls was 0.16 vs 0.09 for those with ADHD (95% CI, 0.03-0.12, \( P \leq .001 \)); for DRD2/DRD3 receptors, the mean accumbens for controls was 2.85 vs 2.68 for those with ADHD (95% CI, 0.06-0.30, \( P = .004 \)); and in the midbrain, it was for controls 0.28 vs 0.18 for those with ADHD (95% CI, 0.02-0.17, \( P = .01 \)). The analysis also corroborated differences in the left caudate: the mean DAT for controls was 0.66 vs 0.53 for those with ADHD (95% CI, 0.04-0.22, \( P = .003 \)) and the mean DRD2/DRD3 for controls was 2.80 vs 2.47 for those with ADHD (95% CI, 0.10-0.56, \( P = .005 \)) and differences in DRD2/DRD3 in the hypothalamic region, with controls having a mean of 0.12 vs 0.05 for those with ADHD (95% CI, 0.02-0.12, \( P = .004 \)). Ratings of attention correlated with DRD2/DRD3 in the accumbens (\( r = 0.35 \), 95% CI, 0.15-0.52; \( P = .001 \)), midbrain (\( r = 0.35 \), 95% CI, 0.14-0.52; \( P = .001 \)), and hypothalamic (\( r = 0.31 \), 95% CI, 0.10-0.49; \( P = .003 \)) regions and with DAT in the midbrain (\( r = 0.37 \), 95% CI, 0.16-0.53; \( P = .001 \)).

Conclusion
A reduction in dopamine synaptic markers associated with symptoms of inattention was shown in the dopamine reward pathway of participants with ADHD.

Context
Attention-deficit/hyperactivity disorder (ADHD)—characterized by symptoms of inattention and hyperactivity-impulsivity—is the most prevalent childhood psychiatric disorder that frequently persists into adulthood, and there is increasing evidence of reward-motivation deficits in this disorder.

Objective
To evaluate biological bases that might underlie a reward/motivation deficit by imaging key components of the brain dopamine reward pathway (mesoaccumbens).

Design, Setting, and Participants
We used positron emission tomography to measure dopamine synaptic markers (transporters and DRD2/DRD3 receptors) in 53 nonmedicated adults with ADHD and 44 healthy controls between 2001-2009 at Brookhaven National Laboratory.

Main Outcome Measures
We measured specific binding of positron emission tomographic radioligands for dopamine transporters (DAT) using [11C]cocaine and for DRD2/DRD3 receptors using [11C]raclopride, quantified as binding potential (distribution volume ratio −1).

Results
For both ligands, statistical parametric mapping showed that specific binding was lower in ADHD than in controls (threshold for significance set at \( P < .005 \)) in regions of the dopamine reward pathway in the left side of the brain. Region-of-interest analyses corroborated these findings. The mean (95% confidence interval [CI] of mean difference) for DAT in the nucleus accumbens for controls was 0.71 vs 0.63 for those with ADHD (95% CI, 0.03-0.13, \( P = .004 \)) and in the midbrain for controls was 0.16 vs 0.09 for those with ADHD (95% CI, 0.03-0.12, \( P \leq .001 \)); for DRD2/DRD3 receptors, the mean accumbens for controls was 2.85 vs 2.68 for those with ADHD (95% CI, 0.06-0.30, \( P = .004 \)); and in the midbrain, it was for controls 0.28 vs 0.18 for those with ADHD (95% CI, 0.02-0.17, \( P = .01 \)). The analysis also corroborated differences in the left caudate: the mean DAT for controls was 0.66 vs 0.53 for those with ADHD (95% CI, 0.04-0.22, \( P = .003 \)) and the mean DRD2/DRD3 for controls was 2.80 vs 2.47 for those with ADHD (95% CI, 0.10-0.56, \( P = .005 \)) and differences in DRD2/DRD3 in the hypothalamic region, with controls having a mean of 0.12 vs 0.05 for those with ADHD (95% CI, 0.02-0.12, \( P = .004 \)). Ratings of attention correlated with DRD2/DRD3 in the accumbens (\( r = 0.35 \), 95% CI, 0.15-0.52; \( P = .001 \)), midbrain (\( r = 0.35 \), 95% CI, 0.14-0.52; \( P = .001 \)), and hypothalamic (\( r = 0.31 \), 95% CI, 0.10-0.49; \( P = .003 \)) regions and with DAT in the midbrain (\( r = 0.37 \), 95% CI, 0.16-0.53; \( P = .001 \)).
nondiagnosed children, those with ADHD do not modify their behavior in the face of changing reward conditions. Indeed recent functional magnetic resonance imaging (fMRI) studies showed decreased nucleus accumbens activation with processing of reward in participants with ADHD. However, to our knowledge no study has directly measured synaptic dopamine markers in the accumbens region of individuals with ADHD.

