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Dopamine transporter gene variation modulates activation of striatum in youth with ADHD

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ABSTRACT

Polymorphisms in the 3′UTR variable number tandem repeat (VNTR) of exon 15 of the dopamine transporter gene (DAT1) have been linked to attention-deficit hyperactivity disorder (ADHD); moreover, variability in DAT1 3′UTR genotype may contribute to both heterogeneity of the ADHD phenotype and differences in response to stimulant medications. The impact of this VNTR on neuronal function in individuals with ADHD remains unclear despite evidence that the polymorphisms influence dopamine transporter expression. Thus, we used event-related functional magnetic resonance imaging to examine the impact of DAT1 3′UTR genotype on brain activation during response inhibition in unmedicated children and adolescents with ADHD. Twenty-one youth with ADHD who were homozygous for the 10-repeat (10R) allele of the DAT1 3′ UTR and 12 youth who were carriers of the 9-repeat (9R) allele were scanned while they performed a Go/No-Go task. Response inhibition was modeled by contrasting activation during correct No-Go trials versus correct Go trials. Participants who were homozygous for the DAT1 3′UTR 10R allele and those who had a single 9R allele did not differ on percent of trials with successful inhibition, which was the primary measure of inhibitory control. Yet, youth with the DAT1 3′UTR 10R/10R genotype had significantly greater inhibitory control-related activation than those with one 9R allele in the left striatum, right dorsal premotor cortex, and bilaterally in the temporoparietal cortical junction. These findings provide preliminary evidence that neural activity related to inhibitory control may differ as a function of DAT1 3′UTR genotype in youth with ADHD.

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders of childhood, with worldwide prevalence rates estimated at 4–10% (as reviewed by Skounti et al., 2007). Genetic studies have demonstrated that ADHD is highly heritable, with estimates ranging from 0.60 to 0.90 (Faraone et al., 2005). Candidate gene studies of ADHD have implicated several dopamine genes in the etiology of the disorder. Recent meta-analyses reported that several genes showed statistically significant evidence of association with ADHD: four of which were dopamine system genes (the dopamine D4 and D5 receptor genes, the dopamine transporter gene (DAT1), and the dopamine beta-hydroxylase gene) (Faraone and Khan, 2006; Gizer et al., 2009). Of these, the dopamine transporter is a principal target of stimulant medications (Zhu and Reith, 2008), which are the primary treatments for ADHD.

DAT1 (SLC6A3) is a membrane protein that binds dopamine and provides the primary mechanism through which dopamine is cleared from synapses (Bannon et al., 2001). DAT1 is found in brain regions where dopamine signaling is widespread, including the striatum, nucleus accumbens, anterior cingulate, posterior parietal cortex, and hippocampus (Ciliax et al., 1999; Lewis et al., 2001). The gene for DAT1 contains 15 exons, is located on chromosome 5p15.3, and has a protein encoding region which is over 64 kb long (Kawarai et al., 1997). Of note, the DAT1 gene has a polymorphic variable number tandem repeat (VNTR) which is 40 bp in length and is located in the 3′ UTR of exon 15. The 10-repeat (10R) and 9-repeat (9R) alleles of this VNTR are the most frequently occurring (Kang et al., 1999; Vandenbergh et al., 1992). Although several studies have reported a significant association between the DAT1 3′UTR 10R allele and ADHD (e.g., Cook et al., 1995; Hawi et al., 2009; see meta-analysis by Yang et al., 2007), others have suggested that it may be the 9R allele that is preferentially transmitted in individuals with ADHD (Franke et al., 2008), and some have reported no association between DAT1 and ADHD (Johansson et al., 2008; Langley et al., 2005) (as reviewed by Plomp et al., 2009).

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Although the functional significance of the different DAT1 3′UTR polymorphisms is still unclear, it has been shown that the 10R variant is associated with greater levels of dopamine transporter protein than the 9R form (Brookes et al., 2007; Fuke et al., 2001; Heinz et al., 2000; Mill et al., 2002; VanNess et al., 2005). Because the variation is located in the 3′UTR, the reported increase in protein expression is likely a result of changes in mRNA stability or protein translation. Accordingly, the increased levels of dopamine transporter in individuals who carry the 10R allele may directly lead to the decreased levels of synaptic dopamine that have been linked to ADHD (Volkow et al., 2007). However, this mechanism of action has been questioned by reports of both lower dopamine transporter density for individuals with 10R-homozygosity compared to carriers of a 9R allele in healthy subjects (Jacobsen et al., 2000; van Dyck et al., 2005), and no difference in dopamine transporter density with differing DAT1 3′UTR genotypes in both ADHD and normal control samples (Krause et al., 2006; Martinez et al., 2001).

