PRELIMINARY COMMUNICATION

# Evaluating Dopamine Reward Pathway in ADHD

## Clinical Implications

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**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 $D_2/D_3$ 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 [$^{11}$C]cocaine and for $D_2/D_3$ receptors using [$^{11}$C]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 $D_2/D_3$ 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 $D_2/D_3$ for controls was 2.80 vs 2.47 for those with ADHD (95% CI, 0.10-0.56; $P = .005$) and differences in $D_2/D_3$ 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 $D_2/D_3$ in the accumbens ($r = 0.35$; 95% CI, 0.15-0.52; $P = .001$), midbrain ($r = 0.35$; 95% CI, 0.14-0.52; $P = .001$), caudate ($r = 0.32$; 95% CI, 0.11-0.50; $P = .003$), and hypothalamic ($r = 0.31$; CI, 0.10-0.49; $P = .003$) regions and with DAT in the midbrain ($r = 0.37$; 95% CI, 0.16-0.53; $P \leq .001$).

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

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ATTENTION-DEFICIT/HYPERACTIVITY disorder (ADHD) is characterized by symptoms of inattention, hyperactivity, or impulsivity that produce impairment across cognitive, behavioral, and interpersonal domains.[1] Although for many years it was believed to be a disorder of childhood and adolescence, it is now recognized to also occur in adulthood. It is estimated that ADHD affects 3% to 5% of the US adult population,[2] 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.[3] Genetic studies have identified a few genes with polymorphisms associated with ADHD, with the most replicated being 2 dopamine genes (eg, *DRD4* and *DAT 1* genes),[3] and environmental studies have identified important nongenetic risk factors (eg, maternal smoking during pregnancy and lead levels) that also may affect the dopamine systems of the brain.[4] Evidence from brain imaging studies have shown that brain dopamine neurotransmission is disrupted in ADHD[5-9] and that these deficits may underlie core symptoms of inattention[8] and impulsivity.[9]

There is also increased awareness that patients with ADHD may have reward and motivation deficits.[10-12] 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

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nondiagnosed children, those with ADHD do not modify their behavior in the face of changing reward conditions.[13] The mesoaccumbens dopamine pathway, which projects from the ventral tegmental area (VTA) in the midbrain to the nucleus accumbens is critically involved in reward and motivation[14] and has been hypothesized to underlie the reward and motivational deficits observed in ADHD.[11,15] Indeed recent functional magnetic resonance imaging (fMRI) studies showed decreased nucleus accumbens activation with processing of reward in participants with ADHD.[16,17] 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 abnormalities 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 $D_2/D_3$ 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 [$^{11}$C]raclopride and [$^{11}$C]cocaine ($D_2/D_3$ receptor and DAT radioligands respectively).[18,19]

## 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[6,8]) 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 of 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[20] 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.

**Table 1.** Demographic and Clinical Characteristics of Participants

| | Controls (n = 44) | ADHD (n = 53) |
|---|---|---|
| Age, mean (SD), y | 31 (6) | 32 (8) |
| Body mass index | 25 (5) | 25 (3) |
| Sex, No. (%) | | |
| Men | 30 (68) | 27 (51) |
| Women | 14 (32) | 26 (49) |
| Education, mean (SD), y | 15 (2) | 15 (4) |
| Smoking status, No. (%) | | |
| Current | 1 (2) | 4 (7) |
| Past[a] | 4 (9) | 1 (2) |
| CGI-severity, mean (SD) | NA | 5 (1) |
| ADHD subtype, No. (%) | NA | |
| Inattentive | | 30 (57) |
| Hyperactive | | 4 (7) |
| Combined | | 19 (36) |
| CAARS, mean (SD), score | | |
| Inattention | 5 (4) | 25 (5) |
| Hyperactivity | 7 (4) | 23 (8) |
| Impulsivity | 4 (3) | 19 (7) |
| Self-concept | 3 (3) | 9 (4) |
| *DSM* inattentive | 3 (3) | 20 (4) |
| *DSM* hyperactive | 3 (3) | 15 (6) |
| Total symptoms | 6 (5) | 36 (7) |
| ADHD index | 4 (3) | 22 (5) |
| SWAN, mean (SD), score | | |
| Attention | −1.5 (1) | 1.6 (1) |
| Hyperactivity | −1.2 (1) | 0.6 (1) |

