

# Brain structure in pediatric Tourette syndrome

Alton C. Williams III, M.D.<sup>6,7</sup>

Deanna J. Greene, Ph.D.<sup>1,3</sup>

Jonathan M. Koller, BSEE, BSBME<sup>1</sup>

Bradley L. Schlaggar, M.D., Ph.D.<sup>1-5</sup>

Kevin J. Black, M.D.<sup>1-4</sup>

The Tourette Association of America Neuroimaging Consortium\*

Departments of <sup>1</sup>Psychiatry, <sup>2</sup>Neurology, <sup>3</sup>Radiology, <sup>4</sup>Neuroscience, and <sup>5</sup>Pediatrics, <sup>6</sup>Washington University School of Medicine, St. Louis, MO, USA.

<sup>7</sup>Current affiliation: Department of Psychiatry, Medical University of South Carolina, Charleston, SC, USA.

\* See Authorship note at end of manuscript.

Address correspondence to Dr. Black at [kevin@WUSTL.edu](mailto:kevin@WUSTL.edu) or at  
Campus Box 8134  
660 S. Euclid Ave.  
St. Louis, MO 63110-1093  
USA

## 1 **Abstract**

2 Previous studies of brain structure in Tourette syndrome (TS) have produced mixed results, and most had  
3 modest sample sizes. In the present multi-center study, we used structural MRI to compare 103 children  
4 and adolescents with TS to a well-matched group of 103 children without tics. We applied voxel-based  
5 morphometry methods to test gray matter (GM) and white matter (WM) volume differences between  
6 diagnostic groups, accounting for MRI scanner and sequence, age, sex and total GM + WM volume. The  
7 TS group demonstrated greater GM volume in posterior thalamus, hypothalamus and midbrain, and lower  
8 WM volume bilaterally in orbital and medial prefrontal cortex. These results demonstrate evidence for  
9 abnormal brain structure in children and youth with TS, consistent with and extending previous findings.  
10 As orbital cortex is reciprocally connected with hypothalamus, our results suggest that structural  
11 abnormalities in these regions may relate to abnormal behavioral inhibition and somatic monitoring in TS.

## 12 **Introduction**

13 Tourette syndrome (TS) is a developmental disorder of the central nervous system defined by the chronic  
14 presence of primary motor and vocal tics (American Psychiatric Association, 2013). Tics are repeated,  
15 nonrhythmic, unwanted but usually suppressible movements or vocalizations (Black, 2010). TS usually  
16 involves one or more additional features, most often obsessions, compulsions, distractibility or impulsivity  
17 (Leckman et al., 2014). A clear neurobiological explanation for TS is not yet available, but research has  
18 provided many relevant clues (Mink, 2006; Martino and Leckman, 2013).

19 A number of studies have now examined the structure of the living brain in TS and have found significant  
20 changes in various brain regions compared to tic-free healthy control subjects (Greene et al., 2013; Church  
21 and Schlaggar, 2014). The largest studies were reported by Peterson and colleagues, with over 100  
22 children and adults with TS and a similar number of control subjects. However, substantial questions  
23 remain about the structural anatomy of the brain in TS because methods and results have varied widely  
24 across studies, and because most studies were from small samples. A multi-center collaborative approach  
25 to brain imaging in TS might address these and other concerns.

26 Here we report the first analysis from such a collaboration, the Tourette Association of America  
 27 Neuroimaging Consortium, applying structural MRI to large, well-matched groups of children and  
 28 adolescents with and without TS.

## 29 Results

### 30 Subjects

31 Existing and newly acquired T1-weighted MP-RAGE images were collected from over 400 children age  
 32 7-17 years, including 230 with a chronic tic disorder (TS or Chronic Tic Disorder). After excluding scans  
 33 with visible artifact, MPRAGE images were available from 109 TS subjects and 169 control subjects age  
 34 7-17 years. Of the 109 TS subjects, 103 could be matched one to one with a control subject for age  
 35 (within 0.5 years), sex and handedness. Demographic and illness variables for these subjects are  
 36 summarized in Table 1.

<b>Table 1. Demographics and illness variables</b>			
	<b>TS group</b>	<b>Control group</b>	<b><i>p</i></b>
N, total → used	230 → 103	216 → 103	1.00
N by site, total → used			0.000 <sup>e</sup>
WUSTL	141 → 78	156 → 70	
UCLA	51 → 13	0 → 0	
NYU	25 → 8	38 → 21	
KKI	13 → 4	22 → 12	
Age (years, mean ± SD) <sup>a</sup>	11.9 ± 2.1	11.9 ± 2.1	0.96
Sex (M : F)	81 : 22	81 : 22	1.00
Handedness (# right-handed)	103	103	1.00
YGTSS Total Tic Score	17.2 ± 8.6 (N = 64) <sup>b</sup>	n/a	—
ADHD clinical diagnosis	55% (43 of 78) <sup>b</sup>	— <sup>d</sup>	—
CY-BOCS score (mean ± SD)	5.3 ± 6.8 (N = 65) <sup>b</sup>	— <sup>d</sup>	—
OCD clinical diagnosis	47% (15 of 32) <sup>b,c</sup>	— <sup>d</sup>	—
IQ (mean ± SD)	108 ± 13 (N = 80) <sup>b</sup>	119 ± 12 (N = 39) <sup>b</sup>	0.000 <sup>f</sup>
<sup>a</sup> Starting with this row, data describe only the final 206 subjects.			
<sup>b</sup> Not available for all subjects.			
<sup>c</sup> 45% (35 of 78) had CY-BOCS score > 0.			
<sup>d</sup> Not available for most control subjects.			
<sup>e</sup> $\chi^2 = 56.4, 3 df$ .			
<sup>f</sup> $t = 4.53, 81.9 df$ (two-sided <i>t</i> test, unequal variance, Welch <i>df</i> modification).			

37 All images were T1-weighted 3D MPRAGE images, voxel size 0.9-1.8mm<sup>3</sup>, from different sites and  
 38 different MR sequences. In all, 8 different scanner / sequence combinations were used to acquire the  
 39 images (Supplemental Table 1).

<b>Supplemental Table 1. Image collection specifications</b>					
	<b>Site</b>	<b>Scanner</b>	<b>Sequence parameters</b>	<b>TSN*</b>	<b>TSC*</b>
1	NYU	Allegra	*tf13d1_ns; 3.0T, TR = 2530 ms, TE = 3.25 ms, TI = 1100 ms, flip angle = 7°, voxel size = 1.0mm × 1.0mm within-plane, 128 sagittal slices acquired 1.33mm apart	8	21
2	WUSTL	Vision	mpr_ns_t1_4b195; Siemens 1.5T MAGNETOM Vision, sagittal magnetization-prepared rapid gradient echo (MP-RAGE), TR = 9.7 ms, TE = 4 ms, flip angle = 10°, voxel size = 1.0 mm × 1.0 mm × 1.25 mm.	11	2
3	WUSTL	Trio, East Building	mprage, 256×256×176 voxels, *tf13d1_ns, 1.0 × 1.0 × 1.0mm, TR 2400, TE 3.12, TI 1000, flip angle = 8°	46	27
4	WUSTL	Trio, CCIR	same	0	39
5	WUSTL	Vision	MPRAGE, voxels 1.0 × 1.0 × 1.25 mm, acquisition time about 6.5 minutes	2	2
6	KKI	Intera	T1TFE; 3.0T, TR = 8.07 sec, TE = 3.689 ms, flip angle = 8°, 1.0mm × 1.0mm within-plane resolution, 200 coronal slices acquired 1.0mm apart	4	12
7	UCLA	Allegra	*tf13d1; 3.0T, TR = 2300 ms, TE = 2.1 ms, TI = 1100 ms, flip angle = 8°, 1.33mm × 1.33mm within-plane resolution, 160 sagittal slices acquired 1.0mm apart	13	0
8	WUSTL	Trio	t1_mpr_ns_sag_ipat; tf13d1_ns; 3.0T, TR = 2200 ms, TE = 2.34 ms, TI = 1000 ms, flip angle = 7°, voxel size = 1.0mm × 1.0mm within-plane resolution, 128 sagittal slices acquired 1.33mm apart, GRAPPA on	19	0
* TSN: Number of TS subjects in this analysis from the specified sequence. TSC: ditto for controls.					