Recent neuroimaging studies have provided preliminary evidence that the DAT1 3′UTR genotype influences cognition-related brain activity. However, the functional impact of the various DAT1 3′UTR alleles is not fully understood, with reports linking the 10R allele to both lower activation during working memory in the prefrontal and anterior cingulate cortices in healthy adults (Bertolino et al., 2006) and greater activation during executive functions in the anterior insula and caudate nucleus in adults with and without schizophrenia (Prata et al., 2009). The impact of the DAT1 3′UTR genotype is similarly variable in individuals with ADHD. Adults with ADHD homozygous for the 10R allele showed dorsal anterior cingulate hypoactivation during executive function compared to 9R carriers (Brown et al., 2009), while boys with ADHD and their unaffected siblings who were 10R homozygotes had reduced striatal activity but increased cerebellar activation during response inhibition compared to carriers of the 9R allele (Durston et al., 2008). In addition, there were no differences in activation in other brain regions where DAT1 is known to be expressed such as the posterior parietal cortex and hippocampus (Ciliax et al., 1999; Lewis et al., 2001). These intriguing, albeit somewhat inconsistent findings clearly warrant further investigation.

The current study was designed to further investigate differential brain activation as a function of the DAT1 3′UTR polymorphism in a larger sample of youth with ADHD. Based on the findings of Durston et al. (2008), we hypothesized that youth with ADHD who were homozygous for the DAT1 3′UTR 10R allele would show reduced striatal activity compared to those who were heterozygous carriers of the 9R allele. We also hoped to identify other dopaminergically innervated brain regions that might be differentially affected by DAT1 3′UTR genotype. Specifically, we used fMRI to compare brain activation during successful inhibition in a Go/No-Go task in 33 children with ADHD.

Materials and methods

Participants

Thirty-three children and adolescents (24 males, 9 females), aged 7 to 16 years, were participants of an NIH-funded treatment study examining the differential effects of treatment with methylphenidate and atomoxetine (Table 1). All participants met *Diagnostic and Statistical Manual-4th Edition* (*DSM-IV*) (American Psychiatric Association, 1994) criteria for ADHD using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime Versions (K-SADS-PL) (Kaufman et al., 1997) and were rated at least one and a half standard deviations above age and gender norms on the ADHD Rating Scale-IV–Parent Version: Investigator Administered (ADHD-RS-IV) (DuPaul et al., 1998). Children who did not respond to prior treatment with methylphenidate or atomoxetine, or had experienced adverse effects, were excluded from the study. Other exclusion criteria included substance abuse history or a positive urine screen, participation in a treatment study in the past 30 days, a past or present diagnosis of a psychotic disorder, a history of head injury with loss of consciousness, neurological, or cardiovascular disease, IQ<75, and any other condition that could affect brain function. Twenty-one participants were medication-naive; all other participants were medication-free for a minimum of 2 weeks prior to the fMRI scan. There was no significant difference in the severity of symptoms on the ADHD-RS-IV between the treatment-naive and previously treated participants ($p>0.05$).

Table 1
Demographic and clinical characteristics of youth with attention-deficit hyperactivity disorder (ADHD) by *DAT1* 3′UTR genotype.

Characteristic	*DAT1* 3′UTR 9R $n=12$	*DAT1* 3′UTR 10R/10R $n=21$
Age (years)	11.0 ± 2.6	11.2 ± 2.4
Male[a]	5 (42%)	19 (90%)
Right-handed	10 (83%)	18 (90%)
Ethnicity		
African-American	3 (25%)	11 (52%)
Hispanic	4 (33%)	6 (29%)
Caucasian	3 (25%)	4 (19%)
Asian	0 (0%)	1 (5%)
Biracial	2 (17%)	2 (9%)
ADHD subtype		
Combined	6 (50%)	11 (52%)
Inattentive	5 (42%)	10 (48%)
Hyperactive–impulsive	1 (8%)	0 (0%)
Comorbid diagnosis of ODD	4 (33%)	8 (38%)
ADHDRS-IV		
Hyperactivity–impulsivity	17.0 ± 5.6	15.2 ± 8.5
Inattention	21.2 ± 4.5	22.5 ± 3.1
Prior treatment for ADHD	6 (50%)	6 (29%)

[a] Significant gender difference ($\chi^2=9.2$, $p=0.002$).

The study was approved by the Institutional Review Board of the Mount Sinai School of Medicine. Written informed consent was obtained from parents; child assent was also obtained, and certified by a witness unaffiliated with the study. Participants and their parents received modest compensation for participation. Consent for the study was obtained for 29 additional youth with ADHD who did not successfully complete the procedures, 19 for excessive motion or anxiety during the scan, 5 who did not have enough correct trials, 4 for whom *DAT1* 3′UTR genotype was not available, and 1 who had a *DAT1* 3′ UTR 8R/10R genotype and did not fit into either of the genotype groups under investigation. The youth who did not successfully complete the study procedures were younger than the 33 study participants ($p<0.01$) but did not otherwise differ in gender or ADHD severity ($p>0.05$).

