Dopamine Transporter Genotype and Stimulant Side Effect Factors in Youth Diagnosed with Attention-Deficit/Hyperactivity Disorder

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Abstract

The dopamine transporter locus (DAT1) has been studied as a risk factor for attention-deficit/hyperactivity disorder (ADHD) and in pharmacogenetic studies of stimulant response. Several prospective studies have reported an association between the homozygous 9 repeat allele of the DAT1 3′ untranslated region (UTR) variable number tandem repeat (VNTR) (DAT1 3′) and decreased efficacy of methylphenidate (MPH). We hypothesized that children with the 9/9 genotype would display higher rates of specific stimulant side effects. Data on adverse events and DAT1 3′ genotypes were combined from two, double-blind, placebo-controlled, crossover studies of MPH conducted in child psychiatric outpatient clinics in Montreal and Washington, D.C. There were 177 participants, 5–16 years old (mean age = 8.99, standard deviation [SD] = 2), with ADHD. Parents completed the Stimulant Side Effect Scale (SERS) after a week of placebo and a week of MPH treatment. Principal components analysis of the SERS resulted in three factors: Emotionality, Somatic Complaints, and Over-focused. Children with the 9/9 genotype displayed higher scores on the Emotionality factor during placebo than children with the 9/10 and the 10/10 genotype, and their Emotionality scores increased further during MPH treatment (F[2,151] = 3.24, $p < 0.05$). Children with the 10/10 genotype displayed a significant increase in Somatic Complaint factor scores during MPH treatment relative to the other genotype groups (F[2,150] = 3.4, $p < 0.05$). These data provide suggestive evidence that DAT1 variants are differentially associated with specific stimulant side effects. Children with the 9/10 genotype displayed less severe stimulant side-effect ratings than either of the homozygous groups, who each displayed increased susceptibility to different types of adverse events. Preliminary evidence suggests that pharmacogenetic analysis using DAT1 variants shows promise for identifying individuals at increased or decreased risk for poor tolerability.

Introduction

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is a highly familial neurobehavioral disorder that is frequently treated with stimulant medications, such as methylphenidate (MPH) or amphetamine (Goldman et al. 1998). Despite robust short-term efficacy in the majority of ADHD efficacy studies, many children and adolescents with ADHD discontinue treatment prematurely (Thiruchelvan et al. 2001; Schachar et al. 2002). This is presumably due to adverse effects contributing to poor tolerability (Efron et al. 1998; Charach et al. 2004). Mild stimulant side effects are common, especially insomnia, decreased appetite, and irritability (Barkley et al.

1990; Efron et al. 1997). Insomnia and decreased appetite are often dose dependent or transitory (Douglas et al. 1986; Greenhill et al. 2001; Rapport and Moffitt 2002; Stein et al. 2003). For example, Barkley et al. reported that decreased appetite, insomnia, stomachaches, and headaches increased significantly in frequency and severity during the two active medication periods as compared to the placebo treatment (Barkley et al. 1990). Irritability is common at baseline and often improves during treatment, although it can also be exacerbated with stimulants or occur as part of a rebound phenomenon as stimulant concentrations decline. More severe, but far less common, stimulant side effects have also been reported, including psychotic symptoms and severe

emotionality (Cherland and Fitzpatrick 1999; Sarampote et al. 2002). It is unclear how prevalent severe dysphoria and other psychiatric side effects are. In one study, 6 of 192 patients reviewed displayed severe behaviors, including several who displayed psychotic symptoms during stimulant treatment.

At present, pharmacological treatment for ADHD is determined empirically (American Academy of Child and Adolescent Psychiatry 2002), as there are few predictors of response to stimulants (Owens et al. 2003), to type of stimulant (i.e., MPH or amphetamine) (Pelham et al. 1990; Barbaresi et al. 2006) or of optimal dose. The strong heritability of ADHD and wide individual variability in dosing and tolerability has increased interest in pharmacogenetic studies of stimulant response (McGough 2005; Stein and McGough 2008). Not surprisingly, the majority of pharmacogenetic studies have examined logical candidates, such as the dopamine transporter gene (DAT1) and other genes related to catecholamine metabolism (Vandenbergh et al. 2000). This is because the primary mechanism of action of stimulants is thought to be through blocking reuptake of synaptic dopamine by binding to the dopamine transporter (Swanson et al. 2000; Volkow et al. 2002; Volkow et al. 2007). The dopamine transporter locus has been investigated in murine knockout models (Heiser et al. 2004), as candidate genes in studies of ADHD susceptibility (Maher et al. 2002; Lee et al. 2007), and more recently pharmacogenetic studies (Greenhill et al. 2001; Rohde et al. 2003; Stein and McGough 2008).

