

Depressed Dopamine Activity in Caudate and Preliminary Evidence of Limbic Involvement in Adults With Attention-Deficit/Hyperactivity Disorder

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Context: Attention-deficit/hyperactivity disorder (ADHD) is the most prevalent psychiatric disorder of childhood. There is considerable evidence that brain dopamine is involved in ADHD, but it is unclear whether dopamine activity is enhanced or depressed.

Objective: To test the hypotheses that striatal dopamine activity is depressed in ADHD and that this contributes to symptoms of inattention.

Design: Clinical (ADHD adult) and comparison (healthy control) subjects were scanned with positron emission tomography and raclopride labeled with carbon 11 (D_2/D_3 receptor radioligand sensitive to competition with endogenous dopamine) after placebo and after intravenous methylphenidate hydrochloride (stimulant that increases extracellular dopamine by blocking dopamine transporters). The difference in [^{11}C]raclopride's specific binding between placebo and methylphenidate was used as marker of dopamine release. Symptoms were quantified using the Conners Adult ADHD Rating Scales.

Setting: Outpatient setting.

Participants: Nineteen adults with ADHD who had never received medication and 24 healthy controls.

Results: With the placebo, D_2/D_3 receptor availability in left caudate was lower ($P < .05$) in subjects with ADHD than in controls. Methylphenidate induced smaller decrements in [^{11}C]raclopride binding in left and right caudate (blunted DA increases) ($P < .05$) and higher scores on self-reports of "drug liking" in ADHD than in control subjects. The blunted response to methylphenidate in caudate was associated with symptoms of inattention ($P < .05$) and with higher self-reports of drug liking ($P < .01$). Exploratory analysis using statistical parametric mapping revealed that methylphenidate also decreased [^{11}C]raclopride binding in hippocampus and amygdala and that these decrements were smaller in subjects with ADHD ($P < .001$).

Conclusions: This study reveals depressed dopamine activity in caudate and preliminary evidence in limbic regions in adults with ADHD that was associated with inattention and with enhanced reinforcing responses to intravenous methylphenidate. This suggests that dopamine dysfunction is involved with symptoms of inattention but may also contribute to substance abuse comorbidity in ADHD.

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ATENTION-DEFICIT/HYPER-activity disorder (ADHD) is considered to be the most prevalent psychiatric disorder of childhood.¹ Despite decades of research, the specific neurobiological mechanisms underlying this disorder still remain unclear. Genetic, clinical, and imaging studies point to a disruption of the brain dopamine (DA) system,² which is corroborated by the clinical effectiveness of stimulant drugs (methylphenidate hydrochloride and amphetamine), which increase extracellular DA in brain.³

Brain imaging studies have provided evidence of differences in markers of DA neurotransmission in subjects with ADHD. However, the results have not always been consistent and do not clarify the abnormal

direction of the differences in DA neurotransmission. For example, the studies measuring levels of dopamine transporters (DATs) cannot distinguish whether abnormalities reflect changes in DAT levels per terminal (up- or down-regulation) vs differences in terminal density. Uncertainty remains because DATs can up-regulate under conditions of high DA neurotransmission and down-regulate under conditions of low DA activity.⁴ The finding of DAT elevation in the striatum of subjects with ADHD (reviewed⁵) might suggest enhanced DA reuptake and weak DA signals or increased DA terminal density and hence enhanced dopaminergic activity. In addition, some studies have not replicated the finding of DAT elevation in subjects with ADHD⁶⁻⁸ and some report lower than normal DATs,^{7,8} which could be in-

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terpreted as down-regulation to compensate for depressed dopaminergic neurotransmission or as lower DA terminal density. Similarly, while the reduction in DA synthesis in prefrontal cortex reported in adults with ADHD⁹ is consistent with decreased DA activity, the increased level of DA synthesis in mesencephalon reported in children with ADHD¹⁰ is consistent with increased activity.

Studies of changes in striatal DA in response to methylphenidate offer another view of the DA system that may clarify the specificity of disorder-related disruption. Since methylphenidate is a DAT blocker and not a DA releaser drug, for an equivalent level of DAT blockade the magnitude of methylphenidate-induced DA increases will reflect the amount of spontaneous DA release.¹¹ One positron emission tomographic (PET) study in adolescents with ADHD reported that methylphenidate-induced DA increases were associated with greater symptom severity,¹² but without a control group this study left unresolved whether the DA responses were abnormal in subjects with ADHD. Here we investigate DA release in adults with ADHD using PET to measure their response to intravenous methylphenidate when compared with that of controls. Our working hypotheses are that subjects with ADHD have lower than normal DA release and that this contributes to symptoms of inattention.

We tested 19 subjects with ADHD who had never received medication and 24 healthy controls with PET and raclopride labeled with carbon 11 (DA D₂/D₃ receptor radioligand whose binding is sensitive to competition by endogenous DA)¹³ with and without an acute pharmacological challenge with intravenous methylphenidate. Differences in specific binding of [¹¹C]raclopride with and without methylphenidate mostly reflect methylphenidate-induced changes in extracellular DA.¹⁴ In parallel we quantified clinical symptoms before the study using the Conners Adult ADHD Rating Scales (CAARS)¹⁵ and “drug liking” after intravenous administration of methylphenidate using self-reports of drug effects to assess the functional significance of methylphenidate-induced DA changes.