Genotyping

Saliva samples for *DAT1* 3′UTR genotyping were obtained using Oragene (DNA Genotek, Ottawa, Ontario, Canada) self-collection vials. After extraction, DNA was quantitated with Quant-iT PicoGreen dsDNA Assay (Invitrogen, Carlsbad, CA) and normalized to a concentration of 10 ng/μL. DNA was amplified with NED-labeled forward primer 5′-NED-TGT GGT GTA GGG AAC GGC CTG AG-3′ (Applied Biosystems, Foster City, CA) and reverse primer (with pigtail sequence in parentheses) 5′-(GTTTCTT) GGT CTG CGG TGG AGT CTG-3′ (Invitrogen, Carlsbad, CA) using Dynazyme EXT Polymerase (Finnzymes, Espoo, Finland) with an initial denaturation step of 96 °C for 12 minutes followed by 45 cycles of 96 °C for 30 seconds, 68 °C for 45 seconds, 72 °C for 3 minutes, one hold at 72 °C for 10 minutes, and a final hold at 10 °C. Products were separated on a 3730 Genetic Analyzer (Applied Biosystems, Foster City, CA) in the UIC Research Resources Center DNA Services Facility. Alleles were called blind to phenotype data using Genemapper v 3.7.

The participants were classified as either homozygous carriers of the *DAT1* 3′UTR 10R allele ($n=21$) or heterozygous carriers of a 9R allele ($n=12$; 11 with a 9R/10R genotype, 1 with a 7R/9R genotype). The two groups did not differ in age, ADHD subtype, comorbidity, severity of ADHD, handedness, or prior history of stimulant treatment (Table 1). However, the homozygous 10R group had a lower ratio of females: males than the heterozygous 9R group ($p<0.01$).

Go/No-Go task

The Go/No-Go task was designed to measure the ability to inhibit responses to rare non-targets (No-Go trials) in the context of frequent targets (Go trials) (Durston et al., 2002). This task has previously been used in longitudinal studies of children (Durston et al., 2006a), to test children with ADHD (Durston et al., 2006b), and to examine differential brain activation as a function of the *DAT1* 3′UTR polymorphism in adolescents with ADHD (Durston et al., 2008). The task consisted of six runs that each lasted 3 minutes and 58 seconds. Each run began with 10 seconds of fixation and contained 57 trials, with 43 (75%) Go trials and 14 (25%) No-Go trials, yielding a total of 84 No-Go trials across the task. Trial order was pseudo randomized so that the occurrence of No-Go trials was jittered from 4 to 20 seconds (i.e., preceded by one to five Go trials). Stimuli were presented for 500 ms with an interstimulus interval of 3500 ms. To make the task more appealing to children, images of Spiderman and the Green Goblin from the "Spiderman" movie (©Columbia Pictures Industries, Inc.) were used as stimuli for Go and No-Go trials, respectively (Fig. 1). Fixation was depicted by a small image of a spider presented at the center of the screen. Participants were reminded at the beginning of each block to respond as quickly as possible while trying not to make mistakes. The Go/No-Go task was compiled and run using E-Prime™ software (Schneider et al., 2002). Stimuli were projected via an SVGA projector system onto a rear-projection screen mounted at the head of the magnet bore that was viewed through a mirror on the head coil. Participants responded with the right hand using the BrainLogics fiber optic button system (Psychology Software Tools, Inc.). Responses were recorded on a desktop computer and provided measures of reaction time (RT) and accuracy.

Image acquisition

Participants were scanned on a 3.0-T Siemens Allegra (Siemens Medical Systems) head-dedicated MRI scanner. Scan sessions began with shimming and sagittal localization. A high-resolution T2-weighted anatomical volume of the brain was then acquired in the axial plane with a turbo spin-echo (TSE) pulse sequence (TR = 5380 ms, TE = 99 ms, flip angle = 170°, FOV = 210 mm, matrix = 512 × 336, 28 slices, slice thickness = 4 mm contiguous, in-plane resolution = 0.41 mm^2). Functional T2*-weighted images depicting the blood oxygenation level-dependent (BOLD) signal were acquired at the same 28 slice locations using gradient-echo echo-planar images (TR = 2000 ms, TE = 40 ms, flip angle = 90°, FOV = 210 mm, matrix = 64 × 64, slice thickness = 3 mm, gap = 1 mm, in-plane resolution = 3.28 mm^2). All images were acquired with slices positioned parallel to the anterior commissure–posterior commissure line.

