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Further Evidence of Dopamine Transporter Receptor Dysregulation in ADHD: A Controlled PET Imaging Study Using Altropane

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Abstract

Background—The dopamine transporter (DAT) is known to be a key regulator of dopamine and recent studies of genetics, treatment and imaging have highlighted the role of DAT in Attention deficit-hyperactivity Disorder (ADHD). However, the findings of in vivo neuroimaging of DAT in ADHD have been somewhat discrepant.

Method—DAT binding was measured using a highly selective ligand (C-11 altropane) and positron emission tomography (PET). The sample consisted of 47 well characterized, treatment naïve, non-smoking, non-comorbid adults with and without ADHD. Additionally, controls had few symptoms of ADHD.

Results—Results showed significantly increased DAT binding in the right caudate in adults with ADHD compared with matched controls without this disorder.

Conclusions—These results confirm abnormal DAT binding in the striatum of adults with ADHD and provide further support that dysregulation of DAT may be an important component of the pathophysiology of ADHD.

Introduction

An emerging literature provides compelling support for the hypothesis that the underlying pathophysiological substrate of Attention deficit-hyperactivity disorder (ADHD) is catecholamine dysregulation and associated fronto-striatal dysfunction (Spencer et al 2002). Dopamine has a central role in the regulation of psychomotor activity and reward seeking

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behavior and the dopamine transporter (DAT) is a key regulator of dopamine. Because the DAT is the main target for stimulant medications, initial molecular genetic (Faraone et al 2005) and molecular neuroimaging studies have focused on the DAT. A recent pooled analysis of association-based studies of the DAT1 VNTR (SLC6A3) revealed a significant association of this polymorphism with ADHD (Faraone et al 2005).

Although imaging studies in ADHD have also focused on the DAT, the available studies have led to inconsistent results (Spencer et al 2005b). Most DAT imaging studies have been small, used Single Photon Emission Computed Tomography (SPECT), and relied on radioligands with variable affinities for CNS DAT and variable lipophilic properties. (Spencer et al 2005b) For example, the radioligands TRODAT and B-CIT have much lower specificities for DAT (3:1 and 1:1 vs. the serotonin transporter, respectively) than that of the radioligand Altropane (28:1). Likewise, differences in the lipophilic properties of the various ligands may detect different proportions of internalized and the externalized DAT (on the cell surface). (Madras et al 2002) In addition, most studies paid insufficient attention to the potential confounders of psychiatric comorbidity, previous treatment, smoking and the presence of ADHD in controls that may affect DAT binding.

The main goal of this investigation was to evaluate brain DAT binding in ADHD attending to the shortcomings of the extant literature. To this end we assessed brain DAT binding in a well powered sample of well matched adults with and without ADHD using sophisticated expert diagnostic methodology, a technically superior radioactive ligand (^{11}C- altropane), and state-of-the-art imaging technology (PET). We tested the hypothesis that adults with ADHD would have greater DAT binding than adults without ADHD.

Methods

Subjects

Subjects consisted of 47 volunteers between 18 and 55 years of age. ADHD subjects had to satisfy full diagnostic criteria for DSM-IV ADHD. (Biederman et al 1993) Control subjects could have at most 2 mild symptoms of ADHD and no family history of ADHD. We excluded potential subjects if they had clinically significant chronic medical conditions, abnormal baseline laboratory values, I.Q. <80, Axis I psychiatric conditions, drug or alcohol abuse or dependence, previous exposure to psychotropics or were smokers. All subjects were right handed. This study was approved by the institutional review board and all subjects completed a written informed consent before inclusion in the study.

Assessment

Comprehensive clinical assessments were identical to those described previously (Biederman et al 1993). Overall severity of ADHD was assessed with the Adult ADHD Investigator Symptom Report Scale (Spencer and Adler 2004).

Procedures

PET imaging procedures and calculation of binding potential values were identical to those described previously (Spencer et al. 2006).