In the first pharmacogenetic study of MPH in ADHD, Winsburg and Comings reported decreased efficacy in African-American children homozygous for the 10-repeat allele as compared to other DAT1 3′ genotype groups (Winsberg and Comings 1999). Subsequently, a handful of studies with markedly different methods and study populations and predominantly small samples have yielded conflicting results in terms of risk genotype and direction of effect (Roman et al. 2004; McGough et al. 2005). However, three recent prospective studies have examined the 9/9 genotype separately from the 9/10 genotype and found decreased efficacy for the 9/9 genotype group relative to other DAT1 genotype groups on parent-report measures of ADHD symptoms (Stein et al. 2005; Joober et at. 2006; McGough et al. 2006).

Genetic variation in DAT1 may be associated with other response characteristics besides efficacy. As described by Roses (Roses 2004), pharmacogenetic analysis can be used to differentiate phenotypic heterogeneity, to segment populations that are responsive or unresponsive to a medication, and to identify accurately individuals who are at increased risk of an adverse event. For example, Zeni et al. (2005) (examined the effects of DAT1 on insomnia and decreased appetite in a naturalistic study of 111 children and did not find any association. However, in the Preschool ADHD study (McGough et al. 2006), McGough et al. reported that preschoolers with the SNAP25 G allele at T1065 had two to three times the risk of irritability and sleep problems than preschoolers homozygous for the more common T variant. In addition, preschool children with the C allele at SNAP25 1069 were two to four times more likely to develop tics than those homozygous for the T allele. The DAT1 3′ genotype was not associated with adverse events in this sample, although there were only 8 subjects with the 9/9 genotype. In contrast, Stein et al. (2005) reported DAT1 3′ genotype differences on total stimulant side

effects in a sample that included 6 children with the 9/9 genotype.

These preliminary efforts at detecting the relationship between DAT 3′ genotypes and susceptibility for specific adverse events have been hampered by the small number of individuals with the 9/9 genotype and the wide range of potential stimulant side effects to examine, necessitating multiple comparisons within small samples. Consequently, the purpose of the present study is to examine more closely the relationship between DAT1 3′ genotypes and statistically derived factor scores rather than individual side effects in children treated with MPH and placebo.

Methods

Participants

Data were combined from two previous studies conducted in North America with clinic-referred children with ADHD. A total of 177 children between 5 and 16 years of age (mean age = 8.99, standard deviation [SD] = 2) with a *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994), diagnosis of ADHD were included in the study. A total of 73.4% (130) were male and 26.6% (47) were female; 87.6% (155) of the subjects were white, 4.5% (8) were African American, and 7.9% (11) reported other ethnicities; 114 children (64.4%) were stimulant naïve.

The study was approved by the Research Ethics Board of Douglas Hospital and by the Institutional Review Boards of Children's National Medical Center and The University of Chicago. Informed consent was obtained from parents, and all children assented to participation in the study.

Medication, side effects, and DAT1 genotyping

At each site, parents blinded to study medication completed the Side Effects Rating Scale (SERS) after a week of a low to moderate dose of MPH and a week of placebo in randomized order. For the Montreal sample, children were administered 0.5 mg/kg per day (2.5 mg/kg dose), whereas children in the Washington, D.C., sample were administered 36 mg of OROS MPH. Barkley developed the SERS, which is a 17-item, parent-rated scale of potential stimulant side effects, where each item is rated from 0 "absent" to 9 "serious" (Barkely et al. 1990). Following the recommendations of Barkley et al., ratings of 7 and higher were considered "severe."

DNA was extracted from blood and the 3′-untranslated region (UTR) variable number tandem repeat (VNTR) polymorphism of the SLC6A3 gene was genotyped using PCR amplification. The genotyping procedure is described in detail in our previous manuscripts (Stein et al. 2005; Joober et al. 2006).

Statistical analysis

Subjects were divided into three genotype groups (9/9, 9/10, 10/10) on the basis of their DAT1 3′ polymorphism. Differences in demographics and intellectual and psychiatric characteristics were considered as dependent variables and were compared across the genotypes using either one-way analysis of variance (ANOVA) or chi-squared analysis, depending on the nature of the data.