Data analysis

The percent of successful inhibitions on No-Go trials served as the measure of response inhibition on the Go/No-Go task. Responses on Go trials faster than 150 ms were considered anticipatory and classified as fast Go responses, while responses with RTs greater than three standard deviations above the individual participant's mean RT were classified as slow Go responses. Responses on Go trials with a RT between these two values were defined as correct hits and served as the primary measure of habitual motor responding. Mean RT was calculated only for correct hits. The effects of *DAT1* 3′UTR genotype on Go/No-Go task performance were analyzed with independent samples *t* tests, in which the behavioral performance of 9R participants was compared to those homozygous for the 10R allele. All reported *p* values are two-tailed, with a significance level of 0.05.

Functional MR images were preprocessed and analyzed using statistical parametric mapping (SPM2; Wellcome Trust Centre for Neuroimaging, London, UK). The six functional time series acquired for each participant were realigned to the first volume in the first series (motion-corrected) and the resultant realignment parameters were examined for motion during each of the time series. Functional series with more than one voxel (4 mm) of motion were dropped from the analyses. The two groups did not differ in the mean number of functional time series or correct Go and No-Go trials (all $p<0.05$). The remaining functional time series were coregistered to the T2 anatomical images, normalized to the standard Montreal Neurological Institute (MNI) template, and resampled using a sinc interpolation, which yielded a voxel size of 2 mm^3. The images were then spatially smoothed with an isotropic 8 mm full-width-at-half-maximum Gaussian kernel.

A general linear model (GLM) was conducted to determine the relationship between observed event-related BOLD signals and regressors that represented expected neural responses to events. Regressors were created by convolving a train of delta functions that represented the individual trial events with the SPM2 base function, which consisted of a synthetic hemodynamic response function, composed of two gamma functions and their derivatives (Friston et al., 1998). There were six regressors that corresponded to the behavioral analyses, representing, (1) correct No-Go events, (2) No-Go errors (false alarms), (3) correct Go events, (4) Go errors (misses),

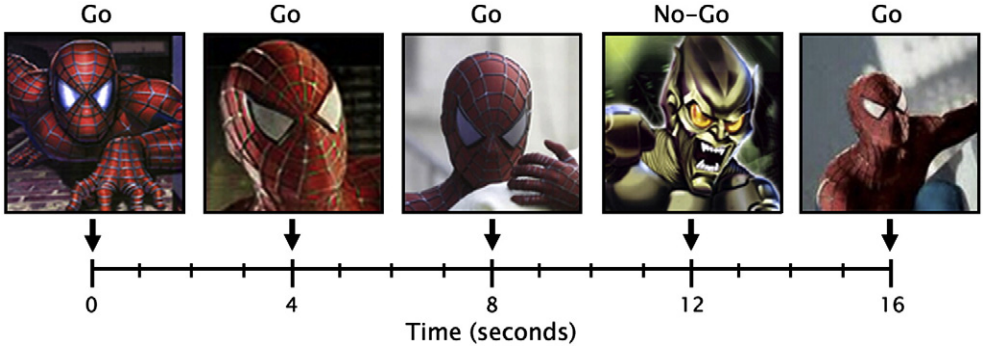

Fig. 1. Schematic diagram of the Go/No-Go task. The diagram illustrates a No-Go trial (Green Goblin) preceded by three Go trials (Spiderman). Stimuli were presented individually at fixation for 500 ms, followed by a 3500-ms interstimulus interval demarcated by a small spider. Trial order was pseudorandomized so that the occurrence of No-Go trials was jittered from 4 to 20 seconds (i.e., preceded by 1 to 5 Go trials). Participants were instructed to "press the button for all Spiderman pictures and not press for Green Goblin." The images of Spiderman and Green Goblin were adapted from promotional images for the "Spiderman" movie (©Columbia Pictures Industries, Inc.).

(5) fast Go responses, and (6) slow Go responses. The six parameters created during motion correction and the global mean of all voxels were entered as covariates of no interest in the GLM (Johnstone et al., 2006). A 0.0125 Hz high-pass filter, a first-order autoregressive function, and global mean scaling of the signal value across scans were applied to the GLM. The neural effect of response inhibition was tested by applying appropriate linear contrasts to the parameter estimates for correct No-Go events minus correct Go events, resulting in a contrast map for each participant.

The contrast images of all participants were entered into second level group analyses that used random-effects statistical models. An initial analysis used a one-sample *t*-test to confirm the neural effects of response inhibition in the whole sample of youth with ADHD. The *a priori* hypotheses were tested with planned contrasts that used two-sample *t*-tests to compare inhibitory-related neural activation in homozygous carriers of the *DAT1* 3′UTR 10R allele versus individuals who carried the 9R allele. The height (intensity) threshold for each activated voxel was set at an uncorrected p value of 0.05 and the resultant voxel-wise statistical maps were thresholded for significance using a cluster-size algorithm that protects against false-positive results (Hayasaka et al., 2004). A Monte Carlo simulation established that a cluster extent of 100 contiguous resampled voxels ($2\times2\times2$ mm^3) was necessary to correct for multiple voxel comparisons at $p<0.05$. The MNI coordinates of any significant activations were converted to atlas system of Talairach and Tournoux (1988) using a nonlinear transformation (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). To illustrate the significant *DAT1* 3′UTR genotype × trial type interaction in the left striatum, volumes of interest (VOI) were extracted from *a priori* activated regions of interest with a radius of 6 mm centered at the local maximum of the mass, located at Talaraich coordinates: $x=-16$, $y=-1$, and $z=9$.