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CAARS, Conners Adult ADHD Rating Scale; CGI, Clinical Global Impressions Severity; *DSM*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); SWAN, Strengths and Weaknesses of ADHD-symptoms and Normal-behavior.

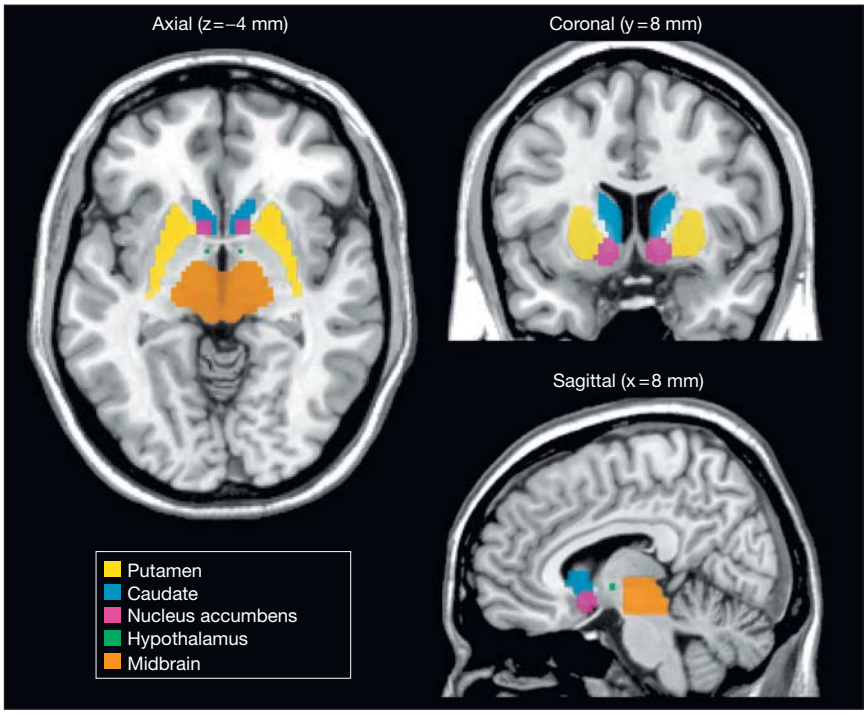
[a] Two participants had quit smoking in the past year, whereas the others had quit more than 2 years before study start.

### 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.[21] 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.[22] 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,

**Figure 1.** Regions of Interest Used to Extract the $D_2$ / $D_3$ Receptor and Dopamine Transporter Measures




The regions of interest for the midbrain are obtained in several planes, and the shadow is projected to the axial image shown in the figure, which explains why the third ventricle is covered by the region. The x coordinate maps the left-right position; the y coordinate, the anterior-posterior position; and the z coordinate, the superior-inferior position.

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 (0-27); F, *DSM-IV* hyperactive-impulsive symptoms (0-27); G, *DSM-IV* symptom total (0-54); and H, ADHD index (0-36).[23] This rating system has been widely used in clinical and research settings and has well-established factor structure, reliability, and validity (Table 1).[24]