Based on this, we hypothesized abnormality in the mesoaccumbens dopamine pathway (composed of dopamine cells in the midbrain and their projections to the accumbens) in ADHD. To test this hypothesis, we evaluated dopamine D2/D3 receptor (dopamine postsynaptic marker) and DAT (dopamine presynaptic marker) availability in these brain regions in 53 adult participants with ADHD (never medicated) and 44 non-ADHD controls using positron emission tomography (PET) and both [11C]raclopride and [11C]cocaine (D2/D3 receptor and DAT radioligands respectively).

**METHODS**

**Participants**

The PET imaging was carried out at Brookhaven National Laboratory and patient recruitment and evaluation occurred at Duke University, Mount Sinai Medical Center, and University of California, Irvine, from 2001-2009. Institutional review board approval was obtained from all participating institutions. Written informed consent was obtained from all participants after the study had been fully explained to them. Participants were paid for their participation. We studied 53 never-medicated ADHD patients (including 20 described in a prior report of striatal DAT and dopamine release) and 44 healthy controls. Participants with ADHD were recruited from clinical referrals to the ADHD programs at each institution.

To minimize confounding from prior drug exposures or comorbidity, participants were excluded if they had a prior history of substance abuse (other than nicotine) or with positive urine drug screen results, prior or current treatment with psychotropic medications (including stimulants), psychiatric comorbidities (axis I or II diagnosis other than ADHD), neurological disease, medical conditions that may alter cerebral function (ie, cardiovascular, endocrinological, oncological, or autoimmune diseases), or head trauma with loss of consciousness (>30 minutes). These rigorous exclusion criteria contributed to the length of the study (from 2001 to 2009).

Two clinicians interviewed the patients to ensure that Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) diagnostic criteria were met, including the presence of at least 6 or 9 inattention symptoms (with or without 6 of 9 hyperactive or impulsive symptoms) as ascertained with a semi-structured psychiatric interview using modifications for adult prompts of ADHD behaviors. The Clinical Global Impressions Severity Scale was used to assess overall impairment. For diagnosis, ADHD participants were required to have at least a moderate severity level of 4 or greater. In addition, evidence was required from each participant’s history that some symptoms of ADHD started before age 7 years. Controls were recruited from advertisements in the local newspapers and met the same exclusion criteria but not the inclusion criteria for diagnosis of ADHD. Controls were excluded if they described symptoms of inattention or hyperactivity that interfered with everyday activities. Table 1 provides demographic and clinical characteristics of the participants.

**Clinical Scales**

The DSM-IV ADHD items were assessed using the Strengths and Weaknesses of ADHD-symptoms and Normal-behavior (SWAN) rating scale, which uses a positive scale for symptoms (1 to 3) and a negative scale for the opposite of the symptoms (−1 to −3) ranging from far below average to far above average. This allows one to assess the full range of functioning in the 2 domains of ADHD defined as dimensions in the population (ie, attention and activity or reflectivity) to be assessed rather than the severity of psychopathology related to presence of inattention and hyperactivity-impulsivity symptoms in those with ADHD. The range for the scores of the SWAN is −3 to 3. The psychometric properties of the SWAN rating scale are superior to those of truncated symptom-severity ratings scales. Ratings on the SWAN were completed on 46 ADHD participants and 38 controls and were used to assess the correlations between these dimensions across all participants and the PET dopamine measures (Table 1).

