





Magnetic resonance imaging demonstrates gyral abnormalities in Tourette syndrome

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Abstract

Tourette syndrome (TS) is a neurological disorder characterized by involuntary and repetitive movements known as tics. A retrospective analysis of magnetic resonance imaging (MRI) scans from 39 children and adolescents with TS was performed and subsequently compared with MRI scans from 834 neurotypical controls. The purpose of this study was to identify any differences in the regions of motor circuitry in TS to further our understanding of their disturbances in motor control (i.e., motor tics). Measures of volume, cortical thickness, surface area, and surface curvature for specific motor regions were derived from each MRI scan. The results revealed increased surface curvature in the opercular part of the inferior frontal gyrus and the triangular part of the inferior frontal gyrus in the TS group compared with the neurotypical control group. These novel findings offer some of the first evidence for surface curvature differences in motor circuitry regions in TS, which may be associated with known motor and vocal tics.

KEYWORDS

cortex neuroanatomy, magnetic resonance imaging, motor, Tourette syndrome

Abbreviations: ADHD, attention deficit hyperactivity disorder; AUC ROC, area under the receiver operating characteristic curve; BA, Brodmann's area; BCH, Boston Children's Hospital; CD, conversion disorder; CSPTC, cortico-striato-pallidal-thalamo-cortical; CT, cortical thickness; *d*, Cohen's *d* statistic; DSM, Diagnostic and Statistical Manual; L, left; M1, right precentral gyrus; MRI, magnetic resonance imaging; OCB, obsessive compulsive behavior; PD, Parkinson's disease; R, right; ROIs, regions of interest; SMA, supplementary motor area; TS, Tourette syndrome.

1 | INTRODUCTION

Tourette syndrome (TS) was first described in 1885 by Georges Gilles de la Tourette, who reported nine patients with motor tics (Jankovic & Rohaidy, 1987). A diagnosis of TS, based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, requires the presence of multiple motor and vocal tics lasting at least a year (Segal, 2010). Common comorbid conditions include attention deficit hyperactivity disorder (ADHD), obsessive compulsive behavior (OCB), self-injurious behavior, anxiety, depression, and personality disorder (Robertson, 2000). TS has a prevalence of 0.05% to 3% worldwide and is approximately four times more common in males for reasons that are still unclear (Freeman et al., 2000). TS is a genetic disorder with an unclear inheritance pattern (Robertson, 2000). Environmental influences such as perinatal factors (e.g., birth injuries), infections and viruses have been shown to possibly affect the expression of TS (Robertson, 2000).

Magnetic resonance imaging (MRI) provides accurate anatomical images of the brain without the use of ionizing radiation (Giedd, 2004) and offers researchers a way to better understand neurological disorders such as autism spectrum disorder and TS. MR images can be analyzed, and its data can be quantified using complex computer programs. FreeSurfer is a post-processing automated quantification technique that provides a range of algorithms to quantify various properties of the brain (e.g., functional, connective, and structural) (Fischl, 2012). It provides extensive analysis of key features of the human brain by creating models of macroscopically visible structures in the brain when provided with an MRI examination. This technology can provide quantitative numerical data for a variety of brain measurements such as brain volume, cortical thickness, surface area, and surface curvature.

Previous MRI studies have investigated patients with TS in order to determine the location of brain abnormalities potentially associated with the condition. These studies have looked mostly at measures of volume and cortical thickness, without consideration of biomarker measurements such as surface area and surface curvature. The most common focus for investigation, and correspondingly, the most commonly reported findings, have been focused in the basal ganglia, with the understanding that it is dysfunctional in TS (Peterson et al., 1993). The basal ganglia are involved in the selection and integration of voluntary behavior (Yin & Knowlton, 2006) and primarily responsible for motor control (Lanciego et al., 2012). TS is recognized as a movement disorder, as is Parkinson's disease (PD) and Huntington's disease, in which the basal ganglia has been