### PET Scans

A Siemens $HR^+$ tomograph was used (Siemens/CTI Knoxville, Tennessee; resolution $4.5 \times 4.5 \times 4.5$ mm full width half-maximum). Dynamic scans were started immediately after injection of 4 to 10 mCi of [$^{11}$C]raclopride (specific activity 0.5-1.5 Ci/μM at end of bombardment) and after injection of 4 to 8 mCi of [$^{11}$C]cocaine (specific activity >0. 53 Ci/μmol at end of bombardment) and were obtained for a total of 60 minutes as previously described.[18,19] Arterial blood was obtained to measure the concentration of unchanged [$^{11}$C]raclopride[18] and [$^{11}$C]cocaine[19] in plasma. For this study, [$^{11}$C]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 the block the norepinephrine or the serotonin transporters)[25]; it provides with reproducible measures when participants are tested on separate occasions[19] and its kinetics are ideal for in vivo quantification.[26] 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 [$^{11}$C]raclopride and the [$^{11}$C]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 $^{11}$C 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.[26] $B_{max}/K_d$ (distribution volume ratio –1, for which $K_d$ and $B_{max}$ are the effective in vivo constants in the presence of endogenous neurotransmitter and nonspecific binding) was used as the measure of $D_2/D_3$ receptor and DAT availability.[26] The ratio $B_{max}/K_d$ measured in this way is referred to as the binding potential, $BP_{ND}$. Also measured was the plasma-to-tissue transfer constant ($K_1$) in striatum and cerebellum for both radioligands using the graphical analysis technique.[26]

Statistical parametric mapping [27] was used to assess the differences in the distribution volume ratio images (for both [$^{11}$C]raclopride and [$^{11}$C]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.

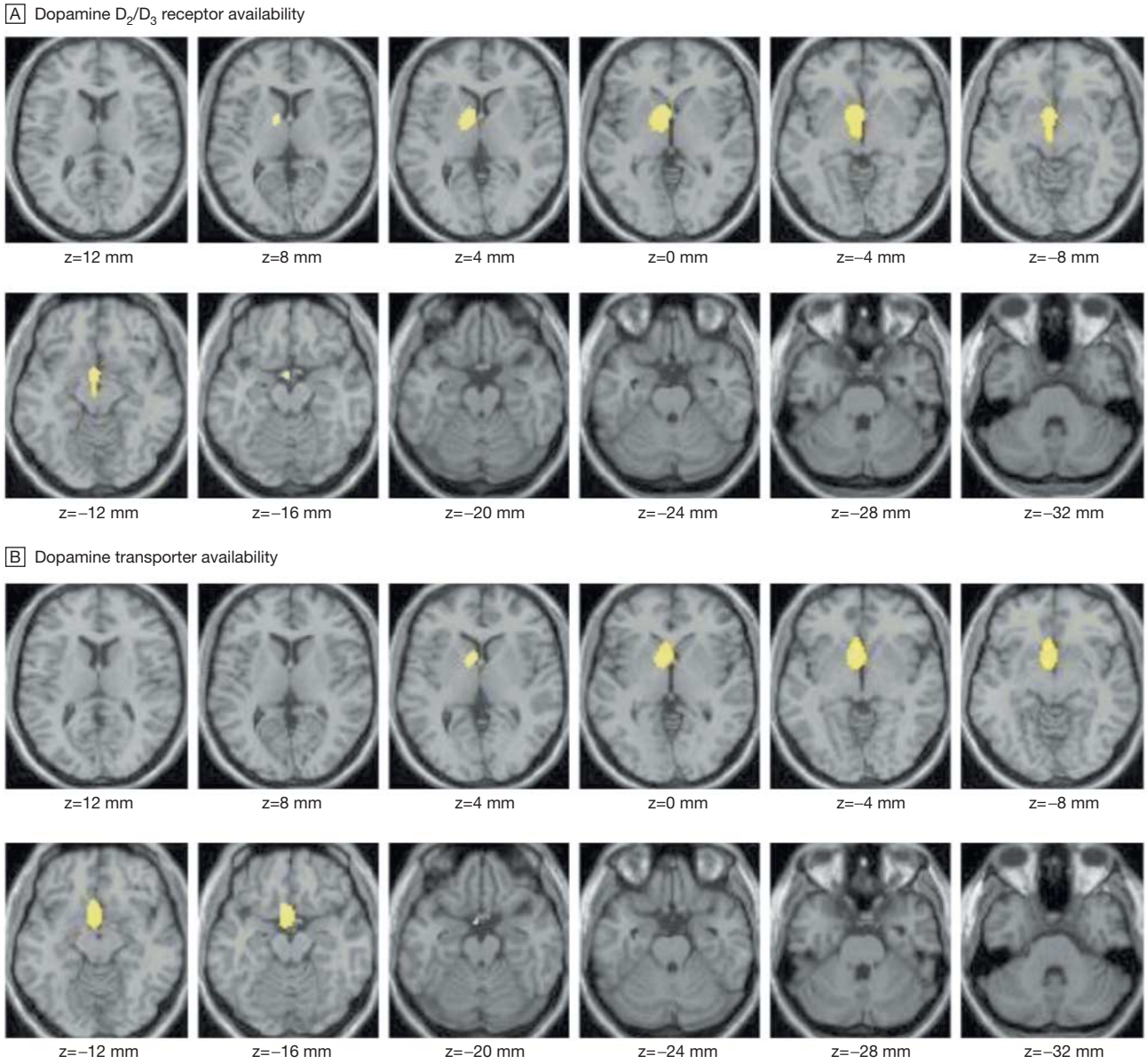
Significance detected by statistical parametric mapping was corroborated with independently drawn region-of-interest analyses using templates from the Talairach Daemon database.[28] FIGURE 1 shows the location of the region of interest used for this analysis. Differences in $D_2/D_3$receptor and DAT 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 $D_2/D_3$ receptors and the 2 dimensions of the SWAN rating score (attention and activity or reflectivity).