40

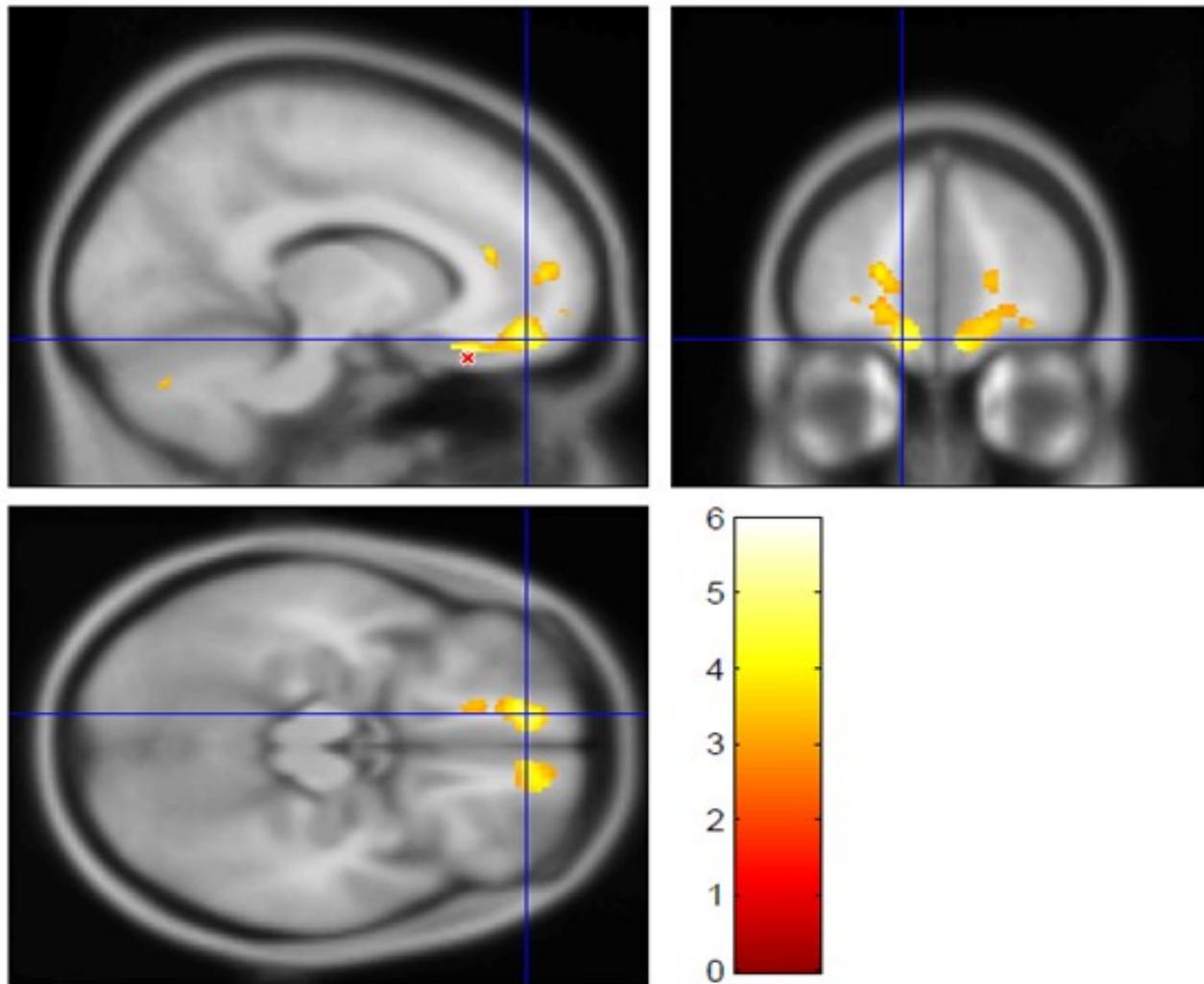
#### 41 **Global volumes**

42 Total GM volume was significantly correlated with age ( $p = 4.23 \times 10^{-7}$ ), but no other factors, covariates or  
 43 interactions were significant in the analysis of total GM or total WM ( $p \geq 0.30$ ).

## 44 Regional differences in white matter volume in TS

45 Table 2 summarizes the VBM results for WM. Two fairly symmetric WM clusters were statistically  
46 significant after correction for multiple comparisons, both with lower WM volume in TS. The cluster  
47 volumes were 5.2 and 4.6ml, each corrected  $p = .001$ , and they were located in WM deep to orbital and  
48 medial prefrontal cortex (see Figure 1 and Supplemental Figure 1).

**Figure 1. Largest cluster showing lower wm volume in TS compared to controls**



**Legend:** The largest cluster from the contrast showing where WM volume is lower in TS than in the control group (5.2 ml,  $p_{FDR} = .001$ ; see Table 1). The  $t$  statistic is shown in color (thresholded at  $t \geq 3.0$ ), laid over the average MP-RAGE image from the entire sample (in grayscale). The crosshairs show  $(-12, 49.5, -16.5)_{MNI}$ , left medial orbital gyrus, BA11. The peak  $t$  value from this contrast,  $t_{193} = 5.95$ , is at  $(-13.5, 31.5, -22.5)_{MNI}$  in left medial orbital gyrus, BA13, near the red “X” in the sagittal image. Supplemental Figure 1 shows the other significant cluster from this contrast, the homologous area on the right side of the brain.

**Table 2. VBM results: white matter**

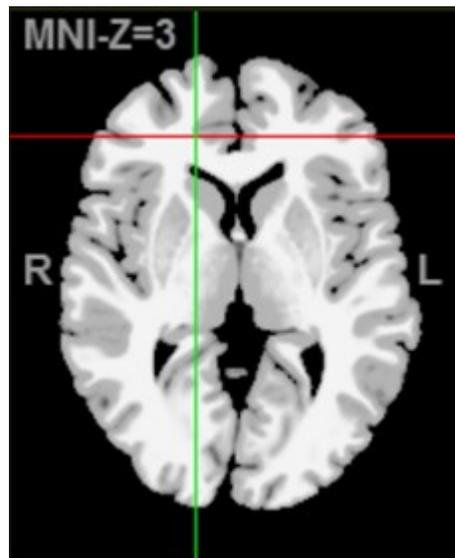
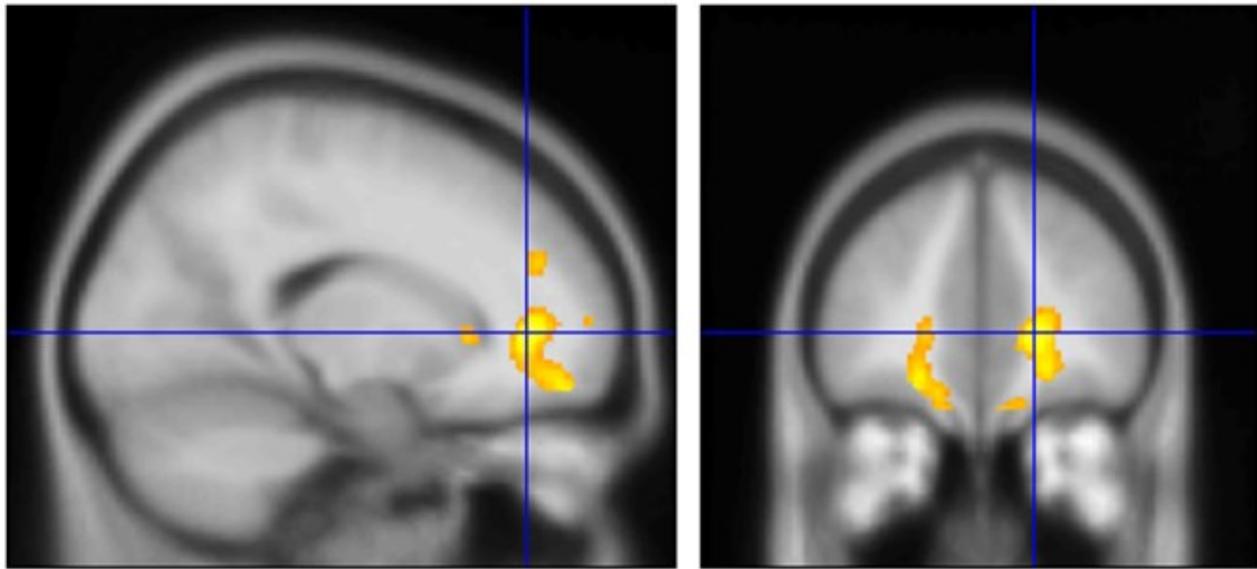
TS < control									
$p_{FDR}$	Volume (ml)	Peak $t$	Peak (MNI)			Peak (TT)			Description
			$x$	$y$	$z$	$x$	$y$	$z$	
0.001	5.2	5.95	-13.5	31.5	-22.5	-14	27	-20	L medial orbital gyrus, BA13*
		4.83	-12.4	9.5	-16.5	-12	44	-17	L medial orbital gyrus, BA11
		4.75	-15	22.5	-21	-15	18	-17	L medial orbital gyrus, BA11
		4.07	-19.5	51	9	-19	47	7	L medial frontal gyrus, BA10
		3.93	-19.5	43.5	-12	-20	39	-11	L OFPFC, BA11
		3.91	-13.5	36	15	-14	33	14	WM deep to L BA32
		3.9	-15	55.5	9	-15	52	7	WM in L anterior PFC
		3.78	-16.5	46.5	3	-16	43	2	WM in L anterior PFC
		3.59	-18	51	-7.5	-18	46	-8	WM deep to L BA 11/12*
		3.54	-27	55.5	-10.5	-27	51	-10	L OFPFC, BA12*
		3.19	-22.5	36	21	-21	34	20	WM, middle of PFC
0.001	4.6	4.6	7.5	49.5	-19.5	6	44	-20	WM deep to R BA11
		4.45	18	42	3	17	38	3	WM deep to R anterior cingulate, BA32
		4.03	16.5	55.5	-15	15	50	-15	R BA11
		4.02	15	63	7.5	14	58	5	R BA10, medial frontal gyrus
		3.93	21	43.5	-7.5	20	38	-5	WM deep to R BA47/12*
		3.69	7.5	58.5	-13.5	6	52	-14	R medial PFC, BA10*
		3.59	30	49.5	-12	29	44	-10	WM deep to R BA47/12*
		3.24	13.5	42	-19.5	12	36	-18	R olfactory sulcus, BA11m/l*
0.196	1.2	3.98	30	-10.5	4.5	29	-11	7	R posterior putamen
		3.46	31.5	-13.5	-4.5	30	-14	0	R posterior putamen
		3.41	34.5	-15	12	33	-15	14	R posterior insula
		3.39	28.5	0	9	27	-1	11	R putamen
0.223	1.1	3.89	-28.5	-10.5	4.5	-27	-11	6	L posterior putamen
		3.5	-33	-6	13.5	-32	-7	14	L posterior insula
		3.46	-25.5	1.5	10.5	-24	-1	11	L putamen

**TS > control**

No significant clusters

**Legend:**  $p_{FDR}$  = False discovery rate corrected  $p$  value for a suprathreshold cluster of this size in the  $t$  image. For each local maximum (peak) in the cluster, the table lists the  $t$  statistic at that voxel (193 df) and the atlas coordinates of that voxel's location. MNI = Montreal Neurological Institute template brain coordinates. TT = Talairach and Tournoux atlas coordinates. L = left hemisphere; R = right hemisphere. PFC = prefrontal cortex. OFPFC = orbitofrontal prefrontal cortex. BA = Brodmann area. \* = description taken from (Öngür and Price, 2000).