Results

Task performance

Performance measures on the Go/No-Go task by *DAT1* 3′UTR genotype are presented in Table 2. There were no differences between the groups on the percent of successful inhibitions on No-Go trials or any other measures of performance, with one exception. Mean RT on Go trials was faster in youth homozygous for the 10R allele compared to those with the 9R allele ($t_{1,31}=2.40$, $p=0.02$). To ensure that there was no confound of gender, a 2×2 factorial analysis of variance (ANOVA) was conducted to examine the influence of gender and *DAT1* 3′UTR genotype on mean RT. This analysis demonstrated no main effects of gender ($F_{1,\ 29}=0.97$, $p=0.35$) and no gender × *DAT1* 3′UTR interaction ($F_{1,\ 29}=0.20$, $p=0.66$) on mean RT. Further, the ANOVA, in contrast to the *t* test, revealed no main effect of *DAT1* 3′ UTR genotype on RT ($F_{1,\ 29}=1.44$, $p=0.24$).

Functional imaging

The successful inhibition of responses on No-Go trials produced significant neural activation in the whole sample of youth with ADHD in a frontostriatal network implicated in response inhibition, including the left inferior frontal gyrus, right middle frontal gyrus, anterior cingulate gyrus, and anterior insula cortex, and bilateral striatum (see Supplementary Table 1). Robust activation was also seen more dorsally in the right posterior cingulate cortex, left precuneus, and bilaterally in the temporoparietal cortical junction (TPJ).

Direct comparison of youth heterozygous for the *DAT1* 3′UTR 9R allele and those homozygous for the 10R allele identified significant differences in inhibition-related neural activity in several *a priori* regions of interest (Table 3). As shown in Fig. 2, youth who were homozygous for the 10R allele showed greater task-related activation in the left striatum, right dorsal premotor cortex, and bilaterally in the TPJ compared to individuals with a 9R allele. The significant *DAT1* 3′ UTR genotype × trial type interaction in the striatum is illustrated in Fig. 3. Youth homozygous for the 10R allele also had greater activation in the left midcingulate cortex, left inferior parietal lobule, right angular gyrus, left middle occipital gyrus, and right thalamus. Conversely, youth with a 9R allele showed greater task-related activation in the left inferior frontal gyrus than those homozygous for the 10R allele (Fig. 2 and Table 3). The 9R allele carriers also had greater activity in the left middle frontal gyrus and inferior parietal lobule, posterior and superior to the TPJ.

Post hoc analyses were conducted with ANOVA models to examine any potential confound of gender. There were significant main effects of gender in the left midcingulate and right thalamic regions that were identified in the direct comparison of the two *DAT1* 3′UTR genotypes (Supplementary Table 2). There were no gender × *DAT1* 3′UTR genotype interactions in any region identified in the a priori contrasts of the two *DAT1* 3′UTR genotypes. Main effects of *DAT1* 3′UTR genotype were again seen in the left striatum, as well as in the other regions identified in Table 3.

Table 2
Behavioral performance on the Go/No-Go Task of youth with attention-deficit hyperactivity disorder (ADHD) by *DAT1* 3′UTR genotype.

Measure	*DAT1* 3′UTR 9R $n=12$	*DAT1* 3′UTR 10R/10R $n=21$
Successful inhibition (%)	79.6 ± 13.5	74.6 ± 14.0
Accurate responses (%)	92.9 ± 8.4	94.0 ± 5.8
Mean RT (ms)[a]	530 ± 117	460 ± 51
RTSD (ms)	149 ± 60	117 ± 61

RT, reaction time; RTSD, reaction time standard deviation.
[a] Significant group difference ($t_{1,31}=2.40$, $p=.02$).

Table 3
BOLD signal increases for successful response inhibition in youth with attention-deficit hyperactivity disorder (ADHD) who are homozygous carriers of the *DAT1* 3′UTR 10R allele versus those have a *DAT1* 3′UTR 9R allele.