Also obtained was the Conners Adult ADHD Rating Scale long version, which provides self-assessment of severity of ADHD symptoms on a 4-point scale (not at all, 0; just a little, 1; pretty much, 2; and very much, 3).
2; and very much, 3). Eight scores are provided (range of possible scores): A, inattention/memory problems (0-36); B, hyperactivity/restlessness (0-36); C, impulsivity/emotional lability (0-36); D, problems with self-concept (0-18); E, DSM-IV inattentive symptoms (0-18); F, DSM-IV hyperactive-impulsive symptoms (0-27); G, DSM-IV symptom total (0-54); and H, ADHD index (0-36). This rating system has been widely used in clinical and research settings and has well-established factor structure, reliability, and validity (Table 1).

PET Scans
A Siemens HR1 tomograph was used (Siemens/CTI Knoxville, Tennessee; resolution 4.5 × 4.5 × 4.5 mm full width half-maximum). Dynamic scans were started immediately after injection of 4 to 10 mCi of [11C]raclopride (specific activity 0.5-1.5 Ci/µM at end of bombardment) and after injection of 4 to 8 mCi of [11C]cocaine (specific activity >0.53 Ci/µmol at end of bombardment) and were obtained for a total of 60 minutes as previously described. Arterial blood was obtained to measure the concentration of unchanged [11C]raclopride and [11C]cocaine in plasma. For this study, [11C]cocaine was chosen as the DAT radioligand because its specific binding is selective for DAT (its binding is inhibited by drugs that block the DAT but not by drugs that block the norepinephrine or the serotonin transporters); it provides with reproducible measures when participants are tested on separate occasions and its kinetics are ideal for in vivo quantification. Moreover, its synthesis is very reliable, which is important when conducting complex multitracer studies like those performed in this study.

Image Analysis and Statistics
The [11C]raclopride and the [11C]cocaine images were transformed into distribution volume ratio images by computing the total distribution volume in each pixel and then dividing it by the distribution volume in the cerebellum. To obtain the distribution volume, circular regions in the cerebellar hemispheres were extracted in 2 planes located at −28 mm and −36 mm from the intercommissural plane. The cerebellar regions were then projected to the dynamic scans to obtain concentrations of [11C] vs time, which along with the concentration of unchanged tracer in plasma were used to calculate the distribution volume in the cerebellum, using a graphical analysis technique for reversible systems. The ratio Bmax/Kd measured in this way is referred to as the binding potential, BPND. Also measured was the plasmato-tissue transfer constant (K1) in striatum and cerebellum for both radioligands using the graphical analysis technique.

Statistical parametric mapping was used to assess the differences in the distribution volume ratio images (for both [11C]raclopride and [11C]cocaine images) between controls and participants with ADHD without an a priori selection of anatomical brain regions. For this purpose the distribution volume ratio images were spatially normalized using the Montreal Neurological Institute template provided in the statistical parametric mapping 99 package (Wellcome Trust Centre for Neuroimaging, London, England) and subsequently smoothed with a 16-mm isotropic Gaussian kernel. Independent samples t tests were performed to compare the differences between groups. Significance was set at P < .005 (cluster corrected >100 voxels) and statistical maps were overlaid on an MRI structural image. Significance detected by statistical parametric mapping was corroborated with independently drawn region-of-interest analyses using templates from the Talairach Daemon database. FIGURE 1 shows the location of the region of interest used for this analysis. Differences in D2/D3 receptor and DAT availability were assessed with independent samples t tests (2 tailed).

Pearson product-moment correlations were used to assess the relationship be-
tween the DAT and D2/D3 receptors and the 2 dimensions of the SWAN rating score (attention and activity or reflectivity).

