Structual and neurochemical correlates of Tourette's disorder and attention-deficit hyperactivity disorder

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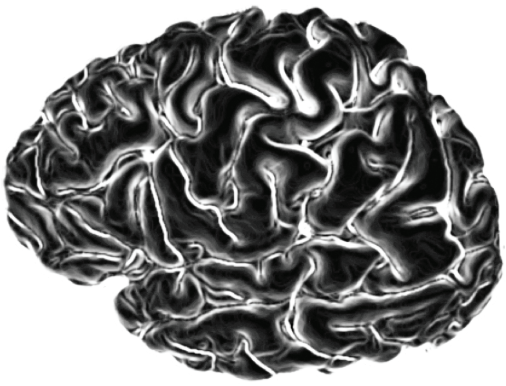
Chapter 3

Basal Ganglia Structure in TS and/or ADHD



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Abstract

Background: Tourette Syndrome 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, 8-12 years) with Tourette syndrome and/or Attention-Deficit/Hyperactivity Disorder and controls were processed with the 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 Syndrome (categorical), Attention-Deficit/Hyperactivity Disorder-severity (continuous across all participants) and their interaction.

Results: Analysis revealed no differences in basal ganglia nuclei volumes or shape between children with and without Tourette Syndrome, no association with Attention-Deficit/Hyperactivity Disorder-severity and no interaction between the two.

Conclusion: We found no evidence that Tourette Syndrome, Attention-Deficit/Hyperactivity Disorder-severity or the combination thereof are associated with structural variation of the basal ganglia in 8-12 year old patients.

Introduction

While Tourette Syndrome (TS) is characterised by the presence of both motor and vocal tics (American Psychiatric Association 2013) there are also frequently concurrent psychiatric comorbidities. These occur in up to 86% of those with TS during their lifetime (Hirschtritt et al. 2015). Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common of these occurring in approximately 40% of TS cases (Rickards 2011). Even more patients with TS have ADHD symptoms without meeting full diagnostic criteria (Robertson 2000).

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) (Felling and Singer 2011; Frodl and Skokauskas 2012; Nakao et al. 2011). However, the literature of TS and ADHD neuroimaging research is inconsistent and determining if BG structural abnormalities are unique or common to the respective disorders is difficult as few studies have examined groups with TS and ADHD together in one study. Furthermore those that have, have been underpowered and inconsistent in their findings (Castellanos et al. 1996; Jeppesen et al. 2014; Peterson et al. 1993; Singer et al. 1993; Zimmerman et al. 2000).

In the present study we aimed to elucidate whether BG structural abnormalities are associated with TS in children and whether they occur in relation to comorbid ADHD symptoms. This was done by investigating BG volumes and shape in participants with TS and/or ADHD and healthy controls side-by-side in a well-sized pediatric sample, thereby focusing on the age range where tics are most frequently present (Bloch and Leckman 2009).

Methods

Participants

All participants (Table 1) satisfied the following inclusion criteria; 8-12 years, IQ>70, Caucasian decent, no previous head injuries or neurological disorders, no contra indications for MRI assessment, no major physical illness and available good quality MR scan. Participants of the TS group met DSM-5 criteria for Tourette's Disorder (n=46) or Persistent (Chronic) Motor or Vocal Tic Disorder (with motor tics only; n=1); psychiatric comorbidities (e.g. ADHD and obsessive-compulsive disorder [OCD]) were not excluded. Participants of the ADHD group had a diagnosis of ADHD or sub-threshold ADHD, those with tics and/or OCD were excluded. Healthy controls had no mental disorders as screened for by the Child Behaviour Checklist (Bordin et al. 2013). Parents/guardians of all participants gave written informed consent, additionally participants who were 12 years of age provided their written assent. This study was approved by the regional ethics board (CMO Regio Arnhem-Nijmegen).

