

Dopamine Transporter Genotype Conveys Familial Risk of Attention-Deficit/Hyperactivity Disorder Through Striatal Activation

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ABSTRACT

Objective: The dopamine transporter (DAT1) gene has been implicated in attention-deficit/hyperactivity disorder (ADHD), although the mechanism by which it exerts its effects remains unknown. The polymorphism associated with ADHD has been shown to affect expression of the transporter in vitro and in vivo. Dopamine transporters are predominantly expressed in the striatum, but also in the cerebellar vermis. Stimulant medication is often effective in ADHD and is believed to exert its effects by blocking dopamine transporters in the striatum. We set out to investigate the effect of the DAT1 genotype in ADHD in a small, preliminary study. We hypothesized that the DAT1 genotype would affect brain activation patterns in a manner similar to that of stimulant medication, with the lesser expressing allele mirroring its effects. **Method:** We investigated DAT1 gene effects on brain activation patterns in an all-male sample of sibling pairs discordant for ADHD ($n = 20$) and controls ($n = 9$). All of the subjects participated in a functional magnetic resonance imaging session using a go/no-go paradigm and provided a DNA sample for analysis. **Results:** DAT1 genotype affected activation in the striatum and cerebellar vermis. The genotype interacted with familial risk of ADHD in the striatum but not the vermis. **Conclusions:** These preliminary results suggest that the DAT1 gene effects in the striatum are involved in translating the genetic risk of ADHD into a neurobiological substrate. As such, this study represents a first step in elucidating the neurobiological mechanisms underlying genetic influences in ADHD. Furthermore, these results may contribute to long-term possibilities for the development of new treatments: If the DAT1 genotype has differential effects on striatal activation, then it may be useful as a surrogate endpoint in individualized treatments targeting genotype/functional magnetic resonance imaging activation profiles. *J. Am. Acad. Child Adolesc. Psychiatry*, 2008;47(1):61–67. **Key Words:** attention-deficit/hyperactivity disorder, functional magnetic resonance imaging, dopamine transporter. Clinical trial registration information—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00143832.

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Attention-deficit/hyperactivity disorder (ADHD) is a common and heritable child psychiatric disorder in which additive genetic effects explain close to 80% of the phenotypic variance.^{1–3} Several candidate genes have been implicated, including the dopamine transporter (DAT1) gene. Stimulant medication such as methylphenidate (MPH) is effective in ADHD¹ and exerts its therapeutic effects by blocking presynaptic dopamine transporters involved in the reuptake of catecholamines,^{4,5} thus increasing the concentration available in the synapse. Dopamine transporters are predominantly expressed in the striatum,⁵ although they are also present in the cerebellar vermis.^{6,7}

Although association studies have produced both positive and negative results, a recent meta-analysis

confirms a modest association between a variable nucleotide tandem repeat (VNTR) polymorphism of the DAT1 gene and ADHD.^{3,8,9} The 9 and 10 repeat (9R and 10R) alleles are the most common forms of this polymorphism and the 10R has been associated with ADHD. The VNTR polymorphism has been shown to affect expression of the transporter *in vitro*^{10,11} and *in vivo*,¹² where the 9R allele is associated with lower expression of the transporter in the striatum.¹²

Neuroimaging studies have shown that stimulants increase task-related activation in the striatum in individuals with ADHD.^{13,14} This normalization of striatal activation has been linked to behavioral improvements in cognitive control, an ability that is compromised in ADHD.¹⁴ Acute stimulant administration also enhances activation of the cerebellar vermis.^{13,15,16} However, inconsistent results have suggested that this may be mediated by other factors, such as baseline rates of the behavior (see, for example, Anderson et al.¹⁵). Because the DAT1 gene affects expression of the dopamine transporter, it may exert effects on brain activation similar to those of MPH. Here, the lesser expressing allele would be hypothesized to mimic the effects of MPH because less dopamine transporter expressed in the synapse should result in increased dopamine availability, similar to the effects of blocking dopamine transporters with MPH. A recent functional magnetic resonance imaging (fMRI) study suggests this because healthy adults in homozygous 10R individuals¹⁷ carrying the DAT1 9R allele were shown to have higher levels of activation in the striatum than in homozygous 10R individuals.¹⁷