Definitions for significant difference for the outcome measures were that statistical parametric mapping comparisons for the DAT and the D2/D3 images had to be significant at $P < .005$ (cluster corrected $>100$ voxels) and the regional findings had to be corroborated by independently drawn region of interests; comparisons for these corroborative measures had to be significant at $P < .05$; correlations analyses had to be significant at $P < .006$, which was chosen to maintain an overall significance level of $P < .05$ based on a Bonferroni correction for 4 regions and 2 clinical measures (attention and activity or reflectivity). The statistical package used was Statview, version 5.0.1 (Abacus Concepts, Berkeley, California).

Figure 2. Regions in the Brain in Which Dopamine Measures Were Lower in Participants With ADHD Than in Controls

A, Regions showed significantly lower dopamine D2/D3 receptor availability in participants with attention-deficit/hyperactivity disorder (ADHD) than in controls (obtained from $[^{11}C]$raclopride images). B, Regions showed significantly lower dopamine transporter availability in the participants with ADHD than in controls (obtained from $[^{11}C]$cocaine images). Significance corresponds to $P < .005$, cluster $>100$ voxels. The yellow regions identify the areas in the brain for which the measures differed between controls and participants with ADHD. The location of the region that differed was similar for the dopamine D2/D3 receptor and for the dopamine transporter and included the locations of the left ventral striatum (including accumbens and ventral caudate), left midbrain, and left hypothalamus. The z coordinate maps the superior-inferior position.
Sample-size calculation for this study was based on our preliminary studies (with smaller sample sizes) on DAT and D2/D3 receptors, which revealed a difference in caudate between groups at an effect size (ratio between the mean difference and the pooled standard deviation) between 0.65 and 0.80. For such effect sizes, to achieve a power of at least 80% using the independent samples t test with a significance level of .05 (2 sided), we needed to recruit at least 40 participants per group. The eventual sample sizes of 53 in the ADHD and 44 in the control groups allowed the detection of the estimated mean differences with a power between 88% and 97% via the independent samples t test with a significance level of .05 (2 sided).

RESULTS

Dopamine D2/D3 Receptors

Statistical parametric mapping analysis of the [11C]raclopride distribution volume ratio images revealed a cluster in the same location as manifested in the [11C]raclopride images. This cluster included the left ventral caudate, accumbal, midbrain, and hypothalamic regions, as well as the hypothalamic region (Figure 2 and eTable available at http://www.jama.com). These findings were confirmed by independently drawn region of interest, which also showed ADHD-control differences in left accumbens, midbrain, caudate, and in hypothalamic regions (Table 2). There were no regions that were higher in ADHD participants than in controls. In contrast the K1 measures for [11C]cocaine (transport of radioligand from plasma to tissue) did not differ either in left caudate with the both groups having a mean 0.11 (95% confidence interval [CI], −0.01 to 0.006 mean difference) or in left accumbens region with the controls having a mean of 0.12 vs a mean of 0.11 for those with ADHD (95% CI, −0.01 to 0.005).

Correlation With ADHD Symptoms Dimensions

The dimension of attention (from the SWAN) was negatively correlated with D2/D3 receptor availability in the left accumbens region (r = 0.35; 95% CI, 0.15-0.52; P = .001), left midbrain (r = 0.33; 95% CI, 0.14-0.52; P = .001), left caudate (r = 0.32; 95% CI, 0.11-0.50; P = .003), and left hypothalamic region (r = 0.31; 95% CI, 0.10-0.49; P = .003) and with DAT availability in left midbrain (r = 0.37; CI, 0.16, 0.53; P < .001; Figure 3). Because the SWAN scale rates symptoms with a positive scale (from 1 to 3) and the opposite of symptoms with a negative scales (from −1 to −3) the negative correlation indicates that the lower the dopamine measures, the greater the symptoms of inattention. None of the correlations with the dimension of activity or reactivity was significant.

COMMENT

This study provides evidence in favor of the predicted disruption in the meso-accumbens dopamine pathway in ADHD. With PET imaging, lower D2/D3 receptor and DAT availability in those with ADHD than in the control group was documented in 2 key brain regions for reward and motivation (accumbens and midbrain). It also corroborates disruption of synaptic dopamine markers in caudate in adults with ADHD and provides preliminary evidence that the hypothalamus may also be affected.