METHODS

SUBJECTS

We completed studies in 19 subjects with ADHD who had never received medication (9 men, 10 women; mean ± SD age, 32 ± 7 years) and 24 adult healthy controls (18 men, 6 women; mean ± SD age, 30 ± 5 years). Note that these subjects are much older than those in a published study that evaluated DA release in adolescents with ADHD.¹² Subjects with ADHD were recruited from a variety of sources, including clinical referrals to the ADHD program at Mount Sinai and advertisements. At least 2 clinicians (psychiatrist or neurologist and clinical psychologist) interviewed the patients to ensure that they met *DSM-IV* diagnostic criteria for ADHD as evidenced by the presence of at least 6 of 9 inattention symptoms (with or without 6 of 9 hyperactive/impulsive symptoms) as ascertained with a semi-structured interview using *DSM-IV* criteria. In addition, evidence was required from each subject's history that some symptoms of ADHD started during childhood (before age 7 years) even when the diagnosis was not made until adulthood. Subjects were excluded if they had a prior history of more than 1

month of medication treatment for ADHD and excluded if this short treatment occurred within the 2 years prior to the study. They were also excluded if they had a present or past history of substance abuse or addiction (except nicotine). Smoking status was assessed with self-reports, and in our final sample only 1 of the controls and 1 of the subjects with ADHD were smokers. Exclusion criteria also included present or past history of psychiatric disease (axis I or II diagnosis other than ADHD) or neurological disease, medical conditions that may alter cerebral function (ie, cardiovascular, endocrinological, oncological, or autoimmune diseases), current use of prescribed or over-the-counter medications, and/or head trauma with loss of consciousness of more than 30 minutes. All subjects had Hamilton Anxiety¹⁶ and Hamilton Depression¹⁷ scores lower than 19. Controls were recruited from advertisements in the local newspapers; exclusion criteria other than allowance for ADHD were the same as for subjects with ADHD. Urine drug screens were obtained on all subjects the day of the PET study to check for psychoactive drug use. Written informed consent was obtained after complete description of the study to the subjects.

CLINICAL SCALES

We measured clinical symptoms using the CAARS long version,¹⁵ which provides self-assessment of ADHD symptoms on a scale of 1 (not at all) to 4 (very much). The CAARS was completed in all subjects with ADHD (CAARS for 1 subject with ADHD was lost) and in 20 of the controls. Mean ± SD averages on the 8 CAARS scales for subjects with ADHD and controls, respectively, were as follows: section A, inattention/memory problems, 25 ± 5 and 5 ± 3; B, hyperactivity/restlessness, 22 ± 8 and 6 ± 4; C, impulsivity/emotional lability, 17 ± 8 and 4 ± 4; D, problems with self-concept, 10 ± 5 and 3 ± 3; E, *DSM-IV* inattentive symptoms, 21 ± 3 and 2 ± 3; F, *DSM-IV* hyperactive-impulsive symptoms, 15 ± 6 and 3 ± 3; G, *DSM-IV* symptom total, 35 ± 6 and 5 ± 5; and section H, ADHD index, 21 ± 5 and 4 ± 3.

BEHAVIORAL MEASURES

Behavioral effects of intravenous methylphenidate were evaluated using analog scales that assessed self-reports of “high,” tiredness, alertness, anxiety, “feel drug,” and restlessness from 0 (felt nothing) to 10 (felt intensely).¹⁸ These self-reports of drug effects have been shown to be reliable and consistent across studies and to predict administration of drugs in human subjects.¹⁹ Subjective ratings were recorded 5 minutes before placebo or methylphenidate and then 27 and 47 minutes after administration. At the end of the study, subjects were asked to rate drug liking and drug disliking (0-10).

SCANS

Positron emission tomographic studies were done with a Siemens HR+ tomograph (Siemens Medical Solutions, Knoxville, Tennessee) in 3-dimensional mode (resolution, 4.5 × 4.5 × 4.5 mm, full-width half-maximum). Each subject underwent 2 scans with [¹¹C]raclopride: 1 after intravenous placebo (3 mL of saline) and 1 after intravenous methylphenidate (0.5 mg/kg). The study was a single-blind design (subjects were blind to the drugs received). 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). Dynamic scans were obtained for a total of 60 minutes as previously described.¹⁴ Arterial blood was obtained throughout the procedure to measure the concentration of unchanged [¹¹C]raclopride in plasma.²⁰

Table 1. Measures for K_1 , Distribution Volume, and B_{max}'/Kd' for Controls and Subjects With ADHD^a