Table 1 Demographic details

	TS	ADHD	Control	Test statistic	*p*-value
n	47	39	55		
ADHD, diagnosis/ subthreshold	22/10	35/4	0/0		
Age years, mean(SD)	10.5 (1.4)	10.7 (1.3)	11.0 (1.0)	2.48	0.29
Sex, male/female	41/6	21/18	39/16	11.72	0.003**
[a]IQ, mean(SD)	105 (11)	102 (13)	109 (12)	3.18	0.04
Handed, right/left	42/5	36/3	50/5	0.22	0.89
[b]ADHD severity, mean(SD)	62.9 (11.3)	70.9 (10.7)	45.5 (4.9)	86.98	<0.0001***
[c]Tic severity, mean(SD)	T=20.6 (8.6) M=13.4 (5.0) V=7.2 (5.5)	-	-		
[c]Age tic onset years, mean(SD)	5.6 (1.7)	-	-		
[c]Duration since tic onset years, mean(SD)	5.0 (1.8)	-	-		
[d]OCD, n	9	-	-		
[e]Medication					
Stimulant	11	26			
Atomoxetine	0	1			
Antipsychotic	8	1			
Clonidine	2	0			

[a]Estimated from a subtest of the Wechsler Intelligence Scale for Children-III (Wechsler, 2002) rating. [b]T-scores from the Conners' Parent Rating Scale – Revised Long version (Conners et al. 1997). [c]Determined with the Yale Global Tic Severity Scale (Leckman et al. 1989). Total (T), Motor (M) and Vocal (V) severity-ratings exclude impairment score. [d]Total-score ≥16 on the Children's Yale-Brown Obsessive Compulsive Scale (Scahill et al. 1997). [e]Current medication status, determined from parental report. *p<0.05, **p<0.01. ADHD – Attention-Deficit/Hyperactivity Disorder, K-W – Kruskal-Wallis, OCD – Obsessive Compulsive Disorder, SD – standard deviation, TS – Tourette Syndrome.

Phenotypic information

Various instruments were used to determine the presence and severity of disorders; TS - Yale Global Tic Severity Scale using 0-50 ratings, not considering overall impairment (YGTSS; Leckman et al. 1989), ADHD and/or other psychiatric disorders - Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Kaufman et al. 1997), screening interview plus appropriate modules if required; OCD - Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Scahill et al. 1997); ADHD severity - Conners' Parent Rating Scale – Revised Long version (CPRS-RL; Conners et al. 1997). Full-scale IQ was estimated by four subtests of the Wechsler Intelligence Scale for Children-III (WISC-III; Wechsler 2002). Medication status was determined from parental report.

MR acquisition and processing

T1-weighted anatomical images were acquired on a 3T Siemens Prisma scanner (Siemens, Erlangen, Germany) with a transversal, 3D MPRAGE parallel imaging sequence (parameters: TE=2.98 ms, TI=900 ms, TR=2300 ms, flip angle=9 degrees,

voxel size=1x1x1.2 mm, acquisition time=5.30 minutes). Datasets were processed with the automated FMRIB integrated registration and segmentation tool (FIRST) (Patenaude et al. 2011; Smith et al. 2004; Woolrich et al. 2009) 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 grey and white matter tissue types were estimated using the VBM8 toolbox (Ashburner and Friston 2000) of Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology). Total brain volume (TBV) was calculated as the voxel-wise sum of both probability maps.

Statistical analysis

A repeated measures analysis of co-variance (ANCOVA) was used to determine the effect of TS and ADHD-severity (continuous measure across all groups) and their interaction on BG nuclei volumes. A categorical factor for TS was deemed more robust than using symptom severity due to the fluctuating nature of tics in TS while a continuous measure for ADHD-severity was utilised as multiple participants, particularly within the TS group, displayed ADHD symptoms without meeting criteria for diagnosis. Hemisphere was included as the repeated measure with hemisphere-by-TS 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 analysed using FSL randomize (Winkler et al. 2014) with 5,000 random permutations and threshold-free cluster enhancement (TFCE; Smith and Nichols 2009). Sex, age and IQ were entered as covariates. Contrasts tested shape differences between those with and without TS and positive or negative associations between shape and ADHD-severity. A separate model was used to assess the interaction effect of TS and ADHD-severity on shape, using the same covariates. The effect of current stimulant medication use on volumes or shape within patients (TS and/or ADHD) was investigated in similar models including TS, ADHD-severity, age, sex and IQ as covariates. Additionally for the volume analysis TBV and hemisphere were included. With similar models current antipsychotic use within the TS group was also analysed.