We previously showed that brain activation is sensitive to familial risk of ADHD, as symptom-free, full siblings of boys with ADHD show reductions in brain activation, similar to their affected counterparts, in particular in the prefrontal regions.¹⁸ This suggests that neuroimaging measures may be suitable as intermediate phenotypes for investigating risk genes in ADHD. In a previous study, we found that the DAT1 genotype affects the caudate nucleus volume, although there was no interaction with familial risk of ADHD, whereas prefrontal areas were sensitive to the dopamine-4 receptor genotype.¹⁹ As such, ADHD risk genes appear to differentially affect aspects of frontostriatal circuitry, where their effects are most obvious in those regions where they are preferentially expressed. In the present study, we set out to investigate the effect of the DAT1

genotype in ADHD in a small sample of subjects with ADHD, their unaffected siblings, and controls. We hypothesized that the DAT1 genotype should affect brain activation patterns in a manner similar to that of MPH. DAT1 effects should only be present in those regions where the gene is preferentially expressed: the striatum and, to a lesser extent, the cerebellar vermis.⁵⁻⁷ Furthermore, we reasoned that if the VNTR polymorphism of the DAT1 gene is involved in the genetic risk of ADHD, there should be differential effects of the DAT1 genotype on brain activation between individuals who are at genetic risk and those who are not. We conducted an fMRI study using a cognitive control task in 29 children and adolescents with and without ADHD. We included 10 male discordant sibling pairs, in which one brother had ADHD and his full sibling was free of ADHD symptoms. The current data set is a subset of the sample included in a previous study.¹⁸ This approach allowed us to separate familial risk of the disorder from ADHD itself because both brothers shared a family background, but not the behavioral disorder. We included nine matched controls free of ADHD symptoms. All of the subjects participated in an fMRI scan while performing a go/no-go task requiring them to suppress a competing, inappropriate action, in favor of an alternative one (cognitive control). This ability was targeted because deficits in control processes are among the best established in ADHD.^{14,18} Finally, of the all subjects provided a buccal swab for DNA analysis.

METHOD

Subjects

A total of 29 boys, ages 11 to 20 years, participated in the present study. Sibling pairs were recruited through the University Medical Center in Utrecht, the Netherlands, whereas controls were recruited through schools in the area. All of the assessments and study participation were conducted in Dutch. All of the fMRI data included in this report were also included in a study of effects of familial risk of ADHD on brain activation patterns.¹⁸ The present study investigates genotype effects, whereas the previous study considered only familial risk, not genotype effects (genotyping data were not available at the time). Furthermore, 25 of 29 participants had previously participated in other MRI studies in our laboratory (eight discordant sibling pairs and nine control subjects). After a complete description of the study, written informed consent was obtained from a parent for all of the subjects. In addition, all of the subjects were asked to sign an assent form. The procedure was approved by the Central Committee on Research Involving Human Subjects in The Netherlands.¹⁸ Subjects with major physical or neurological illness, such as migraine, epilepsy, endocrine disorders,

TABLE 1

Descriptive Variables Per Group (Mean [SD]) and Range

	Controls (<i>n</i> = 9)	Unaffected Siblings (<i>n</i> = 10)	Siblings With ADHD (<i>n</i> = 10)
Age, y	15.28 (2.13), 12.70–19.00	14.84 (2.34), 11.51–20.40	14.57 (2.64), 10.96–18.20
TIQ	105 (14), 91–127	107 (15), 80–127	100 (10), 86–114
VIQ	100 (19), 76–124	105 (14), 80–128	99 (16), 74–124
PIQ	110 (10), 95–125	108 (20), 85–152	101 (12), 88–123
ADHD symptoms, no.	1.1 (1.0), 0–3	0.3 (0.9), 0–3	14.4 (2.6), * 10–18
DAT1 10R homozygotes, no.	5	5	6

Note: TIQ = total IQ; VIQ = Verbal IQ; PIQ = Performance IQ; ADHD = attention-deficit/hyperactivity disorder; DAT1 = dopamine transporter; 10R = 10 repeat.