Analysis of variance and the Pearson correlation were used to examine the relationships between SERS factor scores and

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY
DISORDER STRATIFIED BY DAT1 GROUP

Item	9, 9 (n = 16)	9, 10 (n = 68)	10, 10 (n = 93)	p value
Gender, male/female	14/2	49/19	67/26	$\chi^2 = 1.78$, df = 1, $p = 0.42$
Mean age (SD)	8.59 (2.14)	8.93 (2.04)	9.11 (2.00)	$F(2, 174) = 0.53$, $p = 0.59$
WISC-III				
Full-Scale IQ	103.88 (18.36)	104.85 (14.40)	99.82 (15.32)	$F(2, 159) = 2.04$, $p = 13$
CBCL (T scores)				
Total	69.93 (8.68)	67.04 (8.86)	67.02 (9.99)	$F(2, 169) = 0.64$, $p = 53$
Internalizing	66.87 (8.72)	60.84 (11.89)	61.94 (12.16)	$F(2, 169) = 1.60$, $p = 0.21$
Externalizing	68.67 (13.03)	66.18 (10.48)	66.28 (11.56)	$F(2, 169) = 0.32$, $p = 0.73$

Abbreviations: DAT = dopamine transporter gene; SD = standard deviation; WISC = Wechsler Intelligence Scale for Children, third edition;
IQ = intelligence quotient; CBCL = Child Behavior Checklist.

descriptive and demographic variables; chi-squared analysis
was used to compare the frequency of severe side effects be-
tween genotype groups.

Principal component analysis (PCA) with varimax rotation
was used to reduce the number of variables and to aggregate
side effects into reliable indices reflecting the main domains
affected by MPH. SERS Items with a mean rating ≥1 were
included in the PCA. Items that loaded at 0.5 or greater were
included on each factor. The relationship between polymor-
phism in the DAT1 gene and changes in SERS following ad-
ministration of MPH of children with ADHD was examined
using multicovariate analysis of variance (MANCOVAs),
where: The DAT1 3′ genotype group (9/9, 9/10, 10/10) (3) was
the between-subject independent factor; Condition (MPH,
placebo) (2) was the repeated, within-subject, independent
factor; Side Effects Factor Scores: Somatic, Emotionality,
Overfocused (3) were the dependent variables; and the child's
age and sex were covariates. Significant interaction of the
DAT1 3′ genotype group with medication would indicate that
the effects of MPH were moderated by genotype. To adjust for
pretreatment internalizing scores on measures that could
potentially confound the results, the baseline score on the
CBCL Anxious/Depressed Scale was added as a covariate to
the analyses for the Emotionality factor.

SPSS 12.0 for Windows (SPSS, Inc., Chicago, Ill) was used
for all statistical analyses. *p* values <0.05 were considered to
indicate statistical significance.

Results

Demographic and clinical characteristics of DAT1 genotype groups

Genotype frequencies for the 177 children were as follows:
16 (9%) had 9/9, 68 (38.4%) had 9/10, and 93 (52.5%) had
10/10 genotypes. DAT1 genotype distribution was in Hardy–
Weinberg equilibrium for both sites ($\chi^2 = 0.009$, not significant
[NS], Washington, D.C.; $\chi^2 = 3.25$, NS, Montreal). In Table 1,
we present the means and standard deviations of the demo-
graphic and clinical characteristics of children with ADHD
grouped according to their DAT1 genotype.

No significant differences were found between the DAT1
genotype groups and age, intelligence quotient (IQ), gender
ratio, or externalizing psychopathology. Of note, however,
the mean CBCL Internalizing T score of 65 for the 9/9 geno-
type group was within the clinical range for this measure.

PCA of SERS items

PCA resulted in a three-factor solution, which accounted
for 57.7% of the variance (Table 2). The first factor, Emotion-
ality (eigenvalue 3.25), accounted for 32.6% of the variance in
stimulant SERS scores and was composed of items reflecting
irritability, sadness, proneness to cry, and anxiety. The second
factor, Somatic Complaints (eigenvalue 1.5), accounted for
15% of the variance, and was characterized by three common
stimulant side effects: Decreased appetite, stomachache, and
insomnia. Finally, the third factor, Over-focused, was made
up of two items often associated with high stimulant dosage,
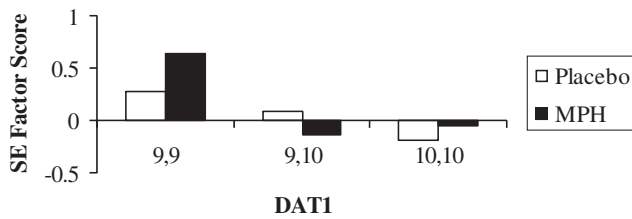staring, and nail biting. This factor accounted for 10.1% of the
variance (eigenvalue 1.1).

