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Basal Ganglia Structure in Tourette's Disorder and/or Attention-Deficit/Hyperactivity Disorder

Natalie J. Forde, MSc,[1,2]* Marcel P. Zwiers, PhD,[2] Jilly Naaijen, MSc,[2] Sophie E. A. Akkermans, MSc,[2] Thaira J. C. Openneer, MSc,[1] Frank Visscher, MD,[3] Andrea Dietrich, PhD,[1] Jan K. Buitelaar, MD, PhD,[2,4] and Pieter J. Hoekstra, MD, PhD[1]

[1]*University of Groningen, University Medical Center Groningen, Department of Psychiatry, Groningen, The Netherlands* [2]*Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Department of Cognitive Neuroscience, Nijmegen, The Netherlands* [3]*Admiraal De Ruyter Ziekenhuis, Department of Neurology, Goes, The Netherlands* [4]*Karakter Child and Adolescent Psychiatry University Centre, Nijmegen, The Netherlands*

ABSTRACT

Background: Tourette's disorder and attention-deficit/hyperactivity disorder often co-occur and have both been associated with structural variation of the basal ganglia. However, findings are inconsistent and comorbidity is often neglected.

Methods: T1-weighted magnetic resonance images from children (n = 141, 8 to 12 years) with Tourette's disorder and/or attention-deficit/hyperactivity disorder and controls were processed with the Oxford Centre for Functional MRI [Magnetic resonance imaging] of the Brain (FMRIB) integrated registration and segmentation tool to determine basal ganglia nuclei volume and shape. Across all participants, basal ganglia nuclei volume and shape were estimated in relation to Tourette's disorder (categorical), attention-deficit/hyperactivity disorder severity (continuous across all participants), and their interaction.

Results: The analysis revealed no differences in basal ganglia nuclei volumes or shape between children with and without Tourette's disorder, no association with attention-deficit/hyperactivity disorder severity, and no interaction between the two.

Conclusion: We found no evidence that Tourette's disorder, attention-deficit/hyperactivity disorder severity, or a combination thereof are associated with structural variation of the basal ganglia in 8- to 12-year-old patients. © 2016 International Parkinson and Movement Disorder Society.

Key Words: Tourette's Disorder; attention-deficit/hyperactivity disorder; basal ganglia; children; comorbidity

Although Tourette's disorder (TD) is characterized by the presence of both motor and vocal tics,[1] there are also frequently concurrent psychiatric comorbidities. These occur in up to 86% of those with TD during their lifetime.[2] Attention-deficit/hyperactivity disorder (ADHD) is the most common of these, occurring in approximately 40% of TD cases.[3] Even more patients with TD have ADHD symptoms without meeting full diagnostic criteria.[4]

Structural neuroimaging studies of both disorders have highlighted alterations in the nuclei of the basal ganglia (BG), caudate nucleus (CN), putamen (Pu), and globus pallidus (GP).[5-7] However, the literature of TD and ADHD neuroimaging research is inconsistent, and determining whether BG structural abnormalities are unique or common to the respective disorders is difficult because few studies have examined groups with TD and ADHD together in 1 study. Furthermore, those studies have been underpowered and inconsistent in their findings.[8-12]

In the present study, we aimed to elucidate whether BG structural abnormalities are associated with TD in children and whether they occur in relation to comorbid ADHD symptoms. This was done by investigating BG volumes and shape in participants with TD and/or ADHD and healthy controls side by side in a well-sized pediatric sample, thereby focusing on the age range when tics are most frequently present.[13]

Participants and Methods

All participants (Table 1) satisfied the following inclusion criteria: 8 to 12 years of age, IQ >70, White, no previous head injuries or neurological disorders, no contraindications for MRI assessment, no major physical illness, and available good-quality MR scan. Participants of the TD group met *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.) criteria for TD (n = 46) or persistent (chronic) motor or vocal tic disorder (with motor tics only; n = 1); psychiatric comorbidities (eg, ADHD and obsessive compulsive disorder [OCD]) were not excluded. Participants of the ADHD group had a diagnosis of ADHD or subthreshold ADHD, those with tics and/or OCD were excluded. Healthy controls had no mental disorders as screened for by the Child Behaviour

*Corresponding author: Natalie J. Forde, Department of Psychiatry, University Medical Center Groningen, Postbus 660, 9700 AR Groningen, The Netherlands; j.n.forde@umcg.nl

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TABLE 1. Demographic description of participants

	Control	ADHD	TD	Test statistic	*P* value
n	55	39	47		
ADHD, diagnosis/subthreshold	0	35/4	22/10		
Age years, mean (SD)	11.0 (1.0)	10.7 (1.3)	10.5 (1.4)	2.48	.29
Sex, male/female	39/16	21/18	41/6	11.72	.003**
IQ, mean (SD)[a]	109 (12)	102 (13)	105 (11)	3.18	.04
Handed, right/left	50/5	36/3	42/5	0.22	.89
ADHD severity, mean (SD)[b]	45.5 (4.9)	70.9 (10.7)	62.9 (11.3)	86.98	<.0001***
Tic severity, mean (SD)[c]	-	-	T = 20.6 (8.6) M = 13.4 (5.0) V = 7.2 (5.5)		
Age tic onset years, mean (SD)[c]	-	-	5.6 (1.7)		
Duration since tic onset years, mean (SD)[c]	-	-	5.0 (1.8)		
OCD, n[d]	-	-	9		
Medication[e]		6			
Stimulant		26	11		
Strattera		1	0		
Antipsychotic		1	8		
Clonidine		0	2		