Region	BA	Talaraich coordinates			Voxels	*t*	*p*
		x	*y*	*z*			
DAT1 3′UTR *10R/10R*>*DAT1* 3′UTR *9R*							
R dorsal premotor cortex	6	34	-4	39	522	3.37	0.001
L midcingulate cortex	32	-6	-1	47	396	3.26	0.001
R temporoparietal cortical junction	40	46	-37	31	329	3.00	0.003
L temporoparietal cortical junction	22	-55	-44	15	342	2.99	0.001
L inferior parietal lobule	40	-40	-24	27	196	3.10	0.002
L inferior parietal lobule	40	-30	-35	46	351	3.45	0.001
R angular gyrus	39	38	-70	27	1,415	3.47	0.001
L middle occipital gyrus	19	-34	-78	24	263	2.80	0.004
R thalamus	–	6	-21	1	353	2.95	0.003
L striatum	–	-16	-1	9	375	2.94	0.003
DAT1 3′UTR *9R*>*DAT13*′UTR *10R/10R*							
L inferior frontal gyrus	47	-42	37	-4	162	2.98	0.003
L middle frontal gyrus	8	-24	33	41	131	3.45	0.001
L inferior parietal lobule	40	-30	-50	45	125	2.84	0.004

L, left; R, right; BA, Brodmann area.

Discussion

These results provide further evidence that the *DAT1* 3′UTR polymorphism influences neural activity in a corticostriatal circuit implicated in the pathophysiology of ADHD. Children and adolescents with ADHD who were homozygous for the *DAT1* 3′UTR 10R allele showed greater activation during response inhibition in the left striatum, right dorsal premotor cortex, and bilateral TPJ than youth with ADHD who were heterozygous for the *DAT1* 3′UTR 9R allele despite similar behavioral task performance. Homozygosity for the 10R allele was also associated with hyperactivation in other regions

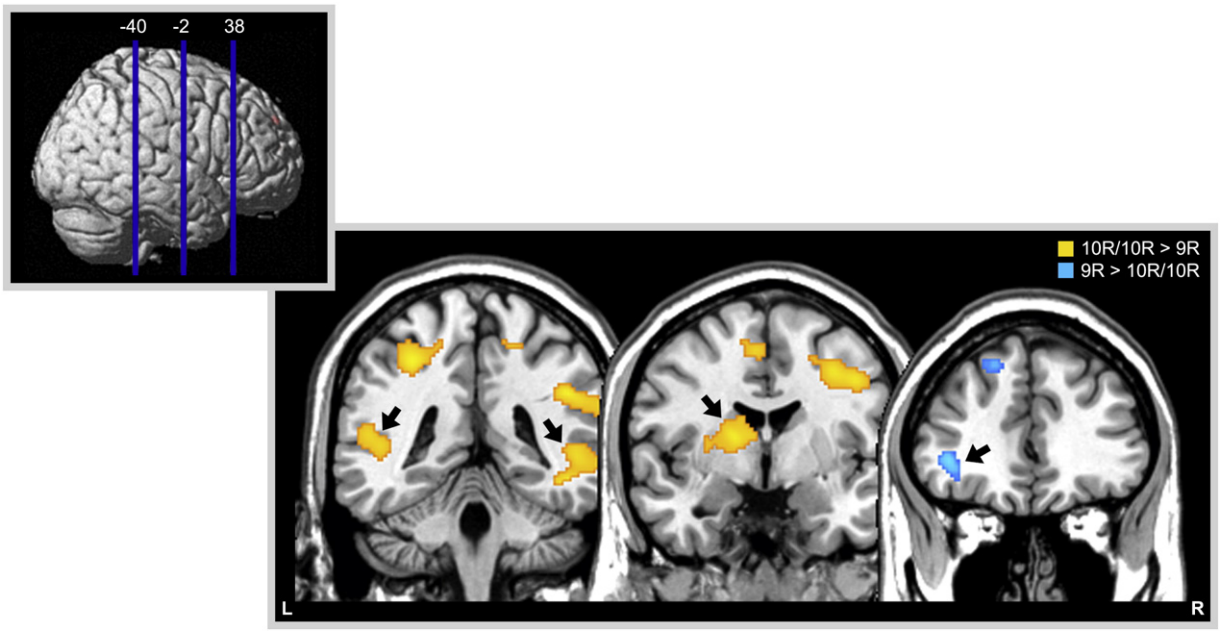

Fig. 2. Regions showing significant differences in BOLD responses to successful response inhibition (correct No-Go events minus correct Go events) in youth with attention-deficit hyperactivity disorder (ADHD) who were homozygous for the *DAT1* 3′UTR 10-repeat (10R) allele compared to those who are heterozygous for the 9-repeat (9R) allele. Arrows indicate the temporoparietal cortical junction (left section), striatum (middle section), and inferior frontal gyrus (right section). The activations were significant at $p<0.05$ corrected with a voxel extent>100 voxels. The inset depicts the position and Talairach coordinates for the sections.

that express dopamine transporters but are generally not engaged by Go/No-Go tasks, like the left middle occipital gyrus (Ciliax et al., 1999), as well as with hypoactivity in inferior frontal regions that are central to the performed task but are sparse in dopamine transporters (Ciliax et al., 1999). These findings together suggest that *DAT1* 3′UTR genotype influences neural activity through a combination of direct effects on dopamine function and indirect effects on the function of "downstream" regions.