### Supplemental Figure 1. Second largest cluster showing lower WM volume in TS compared to controls

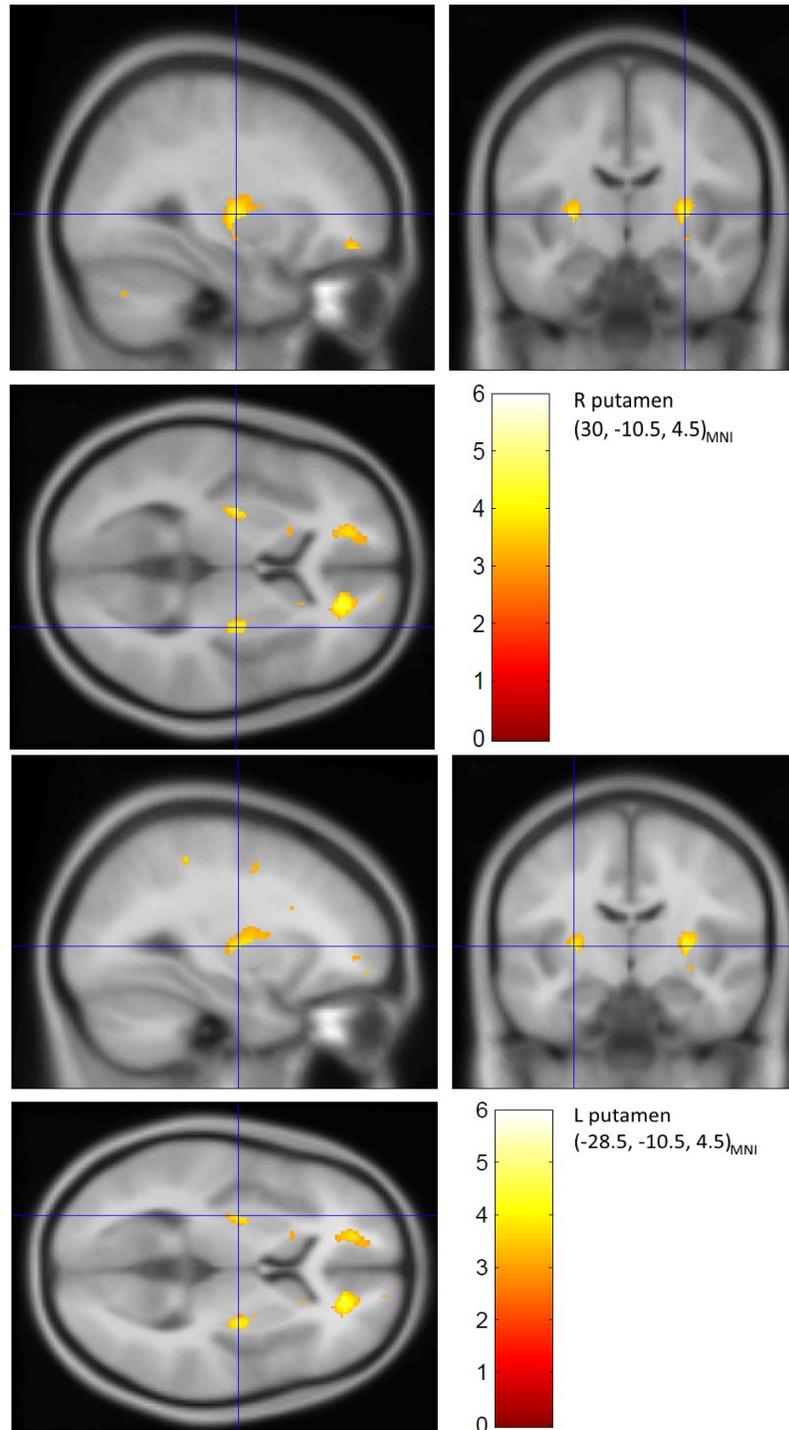


**Legend:** The second largest cluster from the contrast for WM volume lower in TS, 4.6 ml,  $p_{\text{FDR}} = .001$ , peak  $t_{193} = 4.48$  at  $(7.5, 49.5, -19.5)_{\text{MNI}}$  in BA 11. The crosshairs mark a more dorsal location in this same cluster,  $(18, 42, 3)_{\text{MNI}}$  in BA 32. See also legend for Figure 1.

50  
51 Two additional symmetric clusters of decreased WM volume are of interest, though they did not  
52 remain statistically significant after multiple comparisons correction (each  $p = 0.2$ ). These  
53 clusters include parts of posterior putamen and insula bilaterally (see Supplemental Figure 2).

54

## Supplemental Figure 2. Additional clusters showing lower WM volume in TS compared to controls



**Legend:** Clusters 3 and 4 from the contrast showing WM volume lower in TS than in the control group. The right peak is  $t = 3.98$  at  $(30, -10.5, 4.5)_{\text{MNI}} = (29, -11, 7)_{\text{TT}}$ , 1.2ml, corrected  $p = 0.20$ , and the left peak is  $t = 3.89$  at  $(-28.5, -10.5, 4.5)_{\text{MNI}} = (-27, -11, 6)_{\text{TT}}$ , 1.1ml, corrected  $p = 0.22$ . See also legend to Figure 1.

## 56 Regional differences in gray matter volume in TS

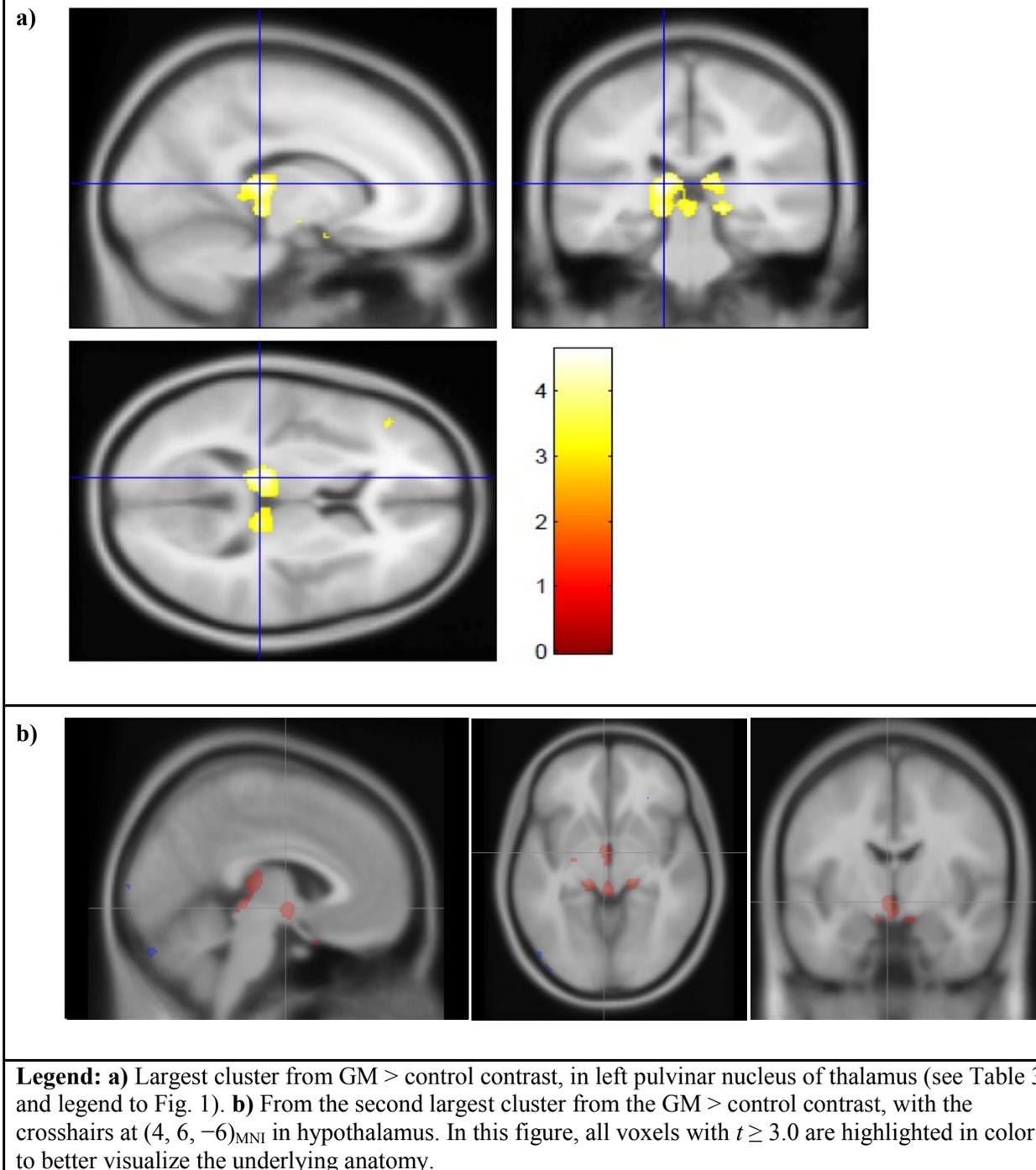
57 Two clusters showed statistically significant increased GM volume in TS after correction for multiple  
 58 comparisons (Table 3). The largest suprathreshold cluster had a volume of 4.4ml (corrected  $p = .001$ ), with  
 59 the peak  $t$  value (4.62, 193 d.f.) in the pulvinar nucleus of the left thalamus (see Figure 2a). A homologous  
 60 cluster in the right pulvinar, peak  $t = 4.13$  at  $(16.5, -28.5, -4.5)_{\text{MNI}} = (15, -29, 0)_{\text{TT}}$ , was 1.6 ml, below the  
 61 significance threshold (corrected  $p = 0.070$ ). The second largest cluster had volume 2.7ml (corrected  $p =$   
 62  $0.011$ ), with peak  $t = 4.06$ , and included the hypothalamus bilaterally and the ventral midbrain (see Figure  
 63 2b).

**Table 3. VBM results: gray matter**

TS > control									
$p_{\text{FDR}}$	Volume (ml)	Peak $t$	Peak (MNI)			Peak (TT)			Description
			$x$	$y$	$z$	$x$	$y$	$z$	
0.001	4.4	4.62	-13.5	-30	9	-12	-30	11	L thalamus, pulvinar n.
		4.26	-15	-28.5	-4.5	-14	-29	0	L thalamus
		3.75	0	-33	-4.5	0	-33	0	dorsal edge of midbrain
		3.46	0	-34.5	-13.5	0	-35	-7	dorsal edge of pons / midbrain
0.011	2.7	4.06	9	-3	-16.5	8	-5	-11	ventral edge of basal forebrain / midbrain
		3.93	-1.5	-6	-7.5	-2	-8	-3	L hypothalamus
		3.76	0	-15	-10.5	0	-16	-5	ventral midbrain, near supramammillary commissure
0.07	1.6	4.13	16.5	-28.5	-4.5	15	-29	0	R thalamus, posterior edge
		3.9	12	-30	12	12	-30	14	R thalamus, posterior edge
TS < control									
No significant clusters									
<b>Legend:</b> See legend for Table 2.									

64

**Figure 2. Largest Clusters Showing Greater GM Volume in TS Compared to Controls**



65

## 66 Secondary analysis: scanner and MR sequence

67 The statistical model included a factor to account for different scanners or MR sequences, but such  
68 statistical control may be imperfect. Accordingly, we checked whether the findings from the overall group  
69 would still be present if the different-scanner concern were eliminated. One site acquired images from 46

70 TS subjects and 27 control subjects on one scanner using the same sequence. For the left thalamus SPM  
71 cluster, for instance, the question is whether GM volume was higher in TS, as it was in the overall  
72 analysis, in these subjects who were all scanned on the same scanner with the same MR sequence. This  
73 question was tested using ANCOVAs with relative GM volume in the SPM cluster as the dependent  
74 variable, diagnosis and sex as factors, age as a covariate, and interactions of sex with diagnosis and age.  
75 As in the full SPM analysis, this cluster was larger in TS (**Figure 3a**, diagnosis factor  $p=.004$ ). Similarly in  
76 this same-sequence subgroup, the hypothalamus GM cluster was larger in TS (**Figure 3b**, diagnosis  
77  $p=.000$ , with a significant diagnosis by sex interaction  $p=.009$ ), and the OFPFC WM clusters were smaller  
78 in TS (**Figure 3c,d**, left WM diagnosis  $p=.000$ , right WM  $p=.000$ ).