Measures	Drug	Left			Right			
		Controls, Mean±SD	ADHD, Mean±SD	ANOVA	Controls, Mean±SD	ADHD, Mean±SD	ANOVA	
K_1	Cerebellum	Placebo	0.12±0.12	0.12±0.12	NS	0.12±0.12	0.12±0.12	NS
		Methylphenidate	0.12±0.05	0.13±0.04		0.12±0.05	0.13±0.05	
Caudate	Placebo	0.11±0.01	0.10±0.10	NS	0.11±0.02	0.11±0.02	NS	
	Methylphenidate	0.11±0.04	0.10±0.02		0.11±0.05	0.10±0.01		
Putamen	Placebo	0.12±0.02	0.12±0.02	NS	0.12±0.02	0.12±0.02	NS	
	Methylphenidate	0.12±0.04	0.11±0.02		0.12±0.04	0.12±0.02		
B_{max}'/Kd'	Caudate	Placebo	3.03±0.40	2.77±0.39 ^b	(D) 0.0001	3.04±0.37	2.84±0.32 ^c	(D) 0.0001
		Methylphenidate	2.63±0.36	2.56±0.35	(I) 0.04	2.64±0.40	2.64±0.35	(I) 0.04
Putamen	Placebo	3.59±0.40	3.40±0.11	(D) 0.0001	3.67±0.44	3.49±0.36	(D) 0.0001	
	Methylphenidate	2.83±0.38	2.83±0.29	(I) NS	2.85±0.43	2.75±0.28	(I) NS	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ANOVA, analysis of variance; D, drug effect; I, interaction effect; NS, not significant.

^aImages scanned with raclopride labeled with carbon 11 were obtained of left and right regions for caudate and putamen, and 1 value was obtained for cerebellum.

^bDifferences were significant ($P < .05$) between controls and subjects with ADHD for the baseline measures (placebo) as assessed by unpaired *t* test (2-tailed).

^cDifferences were significant ($P < .07$) between controls and subjects with ADHD for the baseline measures (placebo) as assessed by unpaired *t* test (2-tailed).

IMAGE ANALYSIS AND STATISTICS

Regions of interest (ROIs) were obtained directly from the [¹¹C]raclopride images as previously described.¹⁴ Briefly, we identified and selected the ROIs on summed images (dynamic images taken from 10–54 minutes) that were resliced along the intercommissural plane (anterior commissural to posterior commissural line). The caudate, putamen, and cerebellum were measured on 4, 3, and 2 planes, respectively, and right and left regions were delineated. These regions were then projected to the dynamic scans to obtain concentrations of carbon 11 vs time, which were used to calculate the K_1 (transport constant from plasma to tissue) and the distribution volumes (DV) using a graphical analysis technique for reversible systems.²¹ We computed the ratio of the DV in caudate and putamen to that in the cerebellum to obtain the DV ratio (DVR). The DVR, which corresponds to $B_{max}'/Kd' + 1$ (Kd' and B_{max}' are the effective in vivo constants in the presence of endogenous neurotransmitter and nonspecific binding), was used as an estimate of D_2/D_3 receptor availability.²¹ The effect of methylphenidate on [¹¹C]raclopride binding was quantified as percentage change in B_{max}'/Kd' from placebo.

Differences in baseline D_2/D_3 receptor availability between the groups were assessed with unpaired *t* tests (2-tailed). Differences in the response to methylphenidate between groups were assessed with analyses of variance with 1 between-subject factor (control vs ADHD) and 1 within-subject factor (placebo vs methylphenidate). Post hoc *t* tests were used to determine which of the conditions differed. Pearson product moment correlations were used to assess the association between the measures in methylphenidate-induced changes in DA and the CAARS. These correlations were done separately for the controls and for the subjects with ADHD and with all the subjects included. We also measured the correlations between methylphenidate-induced DA changes and the behavioral effects significantly affected by methylphenidate. To test the 2 main hypotheses of the study (that methylphenidate-induced DA changes would be smaller in the ADHD group than in the control group and that placebo-methylphenidate differences would be associated with inattention), we set significance at $P < .05$; for the exploratory analysis (correlations of DA changes with behavioral measures), we set significance at $P < .01$.

For exploratory analyses of areas other than striatum affected by methylphenidate, we used statistical parametric mapping (SPM)²² since this allows for the assessment of differences in areas without the need to preselect the regions. The SPM analysis was performed on the DVR images (obtained by computing the DV in each pixel and then dividing it by the DV in cerebellum). The DVR images were spatially normalized using the Montreal Neurological Institute template provided in the SPM 99 package and subsequently smoothed with a 16-mm isotropic Gaussian kernel. Paired *t* tests were performed separately for the controls and the subjects with ADHD to identify the areas where there were significant differences between the DVR images obtained after placebo from those after methylphenidate. Significance was set at $P < .001$ (uncorrected, cluster-size threshold > 100 voxels), and the statistical maps were overlaid on a magnetic resonance imaging structural image. The cluster sizes (number of pixels) that differed significantly between placebo and methylphenidate at the threshold level of $P < .001$ were expressed as percentage of the volume of the pertinent anatomical region (ie, caudate, putamen, amygdala, hippocampus) as defined from the Talairach Daemon.²³ Comparisons of the differences in the percentage of the regional volume changed by methylphenidate between controls and ADHD were assessed using bootstrap resampling.²⁴ For this purpose, we performed random sampling with replacement of the same number of images involved in the SPM comparison for 1000 times to obtain the bootstrap duplicate used for SPM comparisons. The resampling method does not require the use of a parametric model where the large number of voxels per image ($N \sim 50\,000$) renders the usual normal assumption inappropriate for the *N*-dimensional joint distribution of the image that was treated as an *N*-dimensional vector.²⁵

RESULTS

DOPAMINE D_2/D_3 RECEPTORS AT BASELINE (PLACEBO)