The differential impact of *DAT1* 3′UTR genotype on activation in the striatum is of particular interest theoretically and clinically. The striatum is a major target of the dopaminergic nigrostriatal (A9) pathway (Smith and Kieval, 2000) and contains the richest concentration of dopamine transporters in the brain (Ciliax et al., 1999). Dopamine released from these nigrostriatal fibers has a critical modulatory influence on striatal medium spiny neuron signaling by boosting the effective excitatory drive of glutamatergic corticostriatal inputs (Rebec, 1998). Genetically altering dopamine transporter function has profound effects on this corticostriatal signaling (Ghisi et al., 2009; Wu et al., 2007). Overexpression of the dopamine transporter produces a marked reduction in synaptic dopamine that results in an adaptive upregulation of dopamine receptors (Ghisi et al., 2009), which in turn, strengthens corticostriatal glutamate signaling (Ghisi et al., 2009; Wu et al., 2007). These adaptive mechanisms may explain the current finding of elevated striatal activation in youth with ADHD who were homozygous for the *DAT1* 3′UTR 10R allele, which presumably produces more dopamine transporter protein than the 9R allele (VanNess et al., 2005). The *DAT1* 3′UTR genotype × trial type interaction in striatal activation in the current study suggests that these adaptive mechanisms have a particular impact on inhibitory mechanisms in youth with ADHD, consistent with both the inhibitory functions of the striatum (Aron et al., 2007) and the effects of adaptive upregulation of dopamine receptors in animals (Breese et al., 1987; Hu et al., 1990). Youth homozygous for the 10R allele used greater striatal activity to inhibit than execute simple motor responses compared to carriers of the 9R allele, who showed similar levels of activation for the two actions. Further, the 10R homozygotes required more striatal activation to achieve a similar level of inhibitory performance as carriers of the 9R allele. Although the clinical implication of these findings remains uncertain, it is possible that genetically determined differences in striatal function contribute to heterogeneity of the ADHD phenotype, individual differences in response to stimulant medication, or individual differences in the dose required to bring about improvement—all of which have been observed in ADHD populations (as reviewed by Halperin et al., in press; Hermens et al., 2006).

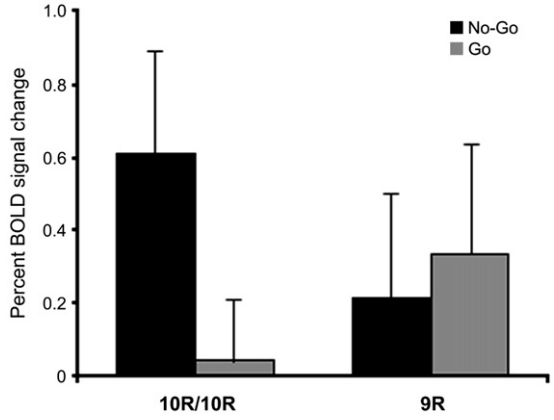

Fig. 3. Percent BOLD signal change in the striatum for successful response inhibition. Bars represent mean signal change for correct No-Go and Go events in youth with attention-deficit hyperactivity disorder (ADHD) who were homozygous for the *DAT1* 3′ UTR 10-repeat (10R) allele versus those heterozygous for the 9-repeat (9R) allele. Error bars represent ± 1 standard error.

The extensive output system of the striatum provides a neural substrate for the influence of *DAT1* 3′UTR genotype on neural activity in brain regions that are not directly innervated by dopaminergic pathways (Hoover and Strick, 1993; Tomasi et al., 2009). For example, corticostriatal excitation of striatal medium spiny neurons releases striatal output neurons from tonic inhibition, which in turn, disinhibits thalamic relay nuclei that project to premotor and other cortical areas (Kelly and Strick, 2004). Thus, alterations in striatal dopamine signaling produced by specific *DAT1* 3′UTR polymorphisms could have resulted in the increased parietal and temporal activation seen in youth

homozygous for the 10R allele compared to those heterozygous for the 9R allele. Alternatively, increased activation in regions such as the middle occipital gyrus may reflect the effect of homozygosity for the *DAT1* 3′UTR 10R allele on intrinsic dopamine signaling (Ciliax et al., 1999).

The reduced task-related activation of inferior frontal gyrus seen in youth homozygous for the *DAT1* 3′UTR 10R allele is more difficult to comprehend. The reduced inferior frontal activation may indirectly reflect the effect of 10R homozygosity on striatal feedback to the prefrontal cortex (Kelly and Strick, 2004). Alternately, this may reflect the uneven distribution of dopamine transporters in the prefrontal cortex (Ciliax et al., 1999; Lewis et al., 2001). This finding warrants further investigation given that this rostral-most region of the inferior frontal gyrus has been shown to convert sensory and contextual inputs into behavioral codes (Sakagami et al., 2001), to be engaged by Go/No-Go tasks (Chikazoe et al., 2007; Schulz et al., 2009), and to be hypoactivated during response inhibition in individuals with ADHD (Rubia et al., 2005; Schulz et al., 2004).