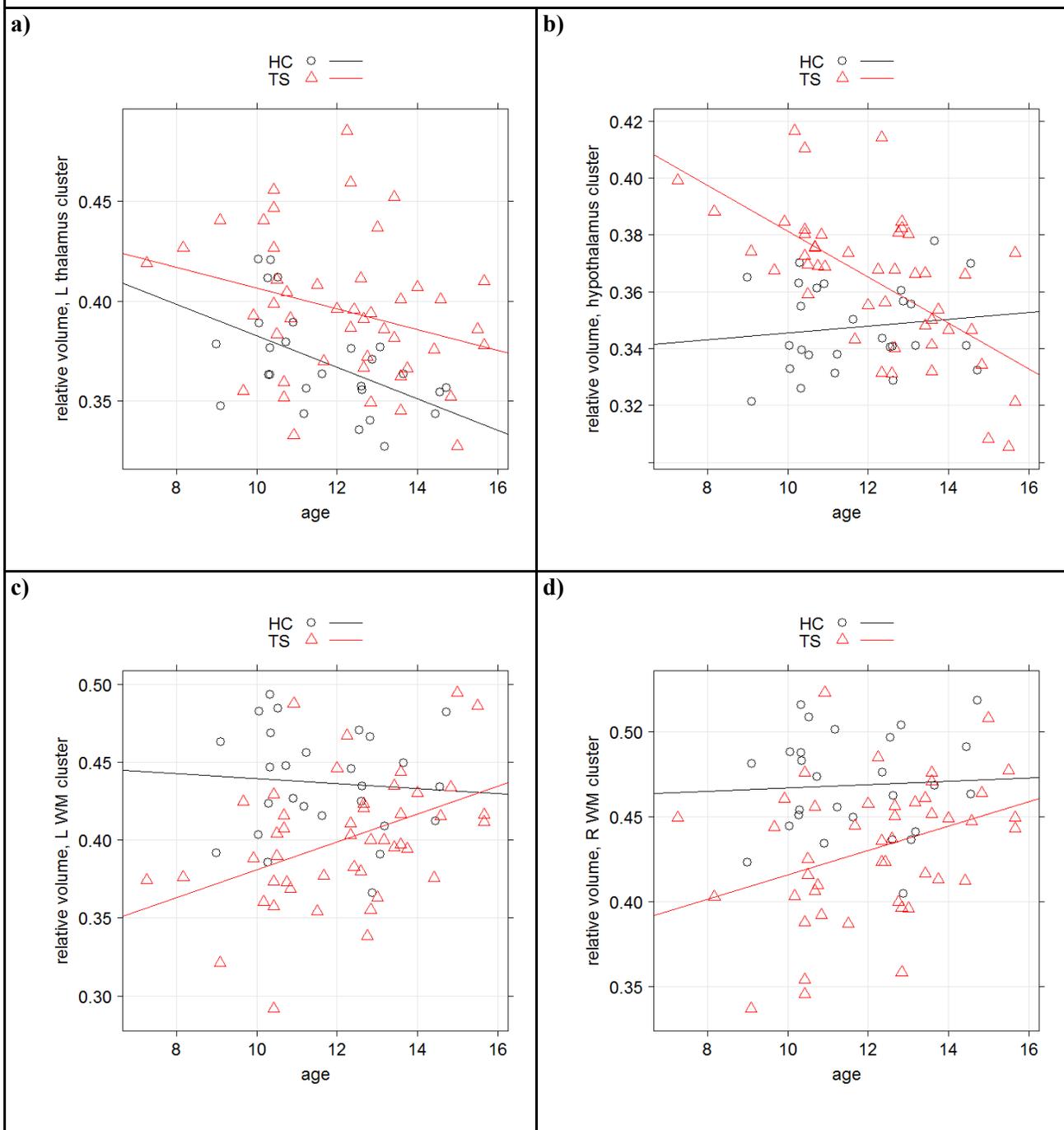
### 79 **Secondary analysis: IQ and comorbidity**

80 We did not have IQ estimates from all sources, but we did for all but 1 subject from the single-sequence  
81 group discussed in the previous section. In this group, IQ differed between the two groups (TS  $107.5 \pm$   
82  $11.9$ , control  $117.8 \pm 13.1$ ,  $p<.002$ , unpaired  $t$  test), so we checked whether IQ explained any of the  
83 primary group differences by modeling relative cluster volume in each subject by ANCOVA with sex as a  
84 factor, age and IQ as covariates, and all interactions. Neither IQ nor interactions with IQ were significant  
85 for any of the 4 significant clusters ( $p$  for IQ was .08 for R OFPFC WM, .27 for L OFPFC WM, .10 for L  
86 thalamus, and .51 for hypothalamus).

87 ADHD was recorded for all TS subjects in that same subgroup. Using a similar approach, with sex and  
88 ADHD diagnosis as factors, age as a covariate, and all interactions, neither ADHD nor interactions with  
89 ADHD were significant for any of the 4 clusters. OCD diagnosis was not recorded in this subgroup, but as  
90 a loose proxy we dichotomized TS subjects based on OCD symptom severity (CY-BOCS scores, zero vs.  
91 greater than zero). This OCD factor was not significant, nor were any interactions with this factor, using  
92 the same analysis strategy as for ADHD.

93

**Figure 3. Key results hold in the single-site, same-sequence subgroup**



**a)** Relative GM volume of L thalamus cluster in a subgroup of subjects studied at one institution using a single MR sequence, plotted against age for TS subjects (triangles and red regression line) and control subjects (circles and black line). **b)** Same plot for hypothalamus. **c)** Same plot for relative volume of L OFPFC WM cluster. **d)** Same plot for R OFPFC WM cluster.

## 95 Discussion

96 Here we present the largest study of brain structure ever reported in children with TS. We matched control  
97 subjects strictly for age, sex and handedness, and the statistical analysis used conservative methods to  
98 minimize Type I error. Our main findings were that the TS group had lower white matter volume than the  
99 control group deep to orbital and medial prefrontal cortex, and greater gray matter volume in the posterior  
100 thalamus and hypothalamus.

### 101 Lower WM volume in prefrontal cortex in TS

102 The finding of decreased WM in orbital cortex is consistent with the decreased volume found in a  
103 predefined orbital frontal cortex area in an earlier large structural MRI study in TS (Peterson et al., 2001).  
104 The present results suggest that the decreased orbital prefrontal cortex (OFPFC) volume may be  
105 attributable to WM. Another study focusing specifically on white matter (Cheng et al., 2014) identified 10  
106 WM tracts with decreased WM integrity (scaled fractional anisotropy) in a group of 15 currently  
107 unmedicated adults with TS compared to 15 tic-free control subjects matched for age and sex. Four of  
108 those 10 tracts involved the OFPFC, specifically those connecting OFPFC with pre-SMA (anterior to  
109 supplementary motor cortex), ventral premotor cortex, primary motor cortex, and supplementary motor  
110 cortex.

111 The orbital prefrontal cortex regions identified in the present study have been linked to behavioral  
112 disinhibition and to visceral and emotional responses (Knutson et al., 2015; Öngür and Price, 2000; Barbas  
113 et al., 2003). Thus, reduced WM volume in this region may contribute to the inability to inhibit unwanted  
114 behaviors, namely tics. Alternatively, the connection of OFPFC to tics may be sensory. Most tic patients  
115 report that tics are often responses to uncomfortable internal sensations, like a tickle in the throat before a  
116 cough. Many tic experts, though not all, conclude that these premonitory sensations may be the primary  
117 phenomenon rather than the observed tics (Leckman et al., 2013). Abnormal white matter connections to  
118 ventromedial OFPFC, a brain region involved in assessing internal sensations, fit well with such a model.

119 The clusters of decreased WM volume also extended to pregenual WM and WM deep to medial frontal  
120 gyrus (BA 10). A previous study that examined WM integrity in TS found a strong correlation between

121 past-week tic severity and WM fractional anisotropy deep to superior frontal gyrus (Müller-Vahl et al.,  
122 2014). Increased tic severity was associated with decreased WM integrity in this region, consistent with  
123 our results, though the specific location of the region was 10mm superior to the BA 10 peak in the current  
124 study.

### 125 **Putamen**

126 The paired clusters of decreased WM volume in posterior putamen are interesting given the posterior  
127 putamen's prominent role in movement. Left and right putamen were the locations at which apparent  
128 diffusion coefficient was most highly correlated with tic severity (Müller-Vahl et al., 2014), though the  
129 most significant voxels in that study are 16-17 mm anterior and inferior from the peaks reported here.  
130 However, the clusters in the present study were not significant after correction for multiple corrections,  
131 and a WM difference might be more easily interpreted as referring to the external capsule or extreme  
132 capsule than the putamen itself. These clusters also extended to bilateral insula.

### 133 **Other**

134 Some previous TS studies found larger volume or reduced fractional anisotropy in corpus callosum, but  
135 otherwise, previous WM findings in TS have been variable (Greene et al., 2013).

## 136 **Greater GM volume in pulvinar nucleus, midbrain and hypothalamus in TS**

### 137 **Pulvinar**

138 Several imaging studies have examined thalamic volume in TS (Greene et al., 2013). The largest of these  
139 found increased total thalamic volume in children and adults with TS (about 5%), with outward  
140 deformation (bulges) compared to thalamic shape in control subjects (Miller et al., 2010). The most  
141 prominent differences were found on the ventral, lateral and posterior surfaces, corresponding to several  
142 motor nuclei and the pulvinar. Thus, that study's results are quite consistent with the present finding of  
143 greater GM volume in the pulvinar in a large group of children and adolescents. Miller *et al.* posit several  
144 possible explanations for finding enlargement in these thalamic regions, including hyperactive motor  
145 circuitry, compensatory mechanisms derived from years of controlling (or attempting to control) tics, or  
146 secondary GM changes in the face of WM alterations.