To examine the criterion-oriented validity of the SES fac-
tors, we examined the association of factor scores with de-
mographic characteristics of age and gender, and with
dimensional measures of psychopathology obtained from the
Child Behavior Checklist (CBCL) prior to medication treat-
ment. Emotionality was positively correlated with CBCL In-
ternalizing T score ($r = 0.16$, $p < 0.05$). This suggests that
children who displayed more emotionality during stimulant
treatment were also likely to display more internalizing
symptoms prior to beginning stimulant treatment.

No significant sex or age differences were found on any of
the factors, and there was no relationship between previous
stimulant treatment and SERS factor scores.

TABLE 2. ROTATED FACTOR LOADINGS FOR SIDE EFFECTS
WHILE ON METHYLPHENIDATE

	Factor loading		
Side effects while on MPH	Emotionality	Somatic	Over-focused
Staring	0.17	0.22	**0.54**
Decreased appetite	0.02	**0.75**	0.13
Irritability	**0.61**	0.13	0.47
Stomach ache	0.24	**0.79**	−0.16
Head ache	0.40	**0.45**	−0.35
Sadness	**0.82**	0.21	0.10
Prone to cry	**0.84**	0.08	0.17
Anxious	**0.79**	0.01	0.07
Biting nails	0.11	−0.05	**0.68**
Insomnia	0.03	**0.62**	0.22

Abbreviations: MPH = methylphenidate.

FIG. 1. Emotionality factor scores for DAT1 genotypes groups during placebo and MPH Treatment. DAT1 = Dopamine transporter gene; MPH = methylphenidate; SE = standard error.
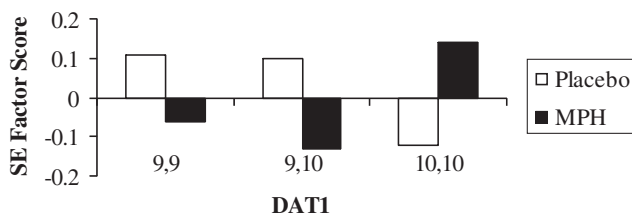
SERS factor scores and DAT1 genotype

ANCOVAs were conducted to detect DAT1 genotype effects on SERS factors, while controlling for age, gender, and site. These analyses revealed significant differences between the DAT1 genotype groups on the Emotionality factor, $F(2,151) = 3.09$, $p < 0.038$, with the 9/9 displaying a higher rated level of negative emotion compared to the 9/10 and the 10/10 genotype groups during placebo. Significant genotype by factor effect was found, with the 9/9's score increasing dramatically following treatment with MPH $F(2,151) = 3.33$, $p < 0.048$ (Fig. 1).

In contrast, children with the 10/10 genotype displayed an increase in Somatic Complaint scores on the SERS with MPH treatment, $F(2,150) = 3.4$, $p < 0.037$, which was not displayed by the other genotype groups (Fig. 2). No significant genotype group differences or interactions were detected for the Over-focused factor.

Comment

For the most part, studies of ADHD treatments and pharmacogenetic studies have emphasized the efficacy of stimulant medications and have focused little on adverse events and tolerability. Not surprisingly, the frequency and severity of adverse events differs markedly among studies depending on sample characteristics, informant, method of ascertainment, and when in the trial adverse events are assessed (Efron et al. 1997; Efron et al. 1998). A common measure of adverse events in ADHD treatment, the SERS, is composed of items that represent a heterogeneous collection of symptoms or behaviors that are considered to be side effects of stimulant treatment. However, individual items on the SERS may also reflect symptoms of co-morbid psychopathology (e.g., irritability, nightmares), or even the beneficial effects of treatment

(e.g., talks less). Using multivariate statistical techniques, we have reduced the number of variables examined and identified factors representing different stimulant side effects.

Although there is general agreement that safety and tolerability of stimulant medications is a high research priority based upon the public health significance of ADHD and the increasing prevalence of stimulant treatment (Vitiello et al. 2003), at present there are few specific or reliable predictors of adverse events in children with ADHD. We report a specific association between the DAT1 3′ 9/9 genotype and increased dysphoria and emotionality that worsens during MPH treatment. While several studies, including the Multimodal Treatment Study of Children with ADHD (MTA) (March et al. 2000; Hinshaw 2007), did not find a significant moderating effect of emotional symptoms on efficacy (Abikoff et al. 2005), other studies suggest that youths with "emotional" symptoms are most likely to display an adverse response to stimulants (Taylor et al. 1987; DuPaul et al. 1994; Goez et al. 2007). The present study opens the possibility that increased emotionality and dysphoria, which occur in a small but significant subgroup of MPH-treated children with ADHD, may be partially moderated by variations in DAT1.