At baseline, there were no differences in K_1 between controls and subjects with ADHD in cerebellum, caudate, or putamen (**Table 1**). In contrast, D_2/D_3 receptors' avail-

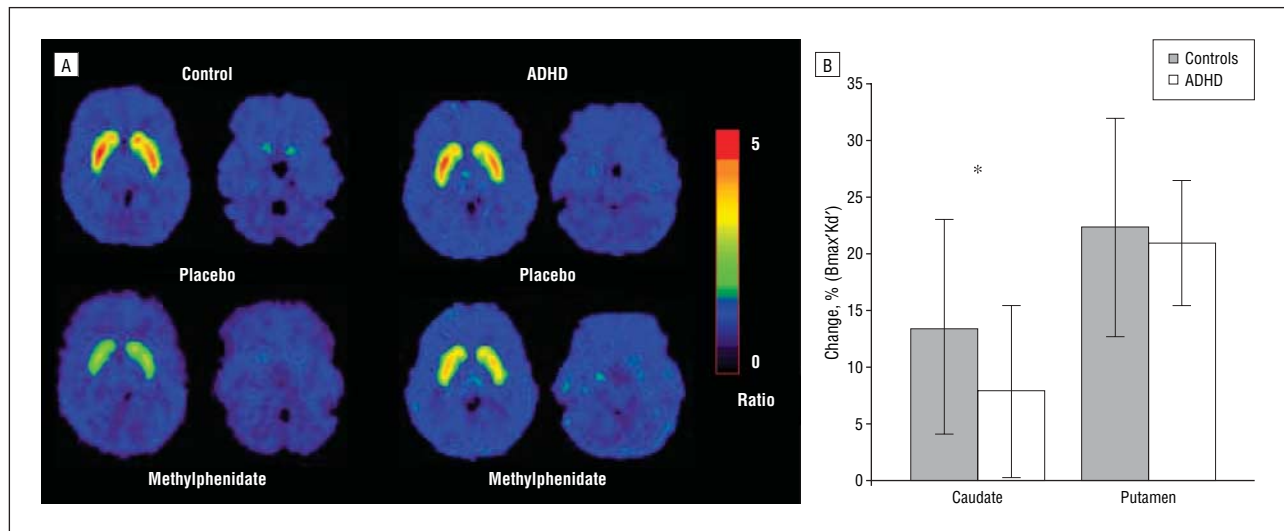


Figure 1. Effects of methylphenidate hydrochloride on brain dopamine. A, Distribution volume ratio images for raclopride labeled with carbon 11 at the level of striatum and the cerebellum in a control and a subject with attention-deficit/hyperactivity disorder (ADHD) after placebo and after methylphenidate. Note the decrease in specific binding (distribution volume ratios) with methylphenidate and the attenuated response to methylphenidate in the subject with ADHD when compared with the control. B, Histogram for percentage change in B_{max}/Kd' (D_2 receptor availability) between placebo and methylphenidate for the caudate (average of left and right) and putamen (average of left and right) for controls and subjects with ADHD. * Indicates repeated factorial analysis of variance significant interaction effect ($P < .05$).

ability (B_{max}/Kd') was significantly lower in subjects with ADHD than in controls in left caudate ($t_{41}=2.12$, $P < .04$) and showed a trend in right caudate ($t=1.87$, $P < .07$) but did not differ in putamen (Table 1).

EFFECTS OF METHYLPHENIDATE ON [^{11}C]RACLOPRIDE BINDING

The analysis of variance on the K_1 measures revealed that neither the drug nor the interaction effects were significant in caudate, putamen, or cerebellum, which indicates that methylphenidate did not change the radio-tracer delivery into the tissue and that there were no differences in the responses between controls and subjects with ADHD (Table 1).

The analysis of variance on the B_{max}/Kd' measures revealed a significant drug effect in left and right caudate ($F_{1,41}=53$, $P < .001$) and in left and right putamen ($F=182$, $P < .001$), which indicates that B_{max}/Kd' was significantly reduced by methylphenidate in both groups (Figure 1 and Table 1). The interaction effect was significant for the left caudate ($F_{1,41}=4.5$, $P < .04$) and for the right caudate ($F=4.9$, $P < .04$), which indicates that the responses in these regions differed between groups. Post hoc t test revealed that the responses to methylphenidate were significantly smaller in subjects with ADHD than in controls in left caudate ($t_{1,41}=2.1$, $P < .04$) and right caudate ($t=2.2$, $P < .04$).

To control for potential confounds, we did separate analyses of variance. One used the DV in occipital cortex as the normalization region for the DVR since the cerebellum has been found to be abnormal in subjects with ADHD, and the other excluded smokers in the event that nicotine could affect the methylphenidate responses. Both yielded the same results. The normalization with occipital cortex showed a significant interaction effect in left caudate ($F_{1,41}=5.3$, $P < .03$) and right caudate ($F=5.1$,

$P < .02$), and post hoc t test corroborated the smaller decrements in subjects with ADHD ($t=2.3$, $P < .03$). The analysis without the smokers also showed a significant interaction effect in left and right caudate ($F_{1,39} > 5.2$, $P < .05$) with post hoc t test showing that reductions were smaller in subjects with ADHD ($t=2.0$, $P < .05$). These analyses indicate that neither the cerebellum nor the smokers accounted for the group differences.