ADHD, attention-deficit/hyperactivity disorder; K-W, Kruskal-Wallis; OCD, obsessive compulsive disorder; SD, standard deviation; TD, Tourette's disorder.
[a]Estimated from a subtest of the Wechsler Intelligence Scale for Children-III[19] rating.
[b]T-scores from the Conners' Parent Rating Scale–Revised long version.[18]
[c]Determined with the Yale Global Tic Severity Scale.[15] Total (T), motor (M), and vocal (V) severity ratings exclude impairment score.
[d]Total score $\geq$ 16 on the Children's Yale-Brown Obsessive Compulsive Scale.[17]
[e]Current medication status, determined from parental report.
**P <.01, ***P < 0.001.

Checklist.[14] Parents or guardians of all participants gave written informed consent; in addition, participants who were 12 years of age provided written assent. This study was approved by the regional ethics board (Commissie Mensgebonden Onderzoek (CMO) Regio Arnhem-Nijmegen).

The following various instruments were used to determine the presence and severity of disorders: for TD, the Yale Global Tic Severity Scale (using 0-50 ratings, not considering overall impairment)[15]; for ADHD and/or other psychiatric disorders, the Schedule for Affective Disorders and Schizophrenia for School-Age Children[16] screening interview plus appropriate modules if required; for OCD, Children's Yale-Brown Obsessive Compulsive Scale[17]; for ADHD severity, Conners' Parent Rating Scale–Revised long version.[18] Full-scale IQ was estimated by 4 subtests of the Wechsler Intelligence Scale for Children-III.[19] Medication status was determined from parental reports.

T1-weighted anatomical images were acquired on a 3T Siemens Prisma scanner (Siemens, Erlangen, Germany) with a transversal, three-dimensional magnetisation-prepared rapid gradient-echo (MPRAGE) parallel imaging sequence (parameters: echo time (TE) = 2.98 ms, inversion time (TI) = 900 ms, repetition time (TR) = 2300 ms, flip angle = 9 °, voxel size = 1 × 1 × 1.2 mm, acquisition time- = 5.30 minutes). Datasets were processed with the automated Oxford Centre for Functional MRI of the Brain (FMRIB) integrated registration and segmentation tool[20-22] standard procedure to generate volumetric data and surface meshes for subcortical structures. BG nuclei surfaces were reconstructed in native space (useReconNative, First_utils), aligned to the average structure shape for the cohort (useRigidAlign) and scaled to account for size differences (useScale). Probability maps for gray and white matter tissue types were estimated using the VBM8 toolbox[23] of Statistical Parametric Mapping (Wellcome Department of Imaging Neuroscience, University College London). Total brain volume (TBV) was calculated as the voxel-wise sum of both probability maps.

A repeated-measures analysis of covariance was used to determine the effect of TD and ADHD severity (continuous measure across all groups) and their interaction on BG nuclei volumes. A categorical factor for TD was deemed more robust than using symptom severity because of the fluctuating nature of tics in TD, whereas a continuous measure for ADHD severity was used because multiple participants, particularly within the TD group, displayed ADHD symptoms without meeting criteria for diagnosis. The hemisphere was included as the repeated measure with hemisphere-by-TD and hemisphere-by-ADHD-severity interaction terms as measures of asymmetry difference associated with the respective disorders. TBV, sex, age, and IQ were used as covariates. BG nuclei shape were analyzed using FMRIB Software Library (FSL) randomize[24] with 5,000 random permutations and threshold-free cluster enhancement.[25] Sex, age, and IQ were entered as covariates. Contrasts tested shape differences between those with and without TD and positive or negative associations between shape and ADHD severity. A separate model was used to assess the interaction effect of TD and ADHD severity on shape using the same covariates. The effect of current stimulant medication use on volumes or shape within patients (TD and/or ADHD) was

investigated in similar models including TD, ADHD severity, age, sex, and IQ as covariates. In addition, for the volume analysis, TBV and hemisphere were included. With similar models, current antipsychotic use within the TD group was also analyzed.

Results

There were no main effects of TD, ADHD severity, or significant interactions between TD and ADHD severity on BG volume (Table 2) or shape.

In the volume analysis, hemisphere was seen to have a significant effect in the CN (left smaller than right) and a trend (uncorrected) toward an interaction with TD. This was not mirrored in the Pu and GP; no significant effects of hemisphere or hemisphere-by-TD interaction were seen (Table 2). No hemisphere-by-ADHD-severity interactions were seen. TBV was significant in each region. It did not differ with TD ($t = -0.90$, $P = .37$), ADHD severity ($t = -0.90$, $P = .37$), or their interaction ($t = 0.78$, $P = .44$). No effect of stimulant or antipsychotic medication was seen on either BG nuclei volume or shape.