An alternative explanation for the foregoing phenomenon is that elevated Emotionality factor scores may be associated with stimulant rebound, or a worsening of symptom and emotionality as stimulant concentrations decrease. In a recent study of stimulant rebound, one third of children displayed rebound on at least one dose, and the symptoms were severe enough to cause discontinuation of treatment in 8% of the sample (Carlson and Kelly 2003). Prospective studies are needed to identify the specific relationship of elevations on this factor to psychiatric co-morbidity and rebound effects. Moreover studies of gene expression, pharmacokinetics, and pharmacodynamics are needed to determine potential mechanisms of differential response (Swanson and Volkow 2002).

Insomnia and decreased appetite, side effects commonly associated with ADHD treatment with stimulants, are components of the Somatic Complaints factor. While the present study design does not evaluate which adverse effects are dose dependent, previous studies suggest that insomnia and decreased appetite increase with higher stimulant dosages (Stein et al. 2003). For example, in a previous crossover study of 234 children with ADHD who were treated with placebo and two MPH doses, 0.3 mg/kg, and 0.5 mg/kg/, insomnia, appetite disturbance, stomachache, headache, and dizziness increased relative to placebo with the increasing MPH dose (Ahmann et al. 1993). In contrast, staring, daydreaming, irritability anxiety, and nail biting decreased with MPH treatment. These items are related to the SERS Emotionality and Over-focused factors.

The results of this study suggest several hypotheses of potential clinical relevance. First, individuals with the 9/9 genotype may be candidates for expanded psychosocial treatment to target mood symptoms or pharmacotherapy with a nonstimulant (e.g., atomoxetine). Further study of the mechanisms related to increased emotionality, *per se*, is needed; these specific symptoms may represent differential effects of MPH on pathways other than the dopaminergic frontal-striatal networks that are frequently associated with ADHD (Pliszka et al. 1996; Taylor 1999; Solanto 2002). Second, individuals with the 10/10 genotype appear to be more susceptible to somatic and sleep problems, which are frequently reported in children

FIG. 2. Somatic complaint scores for DAT1 genotype groups during placebo and MPH treatment. DAT1 = Dopamine transporter gene; MPH = methylphenidate; SE = standard error.

taking stimulant medications. Perhaps individuals with this genotype may respond to lower dosages or a slower titration schedule. Finally, the present study suggests that DAT1 3′ heterozygotes are less likely to experience emotional or somatic side effects during stimulant treatment. The majority of previous pharmacogenetic studies of efficacy have reported improved response rates for this genotype group relative to the homozygous DAT1 3′ genotypes (Winsberg et al. 1999; Rohde et al. 2003). Because longitudinal studies suggest increased severity of impairment in youths with the 9/10 genotype (Barkley et al. 2006), being able to optimize their dose quickly given the decreased risk of adverse events could potentially result in improved effectiveness of stimulant medication for children and adolescents with this common genotype.

There are several limitations, however, which should be considered when interpreting the results of this study. The primary limitation is the small number of individuals with the 9/9 genotype. However, given the relatively small sample size of individuals with the 9/9 genotype, failing to combine samples would have made the analysis impossible and resulted in a missed opportunity for a first look at these effects. Future studies with larger samples are needed to confirm the associations between DAT1 genotypes and stimulant side effects, and to examine gene×environment and gene×gene interactions, which may account for a greater percentage of the variation in response.

Second, the present findings are based on studies of a fixed, low to moderate MPH dose and a very brief, 1-week study period. Thus, the findings may not generalize to wider dose ranges or more subtle side effects that develop over time.

Finally, due to the exploratory nature of this study, multiple statistical tests were conducted, increasing the possibility of a false-positive finding. This is particularly salient given the previous history of false-positive findings in candidate gene studies (McGough 2005).

Furthermore, future genetic analyses in clinical trials may assist in distinguishing symptoms of co-morbidity from ADHD symptoms or stimulant side effects. However, if, as the present study suggests, the types and severity of adverse events during stimulant treatment are related to specific DAT polymorphisms, eventually it may be possible to identify those at greater risk of a specific adverse event, thereby increasing the efficiency of treatment planning and ultimately reducing adverse events that contribute to the poor tolerability and adherence of ADHD treatments in older children and adolescents. Each of these elements has important promise for safer, more prompt, and more effective treatment of ADHD.

Disclosures

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