* *p* < .01.

head trauma in the past or IQ <70 were excluded. All of the subjects who met the inclusion criteria were asked to participate in a 1-hour fMRI scanning session and a neuropsychological assessment to estimate Full Scale IQ (Similarities, Vocabulary, Block Design, and Object Assembly subtests of the WISC-R).²⁰ For each subject, a parent was asked to participate in a semistructured interview session with a trained rater to objectively determine psychiatric diagnosis (Diagnostic Interview Schedule for Children [DISC]–Parent version).²¹ In addition, parents were asked to complete the Child Behavior Checklist and teachers the Teacher Report Form.^{22,23} ADHD subjects were required to meet *DSM-IV*²⁴ criteria for ADHD, as assessed by DISC interview. ADHD subjects with comorbid disorders other than oppositional defiant disorder were excluded. Unaffected siblings and control subjects were excluded if they met *DSM-IV* criteria for any psychiatric diagnosis, as assessed by the DISC interview. In addition, they were excluded if they scored in the clinical range on the Child Behavior Checklist or Teacher Report Form. Control subjects were excluded if they had first-degree relatives who had been diagnosed with ADHD or another disruptive disorder. Data for 10 discordant sibling pairs and nine matched control subjects were included in the fMRI analyses. Subjects were matched at a group level for age, IQ, and socioeconomic status (operationalized as parental education level). All of the subjects were of European descent. Nine of 10 subjects with ADHD met DISC criteria for ADHD, combined subtype. One subject scored subthreshold on the Inattention scale of the DISC (four symptoms) and therefore met criteria for ADHD, hyperactive subtype. In addition, two of the ADHD subjects met DISC criteria for ODD.

Five of 10 subjects with ADHD were taking stimulant medication at the time that they were approached for this study. All of the subjects discontinued medication for at least 24 hours before the scan. There were no differences between groups defined by genotype in matching variables, symptom scores, or MPH response (Table 1).

Paradigm

All of the subjects participated in an fMRI session using a go/no-go paradigm as previously described.^{18,25–27} The subjects’ task was to press a button in response to visually presented stimuli, but to avoid responding to a rare nontarget. The task consisted of five runs, which lasted 3 minutes, 56 seconds each. Each run contained a total of 57 trials, with 75% go trials, resulting in a total of 70 no-go trials. To make the task more interesting, characters from the Pokemon cartoon series were used as stimuli. Stimulus duration was 500 milliseconds, and the interstimulus interval was 3,500 milliseconds (total trial length 4,000 milliseconds). Stimuli were projected using a through-projection screen. Responses were collected using an MRI-compatible air pressure button box.

Scan Acquisition

All of the subjects participated in a practice session before scanning, using an MRI simulator housed at our department. The purpose of this session was to acquaint subjects with the scanner environment, the task, and the researchers present during the MRI session. All of the subjects successfully participated in both the practice and actual

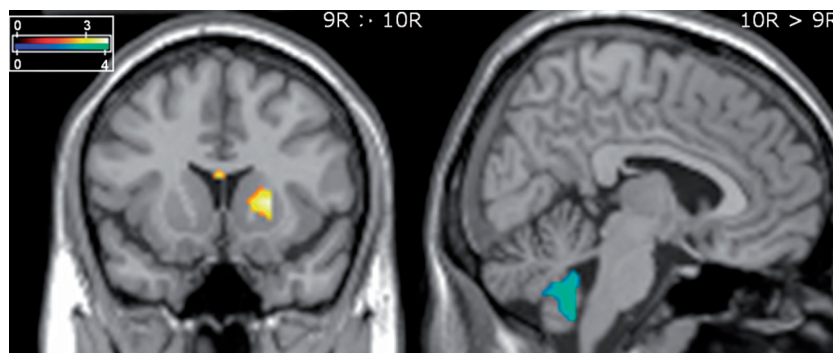


Fig. 1 Activation in the striatum and vermis for the DAT1 genotype. Striatal activation is significantly increased in carriers of the DAT1 9R allele, whereas cerebellar vermis activation is significantly attenuated.