The lower than normal D2/D3 receptor and DAT availability in the accumbens and midbrain regions supports the hypothesis of an impairment of the dopamine reward pathway in ADHD. Because measures of reward sensitivity were not measured, we can only infer that the impairment in the dopamine reward pathway could underlie the clinical evidence of abnormal responses to reward in ADHD. The reward deficits in ADHD are characterized by a failure to delay

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**Table 2. Measures of Dopamine D2/D3 Receptor and Dopamine Transporter Availability**

<table>
<thead>
<tr>
<th>Left Hemisphere</th>
<th>Available, Mean (SD)</th>
<th>Effect Size</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine D2/D3 receptor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accumbens region</td>
<td>2.85 (0.31)</td>
<td>2.68 (0.28)</td>
<td>0.61</td>
<td>0.06 to 0.30</td>
</tr>
<tr>
<td>Caudate</td>
<td>2.80 (0.49)</td>
<td>2.47 (0.61)</td>
<td>0.60</td>
<td>0.10 to 0.56</td>
</tr>
<tr>
<td>Midbrain</td>
<td>0.28 (0.14)</td>
<td>0.18 (0.19)</td>
<td>0.57</td>
<td>0.02 to 0.17</td>
</tr>
<tr>
<td>Hypothalamic region</td>
<td>0.12 (0.13)</td>
<td>0.04 (0.12)</td>
<td>0.61</td>
<td>0.02 to 0.12</td>
</tr>
<tr>
<td><strong>Dopamine transporter</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accumbens region</td>
<td>0.71 (0.16)</td>
<td>0.63 (0.11)</td>
<td>0.59</td>
<td>0.03 to 0.13</td>
</tr>
<tr>
<td>Caudate</td>
<td>0.66 (0.23)</td>
<td>0.53 (0.19)</td>
<td>0.62</td>
<td>0.04 to 0.22</td>
</tr>
<tr>
<td>Midbrain</td>
<td>0.16 (0.10)</td>
<td>0.09 (0.11)</td>
<td>0.66</td>
<td>0.03 to 0.12</td>
</tr>
<tr>
<td>Hypothalamic region</td>
<td>−0.01 (0.10)</td>
<td>−0.05 (0.12)</td>
<td>0.36</td>
<td>−0.01 to 0.09</td>
</tr>
</tbody>
</table>
The dopamine reward pathway in ADHD

Figure 3. Regression Slopes Between Dopamine D2/D3 Receptor and Dopamine Transporter Availability and Scores on Attention

The Dimension of the Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder (ADHD)—symptoms and Normal-behavior (SWAN) rating scale uses a positive scale for symptoms (1 to 3) and a negative scale for the opposite of the symptoms (−1 to −3) ranging from “far below average” to “far above average.” The negative numbers in some of the regions show that the ratio of the specific to nonspecific binding of the radioligand is very low for these regions. The solid line in each scatterplot corresponds to the regression line (line of best fit).

Controls

Participants with ADHD

Dopamine transporter availability

D2/D3 receptor availability

Left accumbens

Left hypothalamic

Left caudate

Left midbrain

D2/D3 receptor availability

Dopamine transporter availability

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The Dimension of the Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder (ADHD)—symptoms and Normal-behavior (SWAN) rating scale uses a positive scale for symptoms (1 to 3) and a negative scale for the opposite of the symptoms (−1 to −3) ranging from “far below average” to “far above average.” The negative numbers in some of the regions show that the ratio of the specific to nonspecific binding of the radioligand is very low for these regions. The solid line in each scatterplot corresponds to the regression line (line of best fit).