Discussion

This is the largest pediatric study of BG structures to investigate TD and ADHD together. Complementary volume and shape analyses of BG nuclei revealed no structural alterations associated with either the presence of TD, ADHD severity, or their interaction.

Although both TD and ADHD have been previously associated with volume alterations in the BG,[5-7] the literature to date is heterogeneous. The current null findings replicate in a larger sample a small number of studies that found no associations between BG nuclei volume and TD (n = 13-38)[26,27] and no association between either TD or ADHD and BG nuclei volumes (n = 14-37)[8-11] in children. Furthermore, consistent with previous findings in children, the current study also found no asymmetry abnormalities associated with TD.[27,28] The few studies that have reported associations between BG volume and TD in children have been inconsistent regarding the regions implicated and direction of change: increased Pu volume bilaterally (n = 49 and 14 TD cases, respectively),[29,30] reduced CN volume bilaterally (n = 154, child and adult sample),[28] or left only (n = 23).[31] Although all of these studies relate to children, there may still be consequential demographics differences. The few studies that have shown associations between BG structure and TD had a slightly higher mean age[30] or a wider age range[28,29,31] than the current study. It is possible, therefore, that the former studies in question identified differences that occur later in development. BG abnormalities have been more consistently reported in adult samples (eg, refs. [28,32]. Along with the results here, this implies that BG abnormalities in TD reflect compensatory mechanisms or an effect of the illness, but do not relate to TD etiology.

Two (overlapping) meta-analyses of BG structure in ADHD[6,7] showed right BG nuclei volume reductions in children with ADHD. However, similar to the current findings, the large NeuroIMAGE study of ADHD (n = 307) in adolescence found no main effect of ADHD on BG volumes either by voxel-based morphometry (VBM)[33] or automated segmentation analyses.[34] The second of these studies did, however, show an age-by-diagnosis interaction. This suggests that differences become apparent with increasing age and may account for the current null findings as the cohort was young (8-12 years). Another possible source of the discrepancy between the current and former studies is the use of a continuous measure for ADHD instead of a categorical group for analysis. The dimensional approach is favored[35] opposed to categorizing participants with arbitrary thresholds, especially considering the large number of participants with TD that display ADHD or subthreshold ADHD.

In addition to volume analysis, we also applied shape analysis, which is more sensitive to subtle morphological differences. In TD, only 1 small study to date examined BG morphology differences in children, and they found no relation between TD and shape,[27] which is in accordance with the findings presented here. In ADHD studies, inward deformation of the BG has been seen in children and adolescents with ADHD when compared with controls.[36-38] The current study did not corroborate these findings. This discrepancy may relate to demographic differences as discussed earlier.

In the current study, we found no stimulant-dependent associations with BG structure in line with the large (n = 540) longitudinal study of BG development in ADHD by Shaw and colleagues,[38] who reported no association between stimulant treatment history and developmental trajectories. However, other studies in ADHD reported normalizing effects of stimulants on BG structure.[6,7,36] Our study was underpowered to determine the effect of antipsychotic treatment on brain structure during development, and this warrants further study.

Our findings should be considered in light of certain limitations. Females were underrepresented in the TD sample, as is expected because males are more frequently

TABLE 2. Results from basal ganglia volume analysis

	Caudate nucleus		Putamen		Globus pallidus	
	F	*P* value	*F*	*P* value	*F*	*P* value
TD	0.29	.59	0.27	.60	3.60	.06
ADHD severity	0.001	.98	0.04	.85	0.06	.81
TD × ADHD Severity	2.55	.11	0.14	.71	0.80	.37
Hemisphere	27.02	**<.001**	2.47	.12	3.50	.06
Hemisphere × TD	3.13	.08	0.80	.37	0.92	.34
Hemisphere × ADHD Severity	0.45	.50	0.19	.67	0.25	.62
TBV	55.09	**<.001**	44.81	**<.001**	100.19	**<.001**

F statistics and uncorrected *P* values are presented from the analysis of basal ganglia volumes in relation to Tourette's disorder (TD), attention-deficit/hyperactivity disorder (ADHD) severity, and hemisphere, including their interaction terms (×). TBV, total brain volume.
Statistically significant *p* values are highlighted in bold.

affected than females.[2] There were, however, no interactions with sex, suggesting the sex imbalance did not confound our findings. A total of 9 participants from the TD group also had OCD. ADHD and OCD were recently shown to have opposing associations with BG structure, although comorbidity was not considered.[39] Here we saw that OCD severity was not predictive of BG nuclei volumes within the TD group, and removal of the participants with OCD did not alter our findings.

In conclusion, we found no evidence that TD, ADHD, or their combination are associated with BG structure in patients 8 to 12 years of age. ■

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