TABLE 2

Genotype Effects on Brain Activation for the Whole Group (10 Siblings With ADHD, 10 Unaffected Siblings, 9 Controls)

Region	Side	Talairach	Maximum <i>t</i>
Cerebellar vermis	Med	4, -52, -24	4.10
Caudate nucleus	L	-24, 12, 4	3.93

Note: $t > 3.42$, $df = 27$; $p < .001$; $k > 5$ voxels. L = left; Med = medial.

MRI sessions. MR images were acquired on a 1.5-T Philips Gyroscan (Philips Medical Systems, Best, The Netherlands), housed in the Department of Radiology in the same hospital. fMRI scans consisted of a navigated three-dimensional PRESTO pulse sequence (TE [echo time] 11 milliseconds, TR [repetition time] 21.74 milliseconds, flip angle 9.0°, matrix 64 × 64 × 24, field of view [FOV] 256 × 256 × 96 mm, voxel size 4 mm isotropic, and scan duration 2.0 seconds/24-slice volume), covering the whole brain. Anatomical T1-weighted three-dimensional fast-field echo scans with 130 to 150 1.5-mm contiguous coronal slices of the whole head (TE 4.6 milliseconds, TR 30 milliseconds, flip angle 30°, FOV 256 mm, in plane voxel size 1 × 1 mm) were also acquired. A FA30 scan with contrast more similar to the T1-weighted scans was acquired to aid in the alignment of PRESTO images with the template (TE 12.10 milliseconds, TR 24.24 milliseconds, flip angle 30°, matrix 64 × 64 × 24, FOV 256 × 256 × 96 mm, voxel size 4 mm isotropic). During anatomical scans, the projection system was used to play cartoons to prevent the subjects from becoming bored or restless.

fMRI Analysis

All of the data were analyzed using a random effects model in Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London). PRESTO images were realigned and normalized to a standard stereotactic space (Montreal Neurological Institute template). Estimated motion parameters were examined on a subject-by-subject basis to ensure that the amount of absolute motion did not exceed 4 mm or the size of 1 voxel. There were no differences between groups in the average amount of motion.

At the first level, six event types were defined (initial fixation, correct and incorrect go trials and no-go trials, and a parametric factor representing the number of go trials preceding a no-go trial [one to

five]). These included three effects of interest (go trials, no-go trials, and the parametric factor) and three effects of no interest (initial fixation, omission errors, and commission errors). The event types were time locked to stimulus by a canonical synthetic hemodynamic response function and its first-order temporal derivative.

For the between-group analysis, a single planned contrast was performed comparing carriers of the DAT1 9R allele to individuals homozygous for the 10R allele. The dependent measure was the difference between activation on no-go trials and go trials. Differences were tested at a threshold of $p < .001$ uncorrected, $k > 5$ voxels.²⁸ The sample size for subgroups was considered too small to investigate genotype × diagnosis interactions using a whole-brain approach. Therefore, a region-of-interest (ROI) analysis was implemented, using the MarsBaR package.²⁹ ROIs were functionally defined from the first planned contrast for the whole group. Here, the first-level analysis comparing carriers of the 9R allele to homozygotes for the 10R allele was run at a more lenient threshold of $p < .01$, $k > 10$ voxels to define ROIs. The individual MR signal was extracted from these ROIs for all of the subjects and was compared post hoc using two-way (genotype × diagnosis) analysis of variance. MNI stereotactic coordinates were transformed to Talairach and Tournoux space.

Genotyping

Genotyping was performed on the samples from the buccal swabs as previously described.^{19,30} Polymerase chain reaction was performed on the PTC-100 Programmable Thermal Controller (MJ Research). A “touchdown” polymerase chain reaction cycling regimen and the addition of dimethylsulfoxide (10% final vol:vol) was used to automatically optimize the hybridization stringency. Gel electrophoresis in Metaphor agarose followed by staining in ethidium bromide was used to resolve and visualize DNA fragments. For genotyping of the DAT1 40-bp repeat (VNTR) polymorphism in the 3′ untranslated region, forward: 5′-TGTGGTGTAGG-GAACGGCCTGAG-3′ and reverse 5′-CTTCTGGAGGT-CACGGCTCAAGG-3′ primers were used at 200 μmol/L as previously described.^{19,30}

RESULTS

There was no effect of genotype or diagnosis on behavioral performance, nor was there an interaction between the two ($F < 1.9$; $df = 2, 23$; $p > .18$; $n = 29$).