147 The medial pulvinar nucleus is widely connected to cortex, including prefrontal, orbital, and cingulate  
148 cortical areas; the lateral pulvinar projects to parietal, temporal, and extrastriate regions; and the inferior  
149 pulvinar has bidirectional connections with visual cortical regions (Benarroch, 2015; Shipp, 2003). Given  
150 these widespread projections and innervations, we speculate that increased GM volume in TS may relate  
151 to multisensory integration in the thalamus, or to the linking of sensory input to cognitive-, motivational-  
152 and movement-related areas of cortex. Sensory symptoms are common in TS (premonitory urges,  
153 hypersensitivity), yet TS patients do not demonstrate primary sensory deficits (Belluscio et al., 2011;  
154 Schunke et al., 2016), suggesting involvement of higher-order functions such as attention. There is  
155 evidence for a functional role of the pulvinar nucleus in spatial attention and attention to salient stimuli  
156 (Grieve et al., 2000; Shipp, 2004).

### 157 **Midbrain**

158 Part of the thalamus GM cluster includes dorsal midbrain. Interestingly, a VBM study of 31 patients and  
159 31 controls also identified a significant increase in GM volume in midbrain (Garraux et al., 2006), though  
160 that statistical peak was inferior and anterior to the one identified in the present study.

### 161 **Hypothalamus**

162 One cluster of increased GM volume included hypothalamus. We are not aware of any previous studies  
163 linking TS to this structure. However, the hypothalamus does receive inhibitory innervation from the  
164 ventral medial OFPFC via the central nucleus of the amygdala (Öngür and Price, 2000; Barbas et al.,  
165 2003). This anatomical connection is intriguing given the OFPFC WM changes in this study. Future work  
166 may study the hypothalamus more specifically.

### 167 **Comparison to OCD**

168 The main findings in the present study largely overlap with previous structural MRI results in OCD. OCD  
169 is relevant here for several reasons, including the high comorbidity rates of OCD and TS and the  
170 phenomenological similarities in symptoms between these conditions, as thoroughly reviewed recently by  
171 (Eddy and Cavanna, 2014). The most prominent overlapping finding between previous OCD studies and  
172 the present TS study is volumetric differences in the orbitofrontal cortex in OCD. However, these reports  
173 are mixed, including both decreased orbitofrontal volume (Atmaca et al., 2007), increased orbitofrontal

174 volumes (Valente et al., 2005; Kim et al., 2001) thicker left and thinner right orbitofrontal cortex related to  
175 an increased likelihood of responding well to treatment (Hoexter et al., 2015). Similarly, left and right  
176 OFPFC GM volume correlated in opposite directions with symmetry/ordering symptom severity in OCD  
177 (Valente et al., 2005). The potential importance of these structural results is highlighted by functional  
178 imaging studies; a meta-analysis of PET and SPECT studies in OCD found that the largest effect sizes for  
179 abnormal function in OCD were for left ( $d = 1.15$ ) and right ( $d = 1.04$ ) orbital gyrus (Whiteside et al.,  
180 2004).

181 Also consistent with previous reports in OCD is the present finding of increased GM volume in thalamus  
182 and hypothalamus. Larger thalamic volumes have been reported in OCD using volume-of-interest (Atmaca  
183 et al., 2007) and VBM approaches (Kim et al., 2001). Kim et al. also found increased GM volume in  
184 bilateral hypothalamus in OCD.

185 Still, OCD *per se* is unlikely to explain our current results, given null results in the secondary analysis  
186 based on current OCD severity. However, this conclusion should be confirmed in a sample with  
187 prospective, systematic psychiatric diagnosis.

### 188 **The dog that did not bark in the night ...**

189 A word is due about previous volumetric findings that were not replicated here. The most notable of these  
190 is decreased caudate volume in TS reported by Peterson et al (Peterson et al., 2003) in a study of 154  
191 children and adults with TS and 130 controls (including a total of 173 children), and by two other groups  
192 (Makki et al., 2008; Peterson et al., 1993; Müller-Vahl et al., 2014; Makki et al., 2009; Müller-Vahl et al.,  
193 2009). The potential relevance of that finding was enhanced by the report that smaller caudate volume in  
194 childhood predicted worse tic severity in young adulthood, showing that decreased caudate volume could  
195 not be just a consequence or adaptation of the brain to tics (Bloch et al., 2005). Conceivably our caudate  
196 non-finding reflects a Type II error.

197 On the other hand, several other studies did not find a significantly smaller caudate in TS (Black et al.,  
198 2003; Moriarty et al., 1997; Zimmerman et al., 2000; Garraux et al., 2006; Kassubek et al., 2006; Ludolph  
199 et al., 2006; Williams et al., 2013; Wang et al., 2007; Roessner et al., 2011; Wittfoth et al., 2012; Roessner

200 et al., 2009). The largest of these included 49 boys with TS and 42 boys without tics (Roessner et al.,  
201 2011). The present study has some merits relative to previous studies beyond the larger sample size; it  
202 excluded adults and handled variation in age and sex by one-to-one age matching in addition to statistical  
203 accounting for linear effects of age. Furthermore, the caudate is a relatively small structure, surrounded by  
204 white matter and CSF, and hence especially susceptible to partial volume effect and, presumably, to the  
205 artifactual reduction in volume with frequent small-amplitude head movements demonstrated with other  
206 techniques (Alexander-Bloch et al., 2016; Reuter et al., 2015). Therefore caudate volume may be normal  
207 in TS.

## 208 **Limitations**

209 The most important limitation is the use of different scanners, different sequences, and possibly different  
210 recruitment sources or diagnostic methods across sites. However, the analysis of the largest subgroup  
211 suggests strongly that the key findings are not driven by differences in site, scanner or sequence.

212 A second limitation is that phenotypic data are limited for many of the “legacy” subjects. For instance,  
213 diagnosis (TS vs. chronic motor tic disorder) is missing for some subjects in the TS group, and for many  
214 subjects we have limited information on comorbid diagnosis. In the available data our key findings are not  
215 significantly linked to IQ, ADHD or OCD, but of course future studies will benefit from adequate  
216 prospective assessment of all these variables (Castellanos et al., 1996).

217 Recently, small head movement not detected by visual inspection of MR images has been shown to  
218 artifactually lower GM volume in VBM analyses, presumably by a mechanism similar to partial volume  
219 effect (Alexander-Bloch et al., 2016; Reuter et al., 2015). Fortunately, group differences in residual head  
220 movement cannot easily explain the decreased WM volume or the increased GM identified in this study,  
221 since the TS group would be expected to show more head movement.

## 222 **Future directions**

223 A prospective study design with additional clinical information can test whether the posterior thalamic  
224 finding in fact relates to sensory symptoms in TS, whether the OFPFC finding relates to measures of  
225 response inhibition, coprophenomena (Black et al., 2014; Eapen et al., 2015), or socially inappropriate

226 non-tic behavior (Kurlan et al., 1996), and to what extent the severity of tics, obsessions and compulsions  
227 explain these findings. Future structural imaging studies can help elucidate at what age the regional  
228 differences in GM and WM volume in TS first manifest and whether they persist into adult life, thus  
229 helping to clarify whether the volumetric differences represent failures of maturation or alterations after a  
230 period of normal development.

231 Studies with different methodology will be required to elucidate the mechanism responsible for the  
232 volumetric abnormalities. Postmortem studies in TS have not typically focused on the regions identified in  
233 this study (Swerdlow and Young, 2001). Thus it is not clear whether, for example, increased GM volume  
234 in posterior thalamus reflects increased neuronal cell number, glial cell number, neuropil (*e.g.* deficient  
235 pruning), or increased water content. On the other hand, this reflects a potential strength of the present  
236 study: an unbiased, whole-brain analysis identified regions of brain that have hardly been studied in TS.

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237

238

## 239 **Methods**

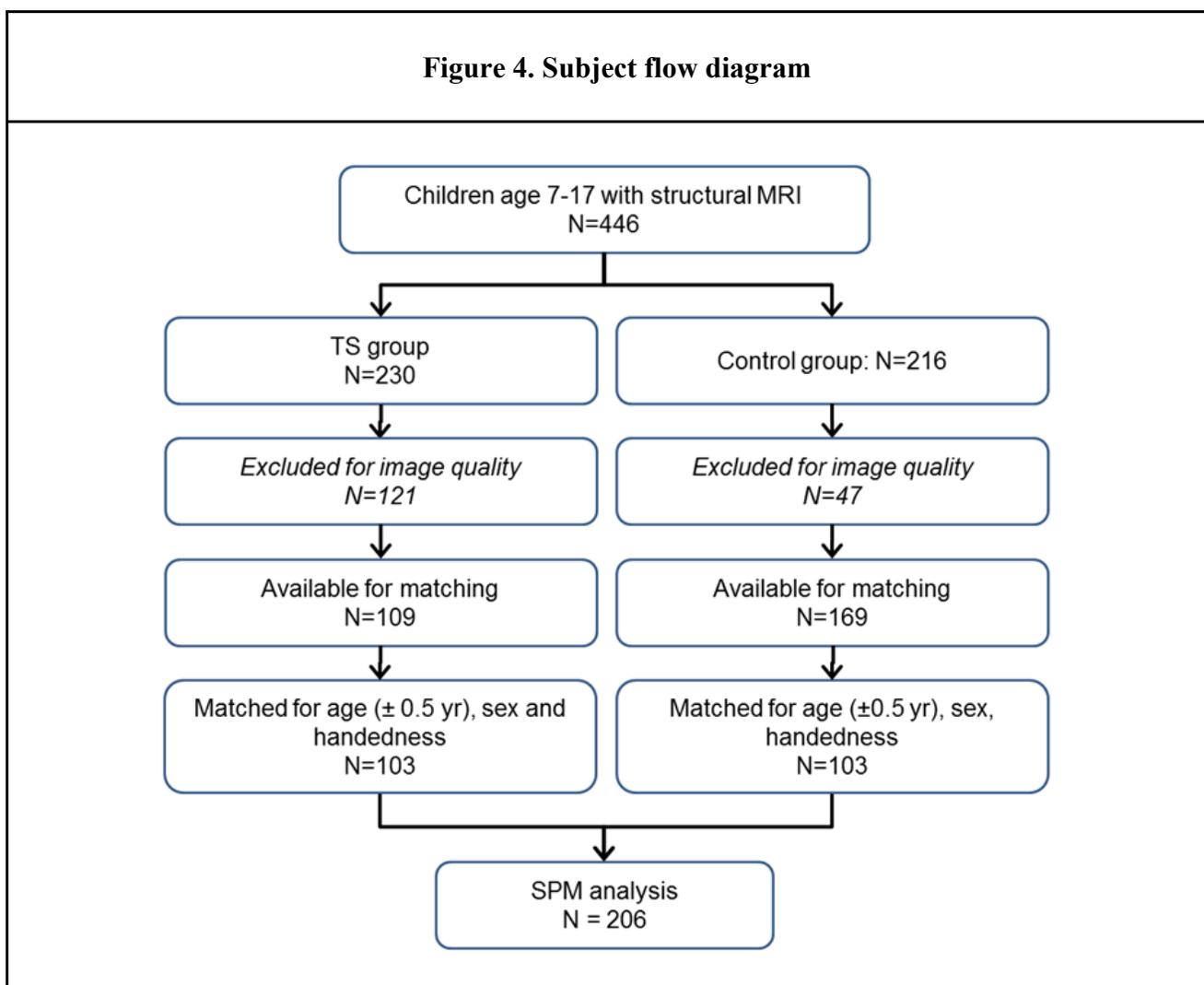
240 This study was approved by the Washington University Human Research Protection Office (IRB),  
241 protocol # 201108220. Most MR images and clinical information were originally collected under different  
242 IRB protocols (independent of this study) at the 4 imaging sites: WUSM, NYU, KKI, UCLA. Herein we  
243 call this “legacy” data. The WUSM, KKI and UCLA sites enrolled additional new subjects specifically for  
244 this study. The transmission of any human subjects data to the consortium was approved by each site’s  
245 respective IRB. Some data were provided anonymously to the consortium under code-sharing agreements.