Statistical Analysis

Categorical data were analyzed by chi square analysis, continuous parametric data by an unpaired t-test and the rank sum test for nonparametric data. Associations between continuous variables were evaluated using Pearson correlations. We chose a significance level of 0.05. **To test DAT binding in 4 subterritories we corrected the alpha for (4) multiple comparisons, an alpha of 0.0125%.** All tests were two tailed.

Results

Although subjects with and without ADHD had similar sociodemographic characteristics, ADHD subjects were somewhat older than controls ($p<0.01$) (Table 1). Thus, subsequent analyses are corrected for age.

In multivariate analyses including both diagnoses and age, DAT binding was statistically significantly different between diagnostic groups only in the right caudate (t=2,77, df=45, p=0.008). **Prior to age correction, right caudate DAT binding was not statistically different (3.2±0.7 vs. 2.9±0.13, t=2.3, df=45, p=0.13)** Regression analyses revealed a statistically significant effect of age on DAT binding in the left putamen (t=−2.55, df=45, p= 0.014) and the right caudate (t=−2.07, df=45, p= 0.045). To further understand the moderating effect of age on DAT findings, we adjusted for age using a linear correction to create DAT binding as if each subject was 30 years of age. **The relationship between age and DAT binding was similar between ADHD and Controls in both right caudate and left putamen (interaction terms, p's=NS).** This analysis showed that DAT binding in the right caudate was15% (effect size 0.82) greater in adults with ADHD than in normal controls (t=7.7, df=45, p=0.008) (Table 2).

Because gender may also moderate DAT binding results (Mozley et al 2001), we examined the influence of gender on DAT binding in the right caudate. This analysis showed that DAT binding in the right caudate was greater in females than in males (t=−3.24, df=44, p= 0.002) regardless of diagnostic status. When simultaneously controlling for sex and age, the differences in DAT binding in the right caudate were found to be somewhat larger than the original estimates (t=3.75, df=44, p<0.001). **For example, DAT binding in the right caudate was 17% greater in male adults with ADHD (t=6.9, df=24, p=0.02) and 22% greater in female adults with ADHD than in normal controls (t=7.3, df=21, p=0.02).** In contrast, neither severity of ADHD, family history of ADHD, symptoms of anxiety and depression (Beck, Ham-A, Ham-D), nor ethnicity moderated DAT findings.

Discussion

This study used a highly selective radioactive ligand (^{11}C- altropane) and PET to examine DAT binding in the striatum in a large sample of well-characterized adults with and without ADHD. Results showed significantly increased DAT binding in the right caudate in adults with ADHD compared with matched controls without this disorder. These results provide further support that dysregulation of DAT may be an important component of the pathophysiology of ADHD.

This study has some noteworthy strengths. It included a sizeable number of well characterized subjects with and without ADHD, used a highly specific radioligand (altropane) that selectively binds to the DAT and relied on PET imaging. In contrast, the previous literature on DAT binding in ADHD consists of mostly SPECT-based studies that used less specific radioligands and often relied on samples of convenience as controls without formally ruling out symptoms of ADHD and other potential confounders. In addition, some previous studies included ADHD subjects with previous exposure to stimulants and did not adequately control for smoking status or exposure to alcohol or drugs, factors that also can affect DAT binding (Krause et al 2003; Spencer et al 2005b).

In our study DAT dysregulation was localized in the right caudate. This finding is consistent with evidence linking the caudate to the regulation of complex cognitive functioning, whereas the putamen is thought to be largely involved in motoric functions (Bhatia and Marsden 1994; Mozley et al 2001). In addition, this hypothesis may be indirectly supported by the only other PET study (Jucaite et al 2005) that found significant correlations between IQ, verbal understanding and speed of perception organization and DAT binding in the caudate (but not

in the putamen) in ADHD subjects. This finding may explain the discrepancies reported in studies that averaged data over the entire striatum. In addition, different specificities and lipophilic properties of the ligands may also have accounted for differences in detection of external and internal DAT (Madras et al 2002).