Definitions for significant difference for the outcome measures[1] were that statistical parametric mapping comparisons for the DAT and the $D_2/D_3$ 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[2]; comparisons for these corroborative measures had to be significant at $P < .05$[3]; 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 $D_2/D_3$ 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 $D_2/D_3$ 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.

**Table 2.** Measures of Dopamine $D_2/D_3$ Receptor and Dopamine Transporter Availability[a]

| Left Hemisphere | Availability, Mean (SD) | | Effect Size[b] | 95% Confidence Interval[b] | *P* Value[c] |
|---|---|---|---|---|---|
| | Controls | ADHD | | | |
| Dopamine $D_2/D_3$ receptor | | | | | |
| Accumbens region | 2.85 (0.31) | 2.68 (0.28) | 0.61 | 0.06 to 0.30 | .004 |
| Caudate | 2.80 (0.49) | 2.47 (0.61) | 0.60 | 0.10 to 0.56 | .005 |
| Midbrain | 0.28 (0.14) | 0.18 (0.19) | 0.57 | 0.02 to 0.17 | .01 |
| Hypothalamic region | 0.12 (0.13) | 0.04 (0.12) | 0.61 | 0.02 to 0.12 | .004 |
| Dopamine transporter | | | | | |
| Accumbens region | 0.71 (0.16) | 0.63 (0.11) | 0.59 | 0.03 to 0.13 | .004 |
| Caudate | 0.66 (0.23) | 0.53 (0.19) | 0.62 | 0.04 to 0.22 | .003 |
| Midbrain | 0.16 (0.10) | 0.09 (0.11) | 0.66 | 0.03 to 0.12 | <.001 |
| Hypothalamic region | –0.01 (0.10) | –0.05 (0.12) | 0.36 | –0.01 to 0.09 | .08 |

[a] Measures of receptor and transporter availability ($BP_{ND}$=DVR –1) obtained using an independent region-of-interest analysis to corroborate the statistical parametric mapping findings.
[b] Mean differences and effect sizes for the comparisons between controls and participants with attention-deficit/hyperactivity disorder.
[c] Comparisons correspond to independent samples 2-tailed *t* tests.

Sample-size calculation for this study was based on our preliminary studies (with smaller sample sizes) on DAT[6] and $D_2/D_3$ receptors,[8] 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 at the significance level of .05 (2 sided).