Exploratory analysis with SPM—to assess whether there were regions other than the striatum where specific [^{11}C]raclopride binding was reduced by methylphenidate—revealed significant ($P < .001$) decrements not only in caudate and putamen but also in hippocampus and amygdala both in controls and in subjects with ADHD (Figure 2). The SPM comparison on the difference image (placebo – methylphenidate) between controls and subjects with ADHD was not significant. However, the comparison of volume differences in the regions where methylphenidate significantly reduced B_{max}/Kd' (threshold level of $P < .001$) revealed a group difference: these volumes were significantly larger for controls than for subjects with ADHD in left and right caudate, left amygdala, and left and right hippocampus ($P < .001$) (Figure 2).

PLASMA CONCENTRATIONS AND BEHAVIORAL RESPONSES TO METHYLPHENIDATE

Mean \pm SD plasma concentrations did not differ between controls and subjects with ADHD at 10 minutes (117 ± 27 vs 113 ± 31 ng/mL, respectively), 25 minutes (84 ± 16 vs 83 ± 22 ng/mL), 40 minutes (64 ± 11 vs 62 ± 21 ng/mL), or 60 minutes (46 ± 10 vs 46 ± 16 ng/mL).

In both groups of subjects, methylphenidate significantly increased self-reports of alertness, anxiety, high, restlessness, feel drug, drug liking, and drug disliking and decreased tiredness (Table 2). The interaction effect was