Results

There were no main effects of TS, ADHD-severity or significant interactions between TS 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) towards an interaction with TS. This was not mirrored in the Pu and GP; no significant effects of hemisphere or hemisphere-by-TS interaction were seen (Table 2). No hemisphere-by-ADHD-severity interactions were seen. TBV was significant in each region. It did not differ with TS (t=-0.90, p=0.37), ADHD-severity (t=-0.90, p=0.37) or their interaction

(t=0.78, p=0.44). No effect of stimulant or antipsychotic medication was seen on either BG nuclei volume or shape.

Table 2 Results from basal ganglia volume analysis

	Caudate Nucleus		Putamen		Globus Pallidus	
	F	***p*-value**	**F**	***p*-value**	**F**	***p*-value**
TS	0.29	0.59	0.27	0.60	3.60	0.06
ADHD severity	0.001	0.98	0.04	0.85	0.06	0.81
TS x ADHD severity	2.55	0.11	0.14	0.71	0.80	0.37
Hemisphere	27.02	<0.001	2.47	0.12	3.50	0.06
Hemisphere x TS	3.13	0.08	0.80	0.37	0.92	0.34
Hemisphere x ADHD severity	0.45	0.50	0.19	0.67	0.25	0.62
TBV	55.09	<0.001	44.81	<0.001	100.19	<0.001

F statistics and uncorrected p-values are presented from analysis of basal ganglia volumes in relation to Tourette Syndrome (TS), attention-deficit/hyperactivity disorder (ADHD) -severity and hemisphere, including their interaction terms (*). TBV – total brain volume.

Discussion

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

Although both TS and ADHD have been previously associated with volume alterations in the BG (Felling and Singer 2011; Frodl and Skokauskas 2012; Nakao et al. 2011) 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 TS (n=13-38; Roessner et al. 2009; Williams et al. 2013) and no association between either TS or ADHD and BG nuclei volumes (n=14-37; Castellanos et al. 1996; Jeppesen et al. 2014; Singer et al. 1993; Zimmerman et al. 2000) in children. Furthermore, consistent with previous findings in children, the current study also found no asymmetry abnormalities associated with TS (Peterson et al. 2003; Williams et al. 2013). The few studies that have reported associations between BG volume and TS in children have been inconsistent regarding the regions implicated and direction of change; increased Pu volume bilaterally (n=49 and 14 TS cases, respectively; Ludolph 2006; Roessner et al. 2011), reduced CN volume bilaterally (n=154, child and adult sample; Peterson et al. 2003) or left only (n=23; Makki et al. 2008). Although all these studies relate to children there may still be consequential demographics differences. The few studies that have shown associations between BG structure and TS had a slightly higher mean age (Ludolph 2006) or a wider age range (Makki et al. 2008; Peterson et al. 2003; Roessner et al. 2011) 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 (e.g. Müller-Vahl et al. 2009;

Peterson et al. 2003). Along with the results here this implies that BG abnormalities in TS reflect compensatory mechanisms or an effect of the illness but do not relate to TS aetiology.

Two (overlapping) meta-analyses of BG structure in ADHD (Frodl and Skokauskas 2012; Nakao et al. 2011) 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 VBM (Bralten et al. 2015) or automated segmentation analyses (Greven et al. 2015). 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 favoured (Robbins et al. 2012) opposed to categorising subjects with arbitrary thresholds, especially considering the large number of subjects with TS that display ADHD or sub-threshold ADHD.