246 Imaging data were stripped of personal identifiers such as name and date of birth and archived at the  
247 Central Neuroimaging Data Archive (CNDA) hosted at <https://cnda.wustl.edu> (Gurney et al., 2015).  
248 REDCap electronic data capture tools hosted at Washington University were used to manage the clinical  
249 data collected at WUSM (Harris et al., 2009).

## 250 **Subjects**

251 T1-weighted MPRAGE images were located from 230 children aged 7-17 with DSM- 5 TS or chronic tic

252 disorder and 216 tic-free controls. Of the subjects with at least one remaining image, 103 TS and 103  
253 controls could be matched 1:1 for age (within 0.5 year), sex, and handedness (Figure 4).  
254 MPRAGE (3D T1-weighted) data were acquired on several MR scanners with varying parameters. The  
255 most common structural image protocol was an MP-RAGE with total scanning time 6-10 minutes and  
256 voxel size 1.0-1.25mm<sup>3</sup> (Supplemental Table 1). Authors ACW, DJG or KJB visually reviewed each  
257 structural MRI and excluded images with any visible artifact in the brain. The provenance of the images  
258 used in this analysis is described further in Supplemental Table 1.  
259



## 260 Image processing

261 If a subject had more than one MPRAGE image of adequate quality, these images were averaged after  
262 mutual rigid-body alignment using a validated method (Black et al., 2001), and the mean image

263 represented that subject in all subsequent steps. Beyond this point all image analyses were performed with  
264 SPM software v.12b using the method of J. Ashburner (Mechelli et al., 2005; Perantie et al., 2011).  
265 Each subject's image was nonlinearly normalized to MNI space, and the atlas-aligned images were  
266 averaged to create an MPAGE template specific to this study, as described elsewhere  
267 (<https://irc.cchmc.org/software/tom.php>) (Wilke et al., 2008). For each subject, segmented images were  
268 created to reflect the probability that each voxel was composed of gray matter (GM), white matter (WM),  
269 or CSF. This computation used a Bayesian approach, with prior probabilities established by population  
270 templates for GM, WM and CSF to inform interpretation of the subject's MR signal at each voxel.  
271 Alignment and segmentation were then refined by tissue-specific realignment (Good et al., 2001). The  
272 tissue density images were multiplied by the local volume in the subject image corresponding to each  
273 voxel in the atlas template to produce images showing at each atlas voxel that subject's GM, WM and CSF  
274 volume contributing to that voxel. The GM volume image from one subject is shown in Supplemental  
275 Figure 3. A 3D Gaussian filter (FWHM 6mm) was applied to the GM and WM images and the smoothed  
276 images were submitted to SPM analysis.

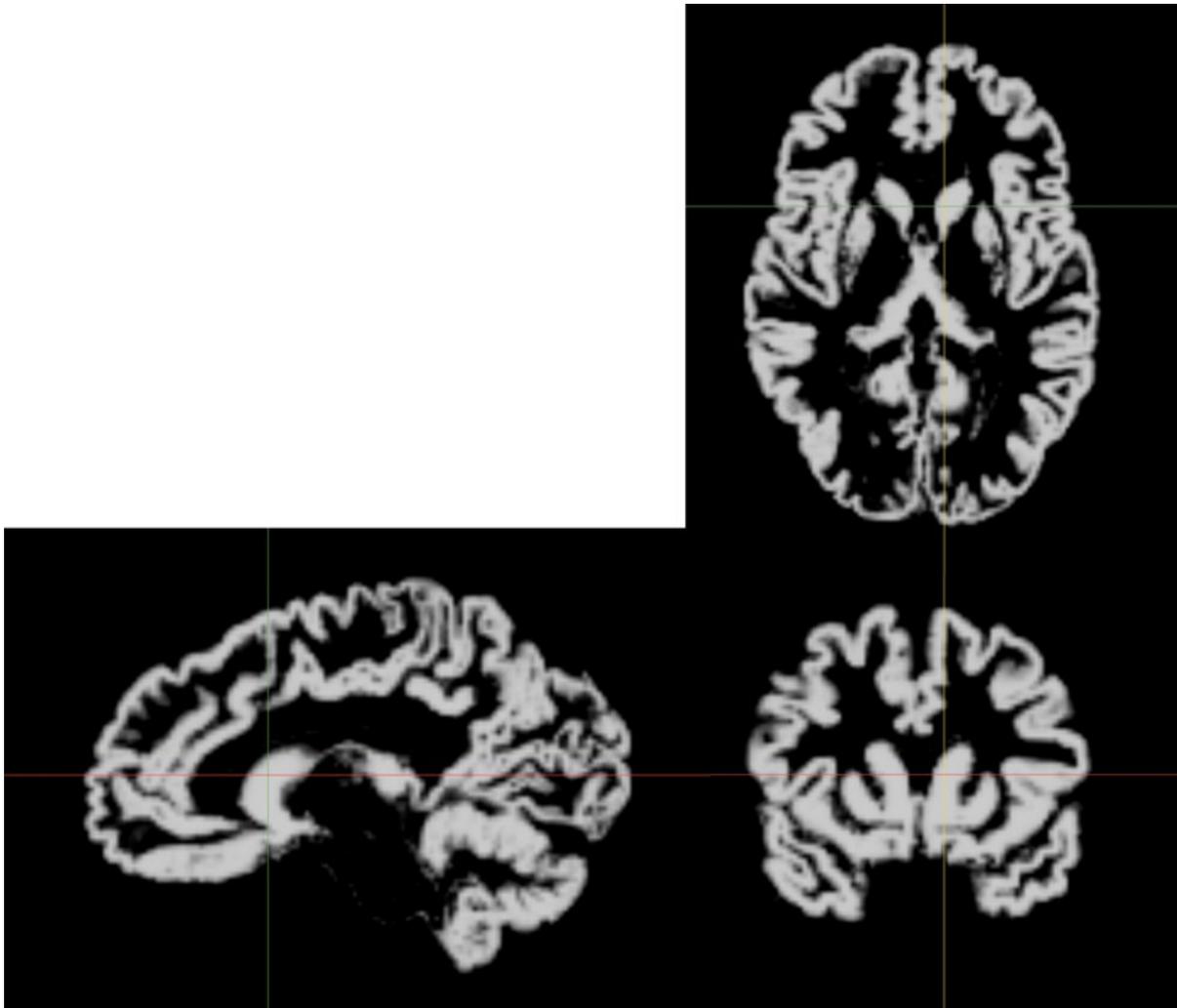
277

## 278 **Analysis**

279 Statistical image analysis was performed using SPM software v. 12b  
280 (<http://www.fil.ion.ucl.ac.uk/spm/software/>), which computed at each voxel a general linear model (GLM)  
281 with dependent variable gray matter volume (GM), factors diagnostic group, MRI scanner and sequence  
282 (Supplemental Table 1), and sex; age at scan as a covariate; and interactions of group  $\times$  sex and sex  $\times$  age.  
283 Proportional scaling by each subject's total GM + WM volume corrected for global brain volume. The GM  
284 analysis was limited to voxels at which GM concentration was  $>20\%$ . The WM analysis used the same  
285 methods.

286 One-tailed contrasts were used to generate t images comparing TS and control groups. Statistical  
287 significance was determined by the volume of clusters defined by contiguous voxels with  $|t|>3.0$ , corrected  
288 to a false discovery rate of 5%. Peak voxel locations in MNI space were transformed to Talairach atlas  
289 coordinates using MNI2TAL (<http://bioimagesuite.yale.edu/mni2tal>) (Lacadie et al., 2008).

### Supplemental Figure 3. GM volume image from one subject



290 Total GM and total WM were modeled similarly, *i.e.* with diagnostic group, MRI sequence, and sex as  
291 factors, age at scan as a covariate, and interactions of group  $\times$  sex and sex  $\times$  age, but of course omitting the  
292 global volume correction, using R statistical software v. 3.1.2 (R Core Team, 2015; RStudio Team, 2014).  
293 Secondary analyses focused on the key findings from the SPM analyses. For each significant cluster from  
294 the SPM analyses of GM, the sum of each subject's GM volume over all voxels in that cluster was  
295 corrected for the subject's total brain volume (GM + WM) by division. The same was done for the  
296 significant WM clusters. These relative cluster volumes for each subject were the dependent variables to  
297 test for effects of scanner and sequence, ADHD, and IQ, either in the entire TS group or in the subjects  
298 scanned with sequence 3 from Supplemental Table 1.