Results support the contention that striatal functioning in youth with ADHD varies as a function of genotype. However, the direction of the finding (i.e., increased or decreased activation) differs here compared to that of the study of Durston et al. (2008), despite the fact that the two studies used the same Go/No-Go task and parameters. In the latter study, inhibition-related striatal activation was lower in 10 boys with ADHD who were homozygous for the *DAT1* 3′UTR 10R allele (Durston et al., 2008), which was interpreted as consistent with findings that homozygosity for the 10R allele produces lower dopamine transporter density in healthy subjects (van Dyck et al., 2005), possibly because reduced dopamine transporter translation produces an adaptive diminution of corticostriatal glutamate signaling (Wu et al., 2007). Discrepancies regarding the direction of striatal activation as a function of *DAT1 3′UTR* 10R polymorphisms parallels the debate over the clinical (e.g., Cook et al., 1995; Franke et al., 2008; Hawi et al., 2009; Johansson et al., 2008) and functional significance of these genotypes (Heinz et al., 2000; Martinez et al., 2001; van Dyck et al., 2005; VanNess et al., 2005). In addition, differences in the direction of striatal activation across the studies may reflect the fact that our sample was somewhat younger, more ethnically mixed, comprised both boys and girls, and included a substantial number of subjects with predominantly inattentive ADHD compared to the sample in Durston et al. (2008). Moreover, differences in the duration of the washout period between the two studies (2 weeks in this study vs. 24 hours in Durston et al. (2008)) should be carefully noted, since stimulant treatment discontinuation produces an upregulation of dopamine transporter density (Feron et al., 2005) and neuronal activity (Langleben et al., 2002).

Results from this study should be understood in the context of some methodological limitations. First, our sample size was modest relative to samples used in genetic studies, but it is larger than other samples that have examined imaging in the context of genetics. In addition, it is the first study of imaging genetics in youth with ADHD to include females (Durston et al., 2008; Szobot et al., 2005). Second, the study consisted of an ethnically diverse sample (Table 1), which may not be optimal for examining genetic differences in brain activation, since allelic frequencies of the DAT1 3′UTR polymorphism differ widely across ethnic populations (e.g., Kang et al., 1999). Third, we included a wide age range of youth with ADHD, potentially confounding our data with multiple stages of brain development and gene expression. To partially account for this, we excluded outliers and calculated data based on individual within-subject performance (rather than a group mean). Future studies with better power should examine the effect of brain development on genotype effects in individuals with ADHD. Also, this study was limited to a sample of youth with ADHD. As a result, we were unable to determine how the *DAT1* 3′UTR polymorphism-related effects we found would compare to that of typically developing youth. Accordingly, it may be that the *DAT1* 3′UTR effect we found is limited to only youth with ADHD or that the magnitude of the effect could differ from that of typically developing youth. In this regard, it might potentially be interesting to examine how corticostriatal circuitry is modulated by ADHD symptom severity either independent of genotype or through interactions with genotype. This is likely to require a larger sample than we utilized in the current investigation, and therefore beyond the scope of this study. However, this would be a fertile topic for future research.

In addition to these overall design considerations, these findings must also be considered in the context of the methodological limitations of the Go/No-Go task used in this study. First, the comparison of Go trials, which required motor responses, and No-Go trials, which did not involve responses, introduced motor activity as a potential confounding factor in the analyses. This is less of an issue in group comparisons like those in the current study than in single-group designs, since the two groups serve as controls for each other. However, we cannot completely rule out that our findings reflect the effects of motor control processes rather than inhibitory control processes. Second, although the current study was designed to test inhibitory control, it is possible that differential affective encoding of the stimuli for the Go and No-Go trials may have contributed to study results.

In conclusion, findings from the present study indicate that youth with polymorphisms of *DAT1* 3′UTR differentially recruit the striatum during the successful implementation of inhibitory control. Heterogeneity in the association between DAT1 genotype and brain activation within ADHD raises the possibility that genotype may contribute to the observed inconsistent findings of striatal hypoactivation during Go/No-Go tasks in children and adolescents with ADHD (e.g., Durston et al., 2003, 2006b), and differential response to medication, and in particular, to stimulants (Gruber et al., 2009; Joober et al., 2007; Kirley et al., 2003; Lott et al., 2005; Roman et al., 2002; Stein et al., 2005; Winsberg and Comings, 1999). Although more research is needed in this area, findings from the present study add to those already published in describing the heterogeneity of DAT neuroanatomy and neurophysiology in ADHD (Volkow et al., 2007) and illustrating the functional consequences of polymorphisms of *DAT1* 3′UTR.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.12.041.

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