Controls

Participants with ADHD

Dopamine transporter availability

D2/D3 receptor availability

Left accumbens

Left hypothalamic

Left caudate

Left midbrain

D2/D3 receptor availability

Dopamine transporter availability

The preliminary finding reported herein of lower than normal dopamine D2/D3 receptor availability in the hypothalamic region of ADHD participants is intriguing because if replicated, it could hypothetically provide a neurobiological basis for the high comorbidity of ADHD with signs and symptoms suggestive of hypothalamic pathology such as sleep disturbances, overweight or obesity, and abnormal responses to stress. Multiple hypothalamic nuclei express dopamine D2 receptors, but the limited spatial resolution of a PET scan does not allow for localizing where the differences between the groups occurred. Relevant to the role of the hypothalamus in ADHD is the association of a mutation in the melanocortin-4 receptor (MC4R) gene, expressed in several hypothalamic nuclei that results in obesity, with ADHD.

Our findings of an association of the mesoaccumbens dopamine pathway...
with ADHD inattention symptoms may have clinical relevance. This pathway plays a key role in reinforcement-motivation and in learning stimulus-reward associations, and its involvement in ADHD supports the use of interventions to enhance the saliency of school and work tasks to improve performance. Both motivational interventions and contingency management have been shown to improve performance in ADHD patients. Also stimulant medications have been shown to increase the saliency of a cognitive task (motivation, interest) in proportion to the drug-induced dopamine increases in striatum.

**Limitations**

[11C]Raclopride measures are influenced by extracellular dopamine (the higher the extracellular dopamine, the less the binding of [11C]raclopride to D2/D3 receptors), and thus low-binding potential could reflect low D2/D3 receptor levels or increased dopamine release. However, the latter is unlikely since we had previously reported that dopamine release in a subgroup of our ADHD participants was lower than in controls. Also although [11C]cocaine’s binding to DATs is minimally affected by competition with endogenous dopamine, DAT availability reflects not only the density of dopamine terminals but also synaptic dopamine tone, because DAT up-regulates when synaptic dopamine is high and down-regulates when dopamine is low. Thus low DAT availability could reflect fewer dopamine terminals or decreased DAT expression per dopamine terminal.

The relatively low affinity of [11C]raclopride and [11C]cocaine for their targets makes them better suited to measure regions with high D2/D3 receptor or DAT density (ie, caudate, putamen, and accumbens) and less sensitive to regions with lower levels such as the hypothalamus and midbrain. However, despite this limitation, significant differences in the latter regions between controls and participants with ADHD was shown.

Another study limitation was that measures of reward sensitivity were not performed. Thus, we can only infer that the decreases in the dopamine markers in the accumbens region could underlie the reward deficits that have been reported in patients with ADHD.

Morphological MRI images were not obtained and thus whether volumetric differences in striatum in those with ADHD that could account for these findings could not be ascertained since volumetric differences in striatum have been reported in ADHD. However, that there were no group differences in measures of K1 (transport of radio-tracer from plasma to tissue) in striatum, which would have also been affected by volumetric changes, indicates that these findings reflect decreased availability of DAT and D2/D3 receptors rather than decreases secondary to partial volume effects.

The correlations with reflectivity or impulsivity and the PET dopamine measures were not significant, which could reflect that the scores were low and thus the sensitivity to observe such a correlation was lacking. Alternatively it could reflect the involvement of frontal regions in impulsivity, which could not be measured with current PET radioligands; D2/D3 receptors and DAT levels in frontal regions are very low.

Although the significant findings in this study are restricted to the left hemisphere, the statistical power may have contributed to the lack of significant ADHD-normal differences in the right brain regions. Moreover, because an a priori laterality hypothesis was lacking and, to our knowledge, no solid evidence exists in the literature to support laterality for reward, the laterality effects should be interpreted as preliminary and in need of replication.

This study was not initially designed to evaluate hypothalamic dopamine involvement in ADHD. Thus, this finding is preliminary and in need of replication. Moreover, future studies designed to evaluate hypothalamic pathology in ADHD and its potential clinical significance should assess sleep pathology and should not exclude obese participants, as was the case for the current study.

In conclusion, these findings show a reduction in dopamine synaptic markers in the dopamine reward pathway midbrain and accumbens region of participants with ADHD that were associated with measures of attention. It also provides preliminary evidence of hypothalamic involvement in ADHD (lower than normal D2/D3 receptor availability).