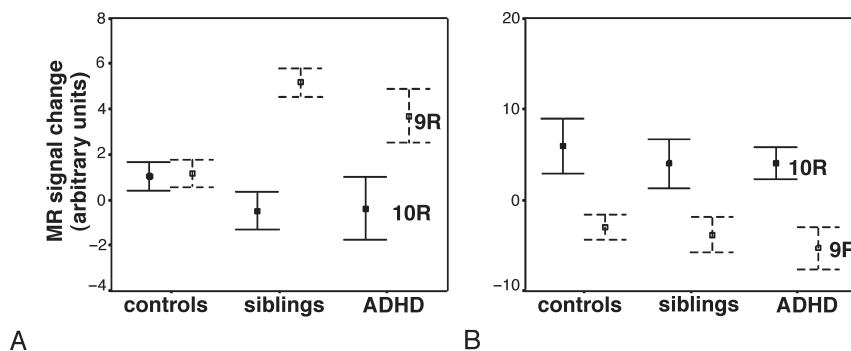


Fig. 2 Dopamine transporter (DAT1) genotype interacts with the diagnosis of striatal activation (A), but not activation in the vermis (B) (error bars represent SEs). ADHD = attention-deficit/hyperactivity disorder; MR = magnetic resonance; R = repeat.

The planned comparison of whole-brain activation for no-go trials compared to go-trials between carriers of the DAT1 9R allele ($n = 13$) and individuals homozygous for the 10R allele ($n = 16$) showed two areas that were different between groups: Activation in the striatum was greater for carriers of the 9R allele ($t = 3.93$, $df = 28$; $p < .001$), whereas activation in the vermis of the cerebellum was significantly greater for individuals homozygous for the 10R allele ($t = 4.10$, $df = 28$; $p < .001$; Fig. 1 and Table 2).

In the ROI analysis there was a significant genotype \times group interaction for striatal activation, where DAT1 genotype influenced MR signal change for individuals at familial risk of ADHD (affected and unaffected siblings) but not for controls ($F = 3.95$, $df = 2, 23$; $p = .033$). In the cerebellar vermis, genotype effects were comparable in all groups (Fig. 2).

DISCUSSION

We report effects of the DAT1 genotype on activation in the striatum and the vermis of the cerebellum in a small sample of subjects with ADHD and their unaffected siblings. This is consistent with previous reports of MPH effects in these regions and the pattern of DAT1 expression in the brain. We show an interaction between genotype and familial risk of ADHD for activation in the striatum, but not the cerebellar vermis. These findings should be considered preliminary given the small sample size. However, potentially, they implicate the striatum in translating the genetic risk of ADHD, as expressed by the DAT1 genotype, into a neurobiological substrate. As such, they represent a first step in elucidating the neurobiological mechanisms underlying the genetic influences in ADHD.

The finding of an interaction between diagnosis and genotype for activation in the striatum is particularly interesting because the DAT1 genotype effects are specific to those individuals at familial risk of the disorder (both affected and unaffected siblings). For controls, activity in this region was not different between carriers of the 9R allele and 10R homozygotes. If replicated, the specificity of this finding may contribute to long-term possibilities of the development of new treatments for ADHD. If the DAT1 genotype has differential effects on striatal activation, then it may become useful as a surrogate endpoint in individualized treatments targeting genotype/fMRI activation profiles.

These results of the present study are best considered within our broader program of research investigating the effects of familial risk and risk genes for ADHD on brain structure and function. To date, we have reported that familial risk of ADHD is most obvious in cortical gray matter volumes and activation in prefrontal areas,^{18,31} whereas the effects of ADHD risk genes are most obvious in the prefrontal and striatal areas (DRD4 on prefrontal gray matter¹⁹ and DAT1 on the striatum [see also Durston et al.¹⁹]). In our initial report, we found that the cerebellum was the only region to differentiate between siblings with and without ADHD because its volume was decreased in affected but not unaffected siblings.³¹ Taken together with the current finding that the DAT1 genotype interacts with familial risk of ADHD in the striatum but not cerebellar vermis, this suggests that the cerebellum may be relatively spared from familial effects in ADHD. However, in a recent report in which cerebellar activity was specifically targeted, we did find effects of familial risk in this region.³² This suggests that although effects of familial risk and dopamine genes may be most obvious in frontostriatal circuits, they do play a part in other regions of the brain. By using tasks that specifically target different regions, we are beginning to address these different influences.