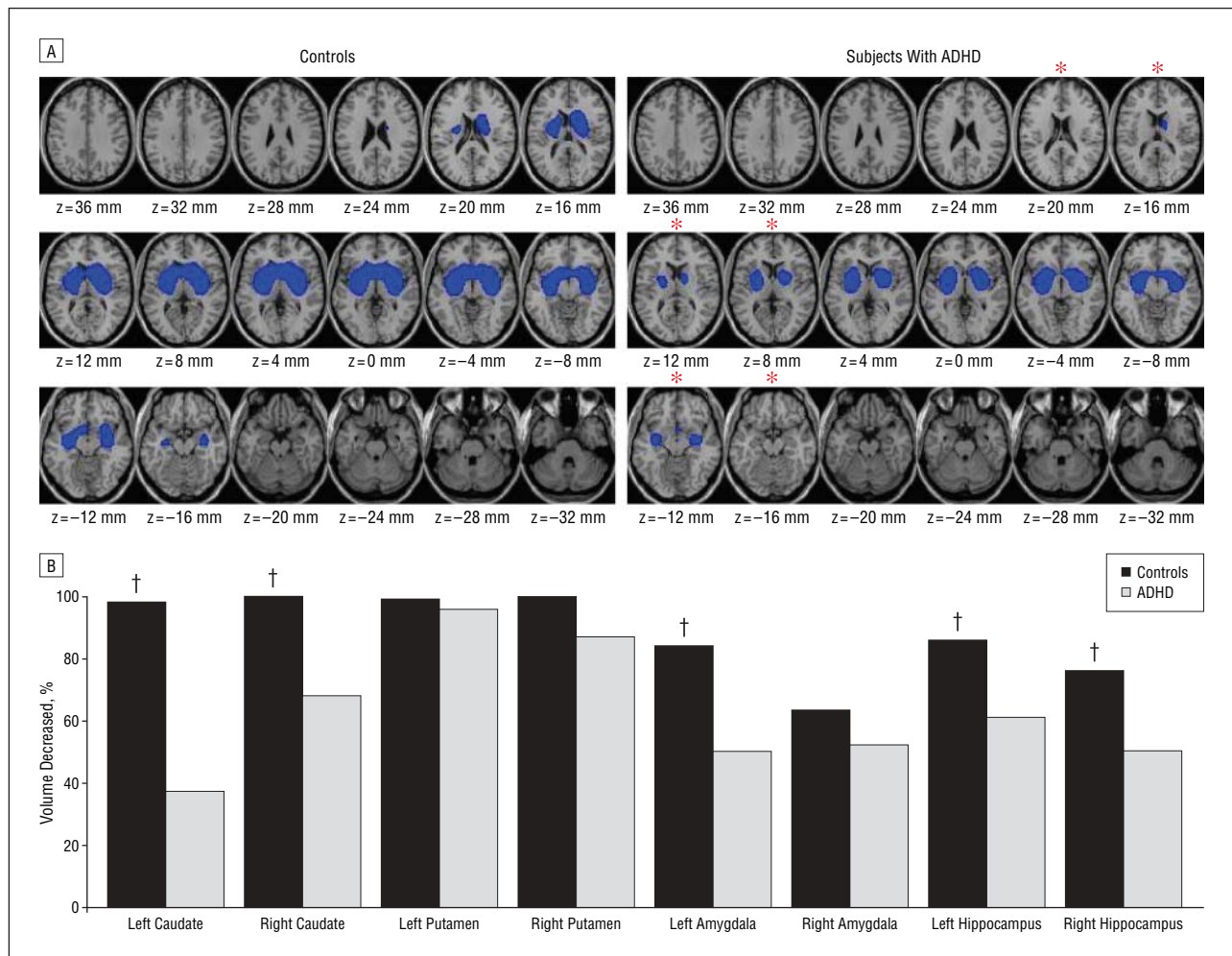


Figure 2. Brain areas where methylphenidate hydrochloride increased dopamine. A, Location of the regions where statistical parametric mapping analysis revealed significant decrements ($P < .001$) in distribution volume ratio (measure for dopamine increases) after methylphenidate in controls and in subjects with attention-deficit/hyperactivity disorder (ADHD). Note that methylphenidate not only reduced binding in striatum but also in amygdala and hippocampus and that the volume of decrements is larger for controls than for subjects with ADHD. * Highlights planes where decrements were smaller in subjects with ADHD than controls. B, Histogram showing the percentage volume of a given region where methylphenidate significantly decreased the distribution volume ratio in controls and in subjects with ADHD. † Indicates bootstrap comparisons where values differed significantly between groups ($P < .001$). Note that the volume of decrements is larger for controls than for subjects with ADHD.

significant for alertness, tiredness, drug liking, and drug disliking. Post hoc t tests revealed that methylphenidate effects were significantly larger in subjects with ADHD than in controls for alertness ($t_{41} = 3.5$, $P < .001$), tiredness ($t = 2.1$, $P < .03$), and drug liking ($t = 2.5$, $P < .02$) and significantly smaller for drug disliking ($t = 2.0$, $P < .05$) (Table 2).

CORRELATION BETWEEN DA MEASURES AND ADHD SYMPTOMS (CAARS)

The correlation between the baseline measures of D_2/D_3 receptor availability and the CAARS were not significant in either controls or subjects with ADHD. In contrast, methylphenidate-induced changes in DA (percentage change in B_{max}/K_d) in the subjects with ADHD were negatively correlated with the scores on CAARS section E (DSM-IV inattentive symptoms) in left caudate ($r = -0.49$, $P < .04$), right caudate ($r = -0.56$, $P < .02$), left putamen ($r = -0.61$, $P < .008$), and right putamen ($r = -0.71$, $P < .001$) and on CAARS section A (inattention/

memory problems) in left caudate ($r = -0.51$, $P < .04$) and showed a trend in right caudate ($r = -0.41$, $P < .09$), left putamen ($r = -0.45$, $P < .06$), and right putamen ($r = -0.45$, $P < .06$). The smaller the DA changes, the greater the symptoms of inattention (Figure 3). These correlations were not significant in control subjects, but this may be due to the restricted ratings range of the CAARS in normal subjects. The analyses were also performed with all subjects (controls and ADHD) and resulted in a similar pattern of significant effects: the correlations were for the CAARS A and the left and right caudate ($r = -0.31$, $P < .05$) and for the CAARS E and the right caudate ($r = -0.34$, $P < .04$) and left caudate ($r = 0.30$, $P < .06$). The correlations in putamen were not significant.

CORRELATION BETWEEN METHYLPHENIDATE-INDUCED DA CHANGES AND ITS BEHAVIORAL EFFECTS

The pattern of correlations obtained for all subjects showed that methylphenidate-induced self-reports of drug

Table 2. Behavioral Effects of Intravenous Methylphenidate in Controls and Subjects With ADHD

Effect	Control Subjects		Subjects With ADHD		ANOVA		
	Placebo, Mean±SD	Methylphenidate, Mean±SD	Placebo, Mean±SD	Methylphenidate, Mean±SD	Group	Drug	Interaction
Alertness	8±2	9±3	5±2	9±2	8 ^a	27 ^b	12 ^b
Tiredness	3±2	2±3	4±3	2±1	NS	11 ^c	4.6 ^d
Anxiety	1±2	5±3	1±2	5±2	NS	40 ^b	NS
Restlessness	1±2	5±3	2±2	5±3	NS	50 ^b	NS
High	0±0.4	6±3	0±0.3	6±3	NS	148 ^b	NS
Feel drug	0±0.3	7±3	0±0.4	7±3	NS	226 ^b	NS
Drug liking	1±0.3	4±4	1±0.9	7±3	6.7 ^d	61 ^b	5.2 ^d
Drug disliking	1±0	6±3	2±2	4±4	NS	38 ^b	4.2 ^d

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ANOVA, analysis of variance; NS, not significant.

^a $P < .01$.

^b $P < .001$.

^c $P < .005$.

^d $P < .05$.

liking were negatively correlated with DA changes in left caudate ($r = -0.39$, $P < .01$) and showed a trend in right caudate ($r = -0.37$, $P < .02$). Methylphenidate-induced self-reports of feel drug showed significant positive correlations in left caudate ($r = -0.43$, $P < .005$), left putamen ($r = -0.41$, $P < .007$), and right putamen ($r = -0.46$, $P < .003$) and showed a trend in right caudate ($r = -0.35$, $P < .05$). The pattern of correlations was the same when done separately for subjects with ADHD or for controls except that the correlations only showed a trend for significant effects ($P > .04$ and $P < .08$). The correlations with the other behavioral measures were not significant.