## RESULTS

### Dopamine $D_2/D_3$ Receptors

Statistical parametric mapping analysis of the [$^{11}$C]raclopride distribution volume ratio images revealed 1 cluster with lower $D_2/D_3$ availability in ADHD participants than controls in the left hemisphere. This cluster included brain regions of the dopamine reward pathway–ventral caudate, accumbens, and midbrain regions, as well as the hypothalamic region (FIGURE 2 and the 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 $K_1$ measures for [$^{11}$C]raclopride (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).

### Dopamine Transporters

Statistical parametric mapping analysis of the [$^{11}$C]cocaine distribution volume ratio images revealed a cluster in the same location as manifested in the [$^{11}$C]raclopride images. This cluster included the left ventral caudate, accumbal, midbrain, and hypothalamic regions, and in these regions the mean DAT availability was lower in ADHD participants than controls (Figure 2 and eTable). There were no regions that were higher in ADHD participants than in controls. 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 left hypothalamic region were not significantly different (Table 2). The mean (95% CI for mean difference) of the $K_1$ measures for [$^{11}$C]cocaine did not differ in the left caudate with 0.49 among the controls vs 0.48 among those with ADHD (95% CI, –0.05 to 0.03) or in left accumbens region with a respective difference of 0.49 vs 0.51 among those with ADHD (95% CI, –0.02 to 0.07).

### Correlation With ADHD Symptoms Dimensions

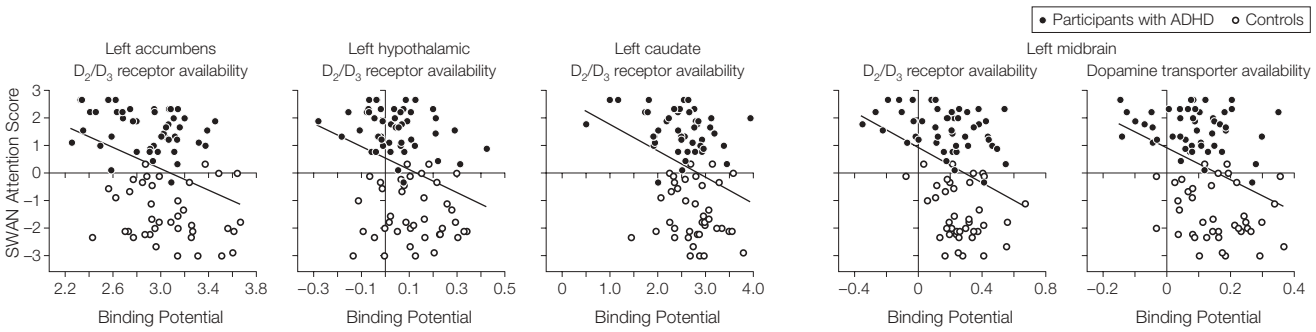
The dimension of attention (from the SWAN) was negatively correlated with $D_2/D_3$ receptor availability in the left accumbens region ($r$=0.35; 95% CI, 0.15-0.52; $P$=.001), left midbrain ($r$=0.35; 95% CI, 0.14-0.52; $P$=.001), left caudate ($r$=0.32; 95% CI, 0.11-0.50; $P$=.003), and left hypothalamic 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 reflectivity 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 $D_2/D_3$ 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).[29] 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 $D_2/D_3$ receptor and DAT availability in the accumbens and midbrain regions supports the hypothesis of an impairment of the dopamine reward pathway in ADHD.[30] 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

**Figure 3.** Regression Slopes Between Dopamine $D_2/D_3$ 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).

gratification, impaired response to partial schedules of reinforcement, and preference for small immediate rewards over larger delayed rewards.[31] Consistent with this important clinical feature of the ADHD syndrome, a recent fMRI study reported decreased activation of the ventral striatum (wherein nucleus accumbens is located) for both immediate and delayed rewards in adult participants with ADHD compared with controls.[17]