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**Author Contributions:** Dr Volkow had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Volkow, Wang, Wigal, Newcorn, Swanson.

**Acquisition of data:** Wang, Kollins, Wigal, Newcorn, Telang, Fowler, Pradhan.

**Analysis and interpretation of data:** Volkow, Wang, Kollins, Wigal, Newcorn, Telang, Zhu, Logan, Ma, Wong, Swanson.

**Drafting of the manuscript:** Volkow, Wang, Fowler.

**Critical revision of the manuscript for important intellectual content:** Volkow, Wang, Kollins, Wigal, Newcorn, Telang, Zhu, Logan, Ma, Pradhan, Wong, Swanson.

**Statistical analysis:** Zhu, Wong, Swanson.

**Obtained funding:** Volkow, Wang, Newcorn.

**Administrative, technical, or material support:** Wang, Kollins, Wigal, Telang, Fowler, Ma, Swanson.

**Study supervision:** Wang, Kollins, Wigal, Fowler.

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**Role of the Sponsor:** The funding agencies did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data.
REFERENCES


Figure. Relationship Between Airway Function at Age 2 Years and Lung Function Change Between Ages 9 and 15 Among 17 Survivors of Bronchopulmonary Dysplasia

Between ages 9 and 15 years, zFEV₁ increased in all patients with a VmaxFRC greater than the 5th percentile (open circles) while it decreased in all but 1 patient with VmaxFRC less than the 5th percentile (filled circles). Dashed lines indicate 95% confidence interval for the regression line; zVmaxFRC, the z score of the maximum flow at functional residual capacity; zFEV₁, the z score of the forced expiratory volume in 1 second.

vs 245 mL/min; 95% CI, 202 to 288 mL/min; P = .01) and a significantly lower zFEV₁ at 15 years (−2.77; 95% CI, −3.90 to −1.64; vs −0.52; 95% CI, −1.44 to 0.40; P = .003).

Comment. Early lung injuries may influence lifetime respiratory health. In the general population, low VmaxFRC values shortly after birth are a primary risk factor for airflow obstruction in adulthood. While our findings should be considered preliminary because of the small sample size, severe early airflow obstruction at 2 years identified survivors of BPD at greater risk of disrupted lung growth during their childhood, suggesting a guarded long-term respiratory prognosis. Patients with better airflow at 2 years showed an improvement in lung function in later childhood, suggesting some degree of functional recovery. In addition, our findings suggest that preterm delivery without BPD may also affect long-term lung function, although to a lesser extent than in patients with BPD.

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Analysis and interpretation of data: Filippone, Bonetto, Cherubin, Carraro, Baraldi.

Drafting of the manuscript: Filippone, Carraro, Baraldi.

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Statistical analysis: Filippone, Cherubin, Carraro.

Administrative, technical, or material support: Baraldi.

Study supervision: Filippone, Baraldi.

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CORRECTIONS

Factual Error: In the Literatim published in the August 19, 2009, issue of JAMA (2009;302[7]:804-806), the last sentence of the second paragraph contained an error. The sentence should have read “But it was John Jacob Astor, the first US multimillionaire, who put Mackinac Island on the map in 1817, when Michigan was still a territory of the United States and Astor chose the island as the main trading post of his fabled American Fur Company, a pelt empire that spanned from the Great Lakes to the Mississippi River.”

Incorrect Wording: The Preliminary Communication titled “Evaluating Dopamine Reward Pathway in ADHD: Clinical Implications” by Volkow et al, published in the September 9, 2009, issue of JAMA (2009;302[10]:1084-1091), had incorrect wording in the “Results” section. On page 1088 in the “Dopamine Transporters” subsection, the sentence that reads “Independently drawn region of interest corroborated significantly lower mean DAT availability in left accumbens among controls than in those with ADHD midbrain and caudate but the reductions in left hypothalamic region were not significantly different (Table 2)” should have read “Independently drawn region of interest corroborated significantly lower DAT availability in left accumbens, midbrain, and caudate among participants with ADHD than among controls, but the reductions in the left hypothalamic region were not significantly different (Table 2).”