COMMENT

DECREASED DA RELEASE

Herein we report that adult subjects with ADHD had lower methylphenidate-induced changes in DA in caudate compared with controls and that the blunted responses were associated with symptoms of inattention and with more positive subjective responses to intravenous methylphenidate. The exploratory analysis also revealed preliminary evidence of lower than normal DA changes in limbic regions (amygdala and hippocampus). Since methylphenidate is a DAT blocker and not a DA releaser, for a given level of DAT blockade the DA changes reflect the amount of spontaneous DA released.¹¹ Inasmuch as the concentration of methylphenidate in plasma, which did not differ between groups, predicts the levels of DAT blockade,^{26,27} the blunted response to methylphenidate suggests that subjects with ADHD have lower DA release than controls.

The mechanisms resulting in reduced DA release in ADHD are unclear, but we consider 2 possibilities. The reduced release could reflect either a primary effect due to disruption in DA cells (ie, DA synthesis, DAT, DA autoreceptors) or a secondary effect from disruption of circuits that regulate DA release (ie, cortical-striatal glutamate pathways). Indeed in adults subjects with ADHD, there is evidence of decreased DA synthesis and metabo-

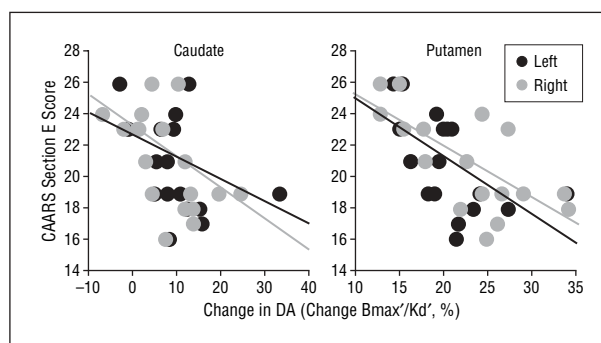


Figure 3. Regression slopes between changes in dopamine (DA) in caudate and in putamen and scores on Conners Adult ADHD Rating Scales (CAARS) section E (*DSM-IV* symptoms of inattention) in subjects with attention-deficit/hyperactivity disorder (ADHD). Correlations correspond for left caudate ($r = -0.49$, $P < .04$), right caudate ($r = -0.56$, $P < .02$), left putamen ($r = -0.61$, $P < .008$), and right putamen ($r = -0.71$, $P < .001$).

lism in the prefrontal cortex.⁹ As discussed earlier, there is also evidence of disruption in DAT levels in subjects with ADHD, although the findings are inconsistent (reviewed⁹) and difficult to interpret because DAT levels are a function of both the density of DA terminals and the number of DATs per terminal. Decreased DA release could also reflect prefrontal pathology, which has been consistently documented in ADHD (reviewed^{28,29}) since frontal-striatal glutamatergic circuits regulate striatal DA release.^{30,31} However, prefrontal pathology in ADHD could also indicate improper dopaminergic regulation of frontal regions.³² The findings of reduced DA release in subjects with ADHD are consistent with the notion that the ability of stimulant medications to enhance extracellular DA underlies their therapeutic effects in ADHD.

DOPAMINERGIC DISRUPTION IN CAUDATE AND INATTENTION IN ADHD

Baseline D_2/D_3 receptor availability (B_{max}'/Kd') on left caudate was also significantly lower in subjects with ADHD than in controls. Since measures of D_2/D_3 receptor availability are influenced by extracellular DA, low B_{max}'/Kd' could reflect either increased DA release or

low D₂/D₃ receptor levels.³³ The observations that subjects with ADHD had reduced DA release discounts the former and supports the latter possibility that lower B_{max}'/K_d' measures at baseline are due to lower than normal D₂/D₃ receptor levels in subjects with ADHD. This finding is opposite to results in patients with schizophrenia who show increases in baseline D₂ receptors and in DA release.³⁴ Although a prior study reported increases in striatal D₂/D₃ receptor availability in children with ADHD when compared with young adults,³⁵ the differences could reflect the normal decreases in D₂ receptors that occur with age.³⁶ The reduction in D₂/D₃ receptors in caudate at baseline coupled with the reduced DA release in this region corroborate findings from prior studies identifying the caudate as a key area involved in ADHD.^{37,38} The association between the DA response in caudate and symptoms of inattention implicates the caudate in attentional process and is consistent with reports that caudate lesions result in attention deficits.³⁹ Future studies should investigate the significance of the caudate DA changes in cognitive symptoms in ADHD.

Our findings differ from those previously reported in adolescents with ADHD in whom methylphenidate-induced striatal DA increases correlated positively with inattention and impulsivity.¹² This discrepancy could be related to age of subjects (adolescents vs adults) since the DA system undergoes major developmental changes from childhood/adolescence to adulthood⁴⁰ and the response to stimulant drugs changes as a function of developmental stage.⁴¹ Moreover, the clinical symptomatology in ADHD also changes during this developmental transition,¹ and thus it is conceivable that DA's involvement in ADHD could also differ.⁴² Indeed, the failure to show a correlation with hyperactivity and impulsivity in our study could reflect the restricted range of symptoms in adults with ADHD since these symptoms decline with age more than the symptoms of inattention, which predominate in adults with ADHD.⁴³ The route of administration used for methylphenidate by these 2 studies (0.3 mg/kg orally vs 0.5 mg/kg intravenously) is also likely to have contributed to the differences in the findings. Oral methylphenidate gets into the brain slowly (peaking 60-90 minutes after administration), inducing a slow and progressive increase in DA that is not rewarding, while intravenous methylphenidate gets into the brain very rapidly (peaking < 15 minutes), inducing a large and abrupt DA increase that is perceived as very reinforcing.⁴⁴