As previously discussed (Madras et al 2002), abnormal DAT binding could be a trait or a state. A trait could be due to “hypertrophy” of dendritic trees or dopaminergic neurons as a result of inadequate pruning during neurodevelopment or arising from abnormalities in the DAT gene. On the other hand, elevated dopamine transporter expression may reflect a state, not a trait of ADHD and arise from neuroadaptive processes that compensate for increased (or decreased) dopamine neurotransmission. Regardless of underlying mechanisms, the observed increase in the dopamine transporter provides leads to further investigate these and other hypotheses.

Our results must be interpreted in view of some limitations. While our study has been able to address DAT binding in the absence of potentially confounding conditions including previous exposure to nicotine, stimulants or substances of abuse as well as various comorbid conditions, a larger study is needed to determine the importance and degree of influence on DAT binding of these confounders which commonly occur in ADHD populations. While age correction of DAT is standard, even when groups are age matched (van Dyck et al. 2005, van Dyck et al. 2002, Volkow et al. 1996), it may be important to reexamine these findings in a more age matched sample.

Despite these considerations, in a large, well characterized sample of adults with and without ADHD, using a highly selective ligand and PET imaging technology, we showed significantly increased DAT binding in the right caudate in treatment naïve adults with ADHD. These results are consistent with a body of literature implicating fronto-striatal structures and catecholamine dysregulation in the pathophysiology of ADHD. If replicated, our findings will have more precisely localized ADHD-associated DAT abnormalities in the brain.

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TABLE 1

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF SAMPLE

	ADHD (N=21)		Controls (N=26)		Test	Significance
Demographics	**No.**	**(%)**	**No.**	**(%)**	**$X^2$1**	**p-value**
Male	14	67	11	42	2.8	0.1
	Mean	**±SD**	**Mean**	**±SD**	**t (45)**	
Age	34.4	9.2	27.4	7.6	2.9	0.006
Socioeconomic Status	1.67	0.62	1.85	0.55	1.0	0.30
Psychosocial Functioning	**Mean**	**±SD**	**Mean**	**±SD**	**t (41)**	**p-value**
Past Global Assessment of Functioning	53.7	5.3	65.0	6.5	6.6	0.00
Current Global Assessment of Functioning	60.1	4.5	70.5	2.2	9.7	0.00
Cognitive Testing (WAIS-R)	**Mean**	**±SD**	**Mean**	**±SD**	**t (41)**	**p-value**
Full Scale IQ[a]	113	9.7	119	14.7	2.53	0.12
Freedom from Distractibility IQ[a]	110.4	13.7	111.2	13.7	0.03	0.86
Achievement Scores	**Mean**	**±SD**	**Mean**	**±SD**	**t (41)**	**p-value**
WRAT Subscale percentile (Arithmetic)[a]	103.3	12.1	105.2	15.1	0.21	0.65
WRAT Subscale percentile (Reading)[a]	106.0	9.4	109.8	6.9	2.22	0.144
School Failure	**No.**	**(%)**	**No.**	**(%)**	**$X^2$1**	**p-value**
Repeated Grade[b]	2	9.5	0	0	2.3	0.13
Placement in Special Class[b]	3	14	0	0	3.5	0.06
Tutoring[b]	8	38.1	8	34.8	0.05	0.82

	ADHD (N=21)		Controls (N=26)		Test	Significance
Demographics	**No.**	**(%)**	**No.**	**(%)**	**$X^2$1**	**p-value**

[a] ADHD (N=21), Controls (N=22)

[b] ADHD (N=21), Controls (N=23)

Socioeconomic Status = Hollingshead Four Factor Index of Social Status WAIS-R= Wechsler Adult Intelligence Scale - Revised WRAT= Wide Range Achievement Test-Revised

TABLE 2

AGE-CORRECTED DAT BINDING

	ADHD (N=21)		Controls (N=26)		Test	Degrees of Freedom	Significance
	Mean	±SD	Mean	±SD	t (x)	Df	p-value
Right Putamen	3.07	0.50	3.00	0.40	0.22	45	0.64
Left Putamen	3.13	0.37	3.02	0.39	0.85	45	0.36
Right Caudate	3.44	0.62	2.99	0.48	7.7	45	0.008
Left Caudate	3.41	0.78	3.10	0.55	2.59	45	0.11