299

## 300 **Authorship note**

301 Consortium investigators, collaborators and other study personnel include:

302 Bradley L. Schlaggar, Investigator, WUSTL,\* consortium co-chair; Kevin J. Black, Investigator, WUSTL,  
303 consortium co-chair; Deanna J. Greene, Investigator, WUSTL; Jessica A. Church, Collaborator, WUSTL,  
304 current affiliation University of Texas at Austin; Steven E. Petersen, Collaborator, WUSTL; Tamara  
305 Hershey, Collaborator, WUSTL; Deanna M. Barch, Collaborator, WUSTL; Joan L. Luby, Collaborator,  
306 WUSTL; Alton C. Williams, III, Study staff, WUSTL, medical student researcher, current affiliation  
307 MUSC; Jonathan M. Koller, Study staff, WUSTL, senior statistical data analyst; Matthew T. Perry, Study  
308 staff, WUSTL, postdoctoral research rotation; Emily C. Bihun, Study staff, WUSTL, site coordinator and  
309 psychiatric interviewer; Samantha A. Ranck, Study staff, WUSTL, psychiatric interviewer; Adriana  
310 Di Martino, Investigator, NYU; F. Xavier Castellanos, Investigator, NYU; Barbara J. Coffey, Investigator,  
311 NYU and Icahn Mount Sinai School of Medicine; Michael P. Milham, Investigator, NYU, current  
312 affiliation Child Mind Institute, New York, NY; Abigail Mengers, Study staff, NYU; Krishna  
313 Somandepalli, Study staff, NYU; Stewart H. Mostofsky, Investigator, KKI and JHU; Harvey S. Singer,  
314 Investigator, JHU; Carrie Nettles, Study staff, KKI; Daniel Peterson, Study staff, KKI; John Piacentini,  
315 Investigator, UCLA; Susan Y. Bookheimer, Investigator, UCLA; James T. McCracken, Investigator,  
316 UCLA; Susanna Chang, Investigator, UCLA; Adriana Galván, Investigator, UCLA; Kevin J. Terashima,  
317 Study staff, UCLA; Elizabeth R. Sowell, Investigator, University of Southern California and Children's  
318 Hospital Los Angeles.

319 \* WUSTL = Washington University in St. Louis. NYU = New York University. KKI = Kennedy Krieger  
320 Institute. JHU = Johns Hopkins University. UCLA = University of California, Los Angeles.

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335 The Tourette Syndrome Association Neuroimaging Consortium: A multi-site voxel-based morphometry  
336 study of Tourette syndrome. *J Neuropsychiatry Clin Neurosci* 27 (2): e190, 2015,  
337 doi: [10.1176/appi.neuropsych.272Abstracts](https://doi.org/10.1176/appi.neuropsych.272Abstracts)), and at the First World Congress on Tourette Syndrome &  
338 Tic Disorders, 25 June 2015 (Williams AC III, Greene DJ, Perry MT, Koller JM, Schlaggar BL, Black KJ,  
339 The Tourette Syndrome Neuroimaging Consortium: A pilot multicenter study of brain structure in  
340 pediatric Tourette syndrome, <http://eventmobi.com/tourette2015/documents/112809>, archived by  
341 WebCite<sup>®</sup> at <http://www.webcitation.org/6gLnEvFBT>).

## 342 **Conflict of interest**

343 The authors declare no conflicts of interest.

344

## 345 **Bibliography**

- 346 Alexander-Bloch, A., Clasen, L., Stockman, M., Ronan, L., Lalonde, F., Giedd, J., and Raznahan, A. (2016).  
347 Subtle in-scanner motion biases automated measurement of brain anatomy from in vivo MRI. *Hum*  
348 *Brain Mapp.* doi:10.1002/hbm.23180.
- 349 American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders*. 5th ed.  
350 Arlington, VA: American Psychiatric Association.
- 351 Atmaca, M., Yildirim, H., Ozdemir, H., Tezcan, E., and Poyraz, A. K. (2007). Volumetric MRI study of key

- 352 brain regions implicated in obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol*  
353 *Psychiatry* 31, 46–52. doi:10.1016/j.pnpbp.2006.06.008.
- 354 Barbas, H., Saha, S., Rempel-Clower, N., and Ghashghaei, T. (2003). Serial pathways from primate  
355 prefrontal cortex to autonomic areas may influence emotional expression. *BMC Neurosci* 4, 25.  
356 doi:10.1186/1471-2202-4-25.
- 357 Belluscio, B. A., Jin, L., Watters, V., Lee, T. H., and Hallett, M. (2011). Sensory sensitivity to external  
358 stimuli in Tourette syndrome patients. *Mov Disord* 26, 2538–2543. doi:10.1002/mds.23977.
- 359 Benarroch, E. E. (2015). Pulvinar: associative role in cortical function and clinical correlations. *Neurology*  
360 84, 738–747. doi:10.1212/WNL.0000000000001276.
- 361 Black, C. F., Hartlein, J. M., Hershey, T., Perlmutter, J. S., and Black, K. J. (2003). A voxel-based  
362 morphometry study of Tourette syndrome. *A voxel-based morphometry study of Tourette syndrome*  
363 (poster). Available at: <http://f1000research.com/posters/1092954> [Accessed February 27, 2016].
- 364 Black, K. D., Augustine, E. F., Adams, H. R., Lewin, A., Thatcher, A., Murphy, T., and Mink, J. W. (2014).  
365 Coprophenomena are associated with high clinical impact in Tourette syndrome [abstract FP26]. *J*  
366 *Int Child Neurol Assoc* 1, 12. Available at: <http://jicna.org/index.php/journal/article/view/19/12>.
- 367 Black, K. J. (2010). “Tics,” in *Encyclopedia of Movement Disorders*, eds. K. Kompolti and L. Verhagen  
368 Metman (Oxford: Elsevier (Academic Press)), 231–236. Available at:  
369 <http://dx.doi.org/10.1016/B978-0-12-374105-9.00385-3>.
- 370 Black, K. J., Snyder, A. Z., Koller, J. M., Gado, M. H., and Perlmutter, J. S. (2001). Template images for  
371 nonhuman primate neuroimaging: 1. Baboon. *Neuroimage* 14, 736–743.  
372 doi:10.1006/nimg.2001.0752.
- 373 Bloch, M. H., Leckman, J. F., Zhu, H., and Peterson, B. S. (2005). Caudate volumes in childhood predict  
374 symptom severity in adults with Tourette syndrome. *Neurology* 65, 1253–1258.  
375 doi:10.1212/01.wnl.0000180957.98702.69.
- 376 Castellanos, F. X., Giedd, J. N., Hamburger, S. D., Marsh, W. L., and Rapoport, J. L. (1996). Brain  
377 morphometry in Tourette’s syndrome: the influence of comorbid attention-deficit/hyperactivity  
378 disorder. *Neurology* 47, 1581–1583.
- 379 Cheng, B., Braass, H., Ganos, C., Treszl, A., Biermann-Ruben, K., Hummel, F. C., Müller-Vahl, K., Schnitzler,  
380 A., Gerloff, C., Münchau, A., et al. (2014). Altered intrahemispheric structural connectivity in Gilles  
381 de la Tourette syndrome. *Neuroimage Clin* 4, 174–181. doi:10.1016/j.nicl.2013.11.011.
- 382 Church, J. A., and Schlaggar, B. L. (2014). Pediatric Tourette syndrome: insights from recent neuroimaging  
383 studies. *J Obsessive Compuls Relat Disord* 3, 386–393. doi:10.1016/j.jocrd.2014.04.002.
- 384 Eapen, V., Snedden, C., Črnčec, R., Pick, A., and Sachdev, P. (2015). Tourette syndrome, co-morbidities  
385 and quality of life. *Aust N Z J Psychiatry*. doi:10.1177/0004867415594429.
- 386 Eddy, C. M., and Cavanna, A. E. (2014). Tourette syndrome and obsessive compulsive disorder:  
387 Compulsivity along the continuum. *J Obsessive Compuls Relat Disord* 3, 363–371.  
388 doi:10.1016/j.jocrd.2014.04.003.
- 389 Garraux, G., Goldfine, A., Bohlhalter, S., Lerner, A., Hanakawa, T., and Hallett, M. (2006). Increased  
390 midbrain gray matter in Tourette’s syndrome. *Ann Neurol* 59, 381–385. doi:10.1002/ana.20765.

- 391 Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., and Frackowiak, R. S. (2001). A  
392 voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14, 21–  
393 36. doi:10.1006/nimg.2001.0786.
- 394 Greene, D. J., Black, K. J., and Schlaggar, B. L. (2013). “Neurobiology and functional anatomy of tic  
395 disorders,” in *Tourette syndrome*, eds. D. Martino and J. F. Leckman (Oxford: Oxford University  
396 Press), 238–275. Available at: [http://global.oup.com/academic/product/tourette-syndrome-  
397 9780199796267](http://global.oup.com/academic/product/tourette-syndrome-9780199796267).
- 398 Grieve, K. L., Acuña, C., and Cudeiro, J. (2000). The primate pulvinar nuclei: vision and action. *Trends*  
399 *Neurosci* 23, 35–39.
- 400 Gurney, J., Olsen, T., Flavin, J., Ramaratnam, M., Archie, K., Ransford, J., Herrick, R., Wallace, L., Cline, J.,  
401 Horton, W., et al. (2015). The Washington University Central Neuroimaging Data Archive.  
402 *Neuroimage*. doi:10.1016/j.neuroimage.2015.09.060.
- 403 Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., and Conde, J. G. (2009). Research electronic  
404 data capture (REDCap)—a metadata-driven methodology and workflow process for providing  
405 translational research informatics support. *J Biomed Inform* 42, 377–381.  
406 doi:10.1016/j.jbi.2008.08.010.
- 407 Hoexter, M. Q., Diniz, J. B., Lopes, A. C., Batistuzzo, M. C., Shavitt, R. G., Dougherty, D. D., Duran, F. L. S.,  
408 Bressan, R. A., Busatto, G. F., Miguel, E. C., et al. (2015). Orbitofrontal thickness as a measure for  
409 treatment response prediction in obsessive-compulsive disorder. *Depress Anxiety* 32, 900–908.  
410 doi:10.1002/da.22380.
- 411 Kassubek, J., Juengling, F. D., and Ludolph, A. G. (2006). Heterogeneity of voxel-based morphometry  
412 findings in Tourette’s syndrome: an effect of age? *Ann Neurol* 59, 872–873. doi:10.1002/ana.20848.
- 413 Kim, J. J., Lee, M. C., Kim, J., Kim, I. Y., Kim, S. I., Han, M. H., Chang, K. H., and Kwon, J. S. (2001). Grey  
414 matter abnormalities in obsessive-compulsive disorder: statistical parametric mapping of  
415 segmented magnetic resonance images. *Br J Psychiatry* 179, 330–334.
- 416 Knutson, K. M., Dal Monte, O., Schintu, S., Wassermann, E. M., Raymont, V., Grafman, J., and Krueger, F.  
417 (2015). Areas of Brain Damage Underlying Increased Reports of Behavioral Disinhibition. *J*  
418 *Neuropsychiatry Clin Neurosci* 27, 193–198. doi:10.1176/appi.neuropsych.14060126.
- 419 Kurlan, R., Daragjati, C., Como, P. G., McDermott, M. P., Trinidad, K. S., Roddy, S., Brower, C. A., and  
420 Robertson, M. M. (1996). Non-obscene complex socially inappropriate behavior in Tourette’s  
421 syndrome. *J Neuropsychiatry Clin Neurosci* 8, 311–317. doi:10.1176/jnp.8.3.311.
- 422 Lacadie, C. M., Fulbright, R. K., Rajeevan, N., Constable, R. T., and Papademetris, X. (2008). More accurate  
423 Talairach coordinates for neuroimaging using non-linear registration. *Neuroimage* 42, 717–725.  
424 doi:10.1016/j.neuroimage.2008.04.240.
- 425 Leckman, J. F., Bloch, M. H., Sukhodolsky, D. G., Scahill, L., and King, R. A. (2013). “Phenomenology of tics  
426 and sensory urges: The self under siege,” in *Tourette Syndrome*, eds. D. Martino and J. F. Leckman  
427 (New York: Oxford University Press), 3–25.
- 428 Leckman, J. F., King, R. A., and Bloch, M. H. (2014). Clinical features of Tourette syndrome and tic  
429 disorders. *J Obsessive Compuls Relat Disord* 3, 372–379. doi:10.1016/j.jocrd.2014.03.004.
- 430 Ludolph, A. G., Juengling, F. D., Libal, G., Ludolph, A. C., Fegert, J. M., and Kassubek, J. (2006). Grey-