In our study, the $D_2/D_3$ receptor measures in accumbens were correlated with the dimension of attention, which would implicate the dopamine reward pathway in the symptoms of inattention in ADHD. This could provide an explanation of why the attentional deficits in individuals with ADHD are most evident in tasks that are considered boring, repetitive, and uninteresting (ie, tasks or assignments that are not intrinsically rewarding).[32] Finally, because a low number of dopamine $D_2/D_3$ receptors in the nucleus accumbens have been associated with a greater risk for drug abuse,[33] future work should determine if the lower than normal $D_2/D_3$ receptor availability in the accumbens region in ADHD underlies the higher vulnerability for substance abuse in this population.[34]

The lower $D_2/D_3$ receptor and DAT availability in the midbrain, which contains most of the dopamine neurons in the brain, is consistent with findings from prior imaging studies of children and adolescents with ADHD documenting midbrain abnormalities.[5,35] This could underlie the decreased dopamine release reported in adults with ADHD[8] because firing of dopamine neurons in the midbrain is responsible for release of dopamine in striatum. Moreover, the negative correlation between dopamine markers in the midbrain and the dimension of attention (DAT and $D_2$ receptors) suggests that impaired signaling from dopamine cells may contribute to severity of symptoms of inattention in ADHD.

Lower than normal $D_2/D_3$ receptors and DAT availability in ADHD in the caudate was also demonstrated. Prior imaging studies had reported smaller caudate volumes[36-40] and caudate functional underactivation[41,42] in ADHD participants compared with controls. In contrast, DAT findings in striatum (including caudate) have been inconsistent in studies of participants with ADHD vs controls, with some studies reporting high,[43] others low,[6] and others no differences.[44] Reason(s) for the discrepancies have been outlined elsewhere[6] and could reflect differences in radiotracers, the methods used (radiotracers; PET vs single photon emission computed tomography), differences in patients characteristics (including prior medication histories; comorbidities, and age of participants), and sample sizes, which vary from 6 to 53 (in this study). These findings differ from those reported in adolescents with ADHD, which showed higher $D_2/D_3$ receptor availability in the left striatum (including caudate) than in young adults, that was interpreted to reflect deficient dopamine occupancy of these receptors.[7] In these adolescents with ADHD, the largest increases in striatal $D_2/D_3$ receptor availability were seen in those patients who at birth had the lowest cerebral blood flow measures, which was interpreted to reflect the adverse consequences of neonatal distress on dopamine brain function.[9]

The preliminary finding reported herein of lower than normal dopamine $D_2/D_3$ 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[45] such as sleep disturbances,[46] overweight or obesity,[47] and abnormal responses to stress.[48] Multiple hypothalamic nuclei express dopamine $D_2$ receptors,[49] 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.[50]

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 stimuli-reward associations,[51] 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.[52] 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.[53]

## Limitations

[$^{11}$C]Raclopride measures are influenced by extracellular dopamine (the higher the extracellular dopamine, the less the binding of [$^{11}$C]raclopride to $D_2/D_3$ receptors), and thus low-binding potential could reflect low $D_2/D_3$ receptor levels or increased dopamine release.[54] 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.[8] Also although [$^{11}$C]cocaine's binding to DATs is minimally affected by competition with endogenous dopamine,[55] 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.[56] Thus low DAT availability could reflect fewer dopamine terminals or decreased DAT expression per dopamine terminal.

The relatively low affinity of [$^{11}$C]raclopride and [$^{11}$C]cocaine for their targets makes them better suited to measure regions with high $D_2/D_3$ 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.[36-40] However, that there were no group differences in measures of $K_1$ (transport of radiotracer 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 $D_2/D_3$ 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,[57] which could not be measured with current PET radioligands; $D_2/D_3$ receptors and DAT levels in frontal regions are very low.

Although the significant findings in this study are restricted to the left hemisphere, low 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 $D_2/D_3$ receptor availability).

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