In addition to volume analysis we also applied shape analysis, which is more sensitive to subtle morphological differences. In TS only one small study to date examined BG morphology differences in children and they found no relation between TS and shape (Williams et al. 2013) 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 compared to controls (Qiu et al. 2009; Shaw et al. 2014; Sobel et al. 2010). The current study did not corroborate these findings. This discrepancy may relate to demographic differences as discussed above.

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 (2014) who reported no association between stimulant treatment history and developmental trajectories. However, other studies in ADHD reported normalising effects of stimulants on BG structure (Frodl and Skokauskas 2012; Nakao et al. 2011; Sobel et al. 2010). Our study was under-powered 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 TS sample, as is expected as males are more frequently affected than females (Hirschtritt et al. 2015). There were, however, no interactions with sex suggesting the sex imbalance did not confound our findings. Nine participants from the TS group also had OCD. ADHD and OCD were recently shown to have opposing associations with BG structure, although comorbidity was not considered (Norman et al. 2016). Here we saw that OCD-severity was not predictive of BG nuclei volumes within the TS group and removal of participants with OCD did not alter our findings.

In conclusion, we found no evidence that TS, ADHD or their combination are associated with BG structure in patients aged 8-12 years.

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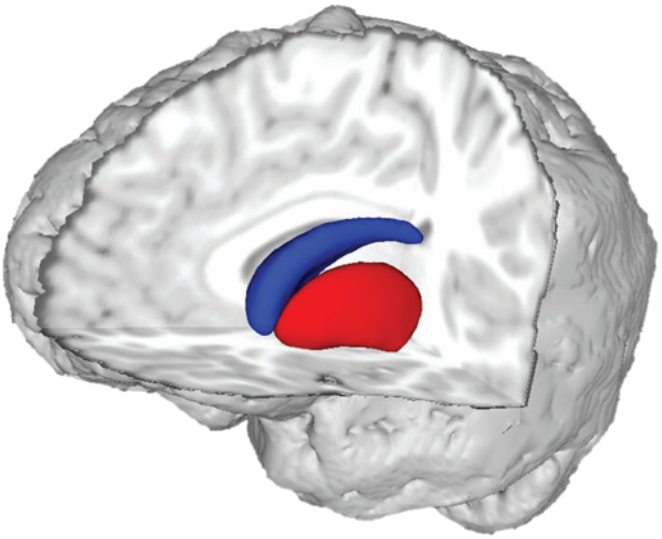
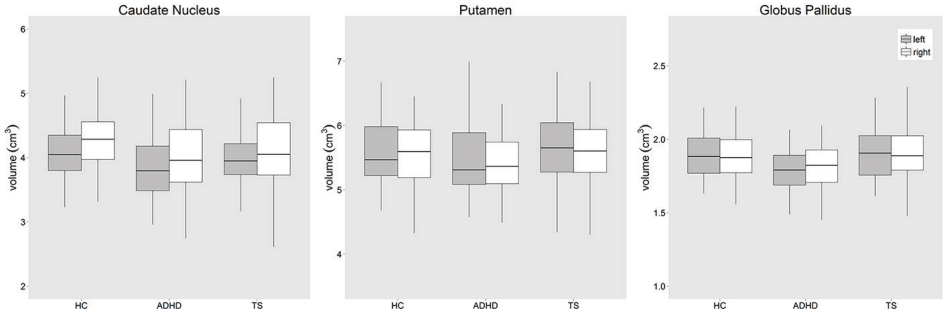
Supplementary Material Chapter 3



Supplementary figure 1 Basal ganglia nuclei
Left caudate nucleus (blue) and left putamen (red). Globus pallidus is hidden behind putamen.



Supplementary figure 2 Basal ganglia nuclei volumes per group
Left (grey) and right (white) volumes are shown for (a) the caudate nucleus, (b) the putamen and (c) the globus pallidus for each group.