Because the discordant sibling pairs in our studies are carefully selected to be truly discordant (i.e., unaffected siblings are not subthreshold for ADHD symptoms), they are hard to find. Therefore, there is overlap between the subjects included in our reports on familial risk (see also Durston et al.^{18,19,31} and Mulder et al.³²). In the present report, 8 of 10 sibling pairs had previously participated in other studies in our laboratory, and all of the fMRI data included in this article were previously included in a study of familial risk effects on cognitive control.¹⁸ We are still recruiting sibling pairs into our program and aim to be able to present larger studies on genotype/familial risk interactions in the future.

The finding of an inverse effect of the DAT1 genotype on activation in the cerebellar vermis was unexpected. This may be related to differences between dopaminergic and noradrenergic neurotransmission because the DAT1 is likely involved in the reuptake of norepinephrine rather than dopamine in the vermis.⁷ Furthermore, there is no obvious coupling of neurotransmitter levels in a given system and activity level as assessed with fMRI, which in itself provides only an

indirect measure of activation. Many transmitter systems have an optimal level for signal transfer, sometimes described as an “inverted U curve,”³³ in which a functional polymorphism may drive a system toward the peak and optimal function in one circumstance and away from it in another. As such, it is difficult to predict in which way polymorphisms in neurotransmitter genes will drive activity levels. For example, Egan and colleagues³⁴ reported opposite effects of a single-nucleotide polymorphism in the GRM3 glutamate receptor gene on activation levels in the prefrontal cortex and hippocampus. Here, carriers of an allele associated with schizophrenia showed decreased activation in the hippocampus, but increased activity in the prefrontal cortex, presumably related to less efficient processing in this region. This demonstrates that genotype effects on brain activation can be regionally specific and that opposite effects may be associated with the same allele in different regions.

Given our finding of differences by genotype in the striatum and cerebellum, it may seem surprising that previous comparisons between diagnostic groups in the same data set did not show effects in these regions.¹⁸ However, this is consistent with reports that show activation associated with this task shifts to a focal cortical pattern in adolescence^{35,36} as well as a previous report showing differences in striatal activation by the DAT1 genotype in a working memory task,¹⁷ not traditionally associated with activation in this region. Another seemingly surprising finding is that we see no support for an association of DAT1 genotype with ADHD. However, meta-analyses have shown that the effect size for this association is modest (odds ratio between 1.03 and 1.243) and, as such, power was likely not sufficient to replicate it in this small sample.

Potentially, our preliminary finding of striatal DAT1 gene involvement in translating genetic risk of ADHD into a neurobiological substrate has broad functional implications, if results can be replicated in larger samples and other factors contributing to this effect can be identified. The 10R allele of the DAT1 gene is clearly not sufficient to convey genetic risk in isolation because the effect was observed in both affected and unaffected siblings, suggesting moderating influences on the vulnerability to the DAT1 10R allele. This is not surprising because DAT does not function in isolation in the catecholaminergic synapse. Neurotransmitter levels

are managed through interactions with postsynaptic receptors (D2, D3, and D4 in the striatum) as well as other factors. Clearly, it would be an oversimplification to view the transporter as the only candidate for translating genetic risk into a neurobiological substrate because it may well interact with other influences, locally in the synapse, or elsewhere in the brain. Future studies including larger samples will allow the investigation of putative interactions more directly. As such, these findings do not have direct clinical implications for individuals with ADHD at this time. However, this type of observation may contribute to insights that facilitate the development of new treatments: If the DAT1 genotype has differential effects on striatal activation, then it may be useful as a surrogate endpoint in individualized treatments targeting genotype/fMRI activation profiles.³⁷

Disclosure: The authors report no conflicts of interest.

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