- 431 matter abnormalities in boys with Tourette syndrome: magnetic resonance imaging study using  
432 optimised voxel-based morphometry. *Br J Psychiatry* 188, 484–485. doi:10.1192/bjp.bp.105.008813.
- 433 Makki, M. I., Behen, M., Bhatt, A., Wilson, B., and Chugani, H. T. (2008). Microstructural abnormalities of  
434 striatum and thalamus in children with Tourette syndrome. *Mov Disord* 23, 2349–2356.  
435 doi:10.1002/mds.22264.
- 436 Makki, M. I., Govindan, R. M., Wilson, B. J., Behen, M. E., and Chugani, H. T. (2009). Altered fronto-  
437 striato-thalamic connectivity in children with Tourette syndrome assessed with diffusion tensor MRI  
438 and probabilistic fiber tracking. *J Child Neurol* 24, 669–678. doi:10.1177/0883073808327838.
- 439 Martino, D., and Leckman, J. F. eds. (2013). *Tourette syndrome*. Oxford: Oxford University Press.
- 440 Mechelli, A., Price, C. J., Friston, K. J., and Ashburner, J. (2005). Voxel-based morphometry of the human  
441 brain: Methods and applications. *Curr Med Imaging Rev* 1, 105–113. Available at:  
442 <http://dx.doi.org/10.2174/1573405054038726>.
- 443 Miller, A. M., Bansal, R., Hao, X., Sanchez-Pena, J. P., Sobel, L. J., Liu, J., Xu, D., Zhu, H., Chakravarty, M.  
444 M., Durkin, K., et al. (2010). Enlargement of thalamic nuclei in Tourette syndrome. *Arch Gen*  
445 *Psychiatry* 67, 955–964. doi:10.1001/archgenpsychiatry.2010.102.
- 446 Mink, J. W. (2006). Neurobiology of basal ganglia and Tourette syndrome: basal ganglia circuits and  
447 thalamocortical outputs. *Adv Neurol* 99, 89–98.
- 448 Moriarty, J., Varma, A. R., Stevens, J., Fish, M., Trimble, M. R., and Robertson, M. M. (1997). A volumetric  
449 MRI study of Gilles de la Tourette’s syndrome. *Neurology* 49, 410–415.
- 450 Müller-Vahl, K. R., Grosskreutz, J., Prell, T., Kaufmann, J., Bodammer, N., and Peschel, T. (2014). Tics are  
451 caused by alterations in prefrontal areas, thalamus and putamen, while changes in the cingulate  
452 gyrus reflect secondary compensatory mechanisms. *BMC Neurosci* 15, 6. doi:10.1186/1471-2202-15-  
453 6.
- 454 Müller-Vahl, K. R., Kaufmann, J., Grosskreutz, J., Dengler, R., Emrich, H. M., and Peschel, T. (2009).  
455 Prefrontal and anterior cingulate cortex abnormalities in Tourette Syndrome: evidence from voxel-  
456 based morphometry and magnetization transfer imaging. *BMC Neurosci* 10, 47. doi:10.1186/1471-  
457 2202-10-47.
- 458 Öngür, D., and Price, J. (2000). The organization of networks within the orbital and medial prefrontal  
459 cortex of rats, monkeys and humans. *Cereb Cortex* 10, 206–219. doi:10.1093/cercor/10.3.206.
- 460 Perantie, D. C., Koller, J. M., Weaver, P. M., Lugar, H. M., Black, K. J., White, N. H., and Hershey, T. (2011).  
461 Prospectively determined impact of type 1 diabetes on brain volume during development. *Diabetes*  
462 60, 3006–3014. doi:10.2337/db11-0589.
- 463 Peterson, B., Riddle, M. A., Cohen, D. J., Katz, L. D., Smith, J. C., Hardin, M. T., and Leckman, J. F. (1993).  
464 Reduced basal ganglia volumes in Tourette’s syndrome using three-dimensional reconstruction  
465 techniques from magnetic resonance images. *Neurology* 43, 941–949.
- 466 Peterson, B. S., Staib, L., Scahill, L., Zhang, H., Anderson, C., Leckman, J. F., Cohen, D. J., Gore, J. C., Albert,  
467 J., and Webster, R. (2001). Regional brain and ventricular volumes in Tourette syndrome. *Arch Gen*  
468 *Psychiatry* 58, 427–440.
- 469 Peterson, B. S., Thomas, P., Kane, M. J., Scahill, L., Zhang, H., Bronen, R., King, R. A., Leckman, J. F., and  
470 Staib, L. (2003). Basal Ganglia volumes in patients with Gilles de la Tourette syndrome. *Arch Gen*

- 471 *Psychiatry* 60, 415–424. doi:10.1001/archpsyc.60.4.415.
- 472 R Core Team (2015). *R: A language and environment for statistical computing*. Vienna, Austria: R  
473 Foundation for Statistical Computing Available at: <http://www.R-project.org/> [Accessed March 4,  
474 2016].
- 475 Reuter, M., Tisdall, M. D., Qureshi, A., Buckner, R. L., van der Kouwe, A. J. W., and Fischl, B. (2015). Head  
476 motion during MRI acquisition reduces gray matter volume and thickness estimates. *Neuroimage*  
477 107, 107–115. doi:10.1016/j.neuroimage.2014.12.006.
- 478 Roessner, V., Overlack, S., Baudewig, J., Dechent, P., Rothenberger, A., and Helms, G. (2009). No brain  
479 structure abnormalities in boys with Tourette’s syndrome: a voxel-based morphometry study. *Mov*  
480 *Disord* 24, 2398–2403. doi:10.1002/mds.22847.
- 481 Roessner, V., Overlack, S., Schmidt-Samoa, C., Baudewig, J., Dechent, P., Rothenberger, A., and Helms, G.  
482 (2011). Increased putamen and callosal motor subregion in treatment-naïve boys with Tourette  
483 syndrome indicates changes in the bihemispheric motor network. *J Child Psychol Psychiatry* 52, 306–  
484 314. doi:10.1111/j.1469-7610.2010.02324.x.
- 485 RStudio Team (2014). *RStudio: Integrated Development for R*. Boston, MA: RStudio, Inc. Available at:  
486 <http://www.rstudio.com/> [Accessed March 4, 2016].
- 487 Schunke, O., Grashorn, W., Kahl, U., Schöttle, D., Haggard, P., Münchau, A., Bingel, U., and Ganos, C.  
488 (2016). Quantitative Sensory Testing in adults with Tourette syndrome. *Parkinsonism Relat Disord*  
489 24, 132–136. doi:10.1016/j.parkreldis.2016.01.006.
- 490 Shipp, S. (2004). The brain circuitry of attention. *Trends Cogn Sci (Regul Ed)* 8, 223–230.  
491 doi:10.1016/j.tics.2004.03.004.
- 492 Shipp, S. (2003). The functional logic of cortico-pulvinar connections. *Philos Trans R Soc Lond, B, Biol Sci*  
493 358, 1605–1624. doi:10.1098/rstb.2002.1213.
- 494 Swerdlow, N. R., and Young, A. B. (2001). Neuropathology in Tourette syndrome: an update. *Adv Neurol*  
495 85, 151–161.
- 496 Valente, A. A., Miguel, E. C., Castro, C. C., Amaro, E., Duran, F. L. S., Buchpiguel, C. A., Chitnis, X., McGuire,  
497 P. K., and Busatto, G. F. (2005). Regional gray matter abnormalities in obsessive-compulsive  
498 disorder: a voxel-based morphometry study. *Biol Psychiatry* 58, 479–487.  
499 doi:10.1016/j.biopsych.2005.04.021.
- 500 Wang, L., Lee, D. Y., Bailey, E., Hartlein, J. M., Gado, M. H., Miller, M. I., and Black, K. J. (2007). Validity of  
501 large-deformation high dimensional brain mapping of the basal ganglia in adults with Tourette  
502 syndrome. *Psychiatry Res* 154, 181–190. doi:10.1016/j.psychresns.2006.08.006.
- 503 Whiteside, S. P., Port, J. D., and Abramowitz, J. S. (2004). A meta-analysis of functional neuroimaging in  
504 obsessive-compulsive disorder. *Psychiatry Res* 132, 69–79. doi:10.1016/j.psychresns.2004.07.001.
- 505 Wilke, M., Holland, S. K., Altaye, M., and Gaser, C. (2008). Template-O-Matic: a toolbox for creating  
506 customized pediatric templates. *Neuroimage* 41, 903–913. doi:10.1016/j.neuroimage.2008.02.056.
- 507 Williams, A. C., McNeely, M. E., Greene, D. J., Church, J. A., Warren, S. L., Hartlein, J. M., Schlaggar, B. L.,  
508 Black, K. J., and Wang, L. (2013). A pilot study of basal ganglia and thalamus structure by high  
509 dimensional mapping in children with Tourette syndrome. [version 1; referees: 2 approved].  
510 *F1000Res* 2, 207. doi:10.12688/f1000research.2-207.v1.

- 511 Wittfoth, M., Bornmann, S., Peschel, T., Grosskreutz, J., Glahn, A., Buddensiek, N., Becker, H., Dengler, R.,  
512 and Müller-Vahl, K. R. (2012). Lateral frontal cortex volume reduction in Tourette syndrome  
513 revealed by VBM. *BMC Neurosci* 13, 17. doi:10.1186/1471-2202-13-17.
- 514 Zimmerman, A. M., Abrams, M. T., Giuliano, J. D., Denckla, M. B., and Singer, H. S. (2000). Subcortical  
515 volumes in girls with Tourette syndrome: support for a gender effect. *Neurology* 54, 2224–2229.