ENHANCED REINFORCING EFFECTS OF INTRAVENOUS METHYLPHENIDATE IN ADHD

Here we also document that subjects with ADHD reported more intense reinforcing effects (drug liking) after intravenous methylphenidate than controls. The reinforcing responses to methylphenidate were negatively correlated with the DA increases, suggesting that decreased dopaminergic activity may also be involved in modulating the magnitude of the reinforcing effects of methylphenidate. This association could contribute to the higher vulnerability for substance abuse comorbidity in adult subjects with ADHD.⁴⁵ Indeed substance abusers show blunted DA responses to intravenous methylphenidate or amphetamine administration.^{46,47} The finding

would also be consistent with clinical studies indicating a protective effect of treatment with stimulants on development of substance abuse in individuals with ADHD⁴⁸ since stimulant treatment will increase DA tone.

It is important to emphasize that the behavioral effects (drug liking) of intravenous methylphenidate as used in this study are quite different from those of oral methylphenidate as used when given in the treatment of ADHD where reinforcing effects are not observed. This is due, as discussed here, to differences in pharmacokinetics but also to differences on the doses used, which in this study led to much higher plasma methylphenidate concentrations than those achieved therapeutically (reviewed⁴⁴). Thus the present report of methylphenidate-induced drug liking does not have a parallel in the therapeutic effects of oral methylphenidate and should not detract from its use. Elsewhere⁴⁴ a more detailed discussion on the differences in use and abuse of methylphenidate that depend on route of administration has been presented with a discussion of why the clinical use in the treatment of ADHD is associated with oral administration and the abuse is associated with intravenous administration.

DOPAMINE RELEASE IN AMYGDALA AND HIPPOCAMPUS

In this study, we also provide preliminary evidence of disrupted DA release in hippocampus and amygdala. Although these regions have been much less investigated in ADHD than the striatum and the prefrontal cortex, recent studies have shown volumetric changes in the hippocampus (larger in ADHD) and the amygdala (smaller in ADHD) of children with ADHD.⁴⁹ Similarly, functional imaging studies have reported inadequate activation of the hippocampus during a decision task in adults with ADHD.⁵⁰ Inasmuch as DA release in amygdala and hippocampus has been associated with performance on working memory and attention in healthy controls,⁵¹ the preliminary findings of a blunted release in ADHD could also contribute to their impairments in these tasks.⁵²

LIMITATIONS

First, although changes in [¹¹C]raclopride binding are related to extracellular DA, the precise relationship with extracellular DA is not understood.^{33,53} The poor temporal resolution of PET allowed us to detect DA changes only over a 20- to 30-minute period, reflecting mostly tonic DA activity, and thus we could not assess if there are abnormalities in phasic DA activity in ADHD. Also we cannot rule out the possibility that the blunted DA responses to methylphenidate in subjects with ADHD could reflect higher baseline DA tone that would interfere with further increase by methylphenidate via activation of autoreceptors.

Second, the [¹¹C]raclopride method is best suited to detect DA release in regions of high D₂/D₃ receptor density such as striatum and thus is much less sensitive to detect differences in extrastriatal regions. Although we were able to document robust effects of intravenous methylphenidate on amygdala and hippocampus and significant differences on the effects of methylphenidate be-

tween controls and subjects with ADHD on volume sizes in these regions, the SPM between group comparisons on the delta images (methylphenidate – placebo) was non-significant. This is likely to reflect the low statistical power in the SPM comparisons of the delta images, which are noisy and have large standard deviations (approximately the square root of 2 times the standard deviations of the nonsubtracted images). The failure to document significant group differences on the SPM comparisons on the delta images leads us to interpret the findings in hippocampus and amygdala as preliminary and in need of replication.

Here we detected lower D₂/D₃ receptor availability and decreased DA release in caudate, which is a brain region where prior studies have documented reduced volume in subjects with ADHD.⁵⁴⁻⁵⁶ Even though decreased caudate volume could result in an underestimation of D₂/D₃ receptor availability measures because of a reduced recovery coefficient,⁵⁷ this is unlikely to be the case since the K₁ measures in caudate did not differ between groups.

Finally in this study, we did not obtain magnetic resonance imaging structural images and the ROIs were obtained directly from the [¹¹C]raclopride images. Since measures of D₂/D₃ receptor availability obtained using ROIs selected directly from [¹¹C]raclopride images are almost identical to those obtained when the ROIs were selected from the subject's magnetic resonance images,⁵⁸ it is unlikely that this limitation influenced our findings. However, we cannot rule out the possibility that in subjects with ADHD who may have smaller caudates, the 2 methods may have yielded different results.

CONCLUSION

These results provide evidence of depressed DA activity in ADHD. Moreover, the significant association between the blunted changes in DA in caudate and the severity of clinical symptoms suggests that reduced dopaminergic input into the caudate may underlie the symptoms of inattentiveness in adult subjects with ADHD. In addition, preliminary evidence of DA abnormalities in hippocampus and amygdala corroborates the involvement of the limbic system in the pathophysiology of ADHD.

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