implicated. Furthermore, treatments for motor tics often block the dopamine receptors within the basal ganglia, and electrochemical manipulation and lesions of the basal ganglia have been linked to the development of tics or increased severity of tic symptoms (Baldwin et al., 1954; Kelley et al., 1988). Study findings have reported reductions in the volume of the caudate nucleus across all age groups in TS, and reductions in the volume of the lentiform nuclei (i.e., putamen and globus pallidus nuclei) in adults with TS (Peterson et al., 2003). The finding of reduced caudate nucleus volumes is consistent with previous findings in a functional MRI study of tic suppression (Peterson et al., 1993), which suggests that the primary disturbance in the cortico-striato-pallidal-thalamo-cortical (CSPTC) circuits is centered around the projections in and out of the caudate nucleus. This finding is also consistent with a study of monozygotic twins that found that caudate nucleus volumes were smaller in the more severely affected twin (Hyde et al., 1995). These results suggest that reduced caudate nucleus volumes may be related to non-genetic determinants in predisposed individuals. Thus, reduced caudate nucleus volumes suggest basal ganglia abnormalities in TS, and caudate nucleus abnormalities may also be a good biomarker for individuals with TS.

Research studies on TS have tended to focus on the basal ganglia portions of the CSPTC circuits. Consequently, sensorimotor cortices in these circuits have often been overlooked. Sowell et al. (2008) addressed this concern by conducting a study that investigated the cortical thickness of frontal and parietal lobes in children with TS. Results showed that children with TS had decreased cortical thickness in the ventral frontal regions, including the precentral gyrus, postcentral gyrus, and inferior frontal gyrus and in more posterior regions such as the right dorsal parietal cortex. In older children and adolescents with TS, cortical thinning in the lateral temporal and inferior parietal cortices, including the inferior primary sensory cortex, was also observed. The study also identified correlations between cortical thinning of the dorsal regions of the sensorimotor cortices and tic severity and between cortical thinning of ventral portions of the sensorimotor cortex and the number of simple facial tics.

To the best of our knowledge, there are no studies that have investigated how differences in surface area or surface curvature in motor areas of the brain might present in individuals with TS, who were diagnosed based on the presence of motor tics. Therefore, the aim of this study is to investigate the presentation of surface area and curvature of the brain regionally, in TS. Previous MRI studies have shown that brain volume, cortical thickness, surface area, and surface curvature may be altered in areas of motor circuitry in various populations

who have movement deficits (e.g., reduced thalamic volumes in motor conversion disorder) (Nicholson et al., 2014). This gives us reason to believe that the motor tics that are often reported in TS may be reflected in brain differences in measures such as volume, cortical thickness, surface area, and surface curvature. The purpose of the present study is to analyze MRI data collected from a sample of children with TS who present with motor tics to identify brain abnormalities in the motor circuitry specifically. Moreover, our findings have the potential to further elucidate our understanding of motor control abnormalities associated with the condition (e.g., motor tics such as blinking, nose twitching, head jerking, sniffing, throat clearing, head shaking, scratching, hitting, and speaking), identify regional motor-related abnormalities not detected in previous studies, as well as clinically validate findings observed in previous research (Albin & Mink, 2006; Peterson et al., 2003; Singer et al., 1993; Sowell et al., 2008). We hypothesize that there will be regional brain differences (i.e., increases or decreases) in motor regions in terms of volume, cortical thickness, surface area, and/or surface curvature in the group with TS compared with a neurotypical cohort.

2 | MATERIALS AND METHODS

2.1 | Participants

Following approval by Boston Children's Hospital's (BCH) Institutional Review Board (informed consent was waived because of the lack of risk to participants in this retrospective analysis), the clinical imaging electronic database at BCH was reviewed from 01/01/2008 until 02/24/2016. All brain MRI examinations of participants were included in the analysis if TS was indicated in the participant's electronic medical records. Images judged to be of low quality (due to excessive participant motion, large metal artifact from participant's dental hardware, lack of a T1 structural imaging volume providing diagnostically useful axial, sagittal, and coronal oriented images, etc.) were excluded from the analysis. Images inaccessible for technical reasons were also excluded. The assessment yielded 58 brain MRI examinations from

39 participants with TS. The participants ranged from the ages of 2.4 to 17.5 years, with an average age of 10.5 years and a male to female ratio of 34 to 5 participants. Neurotypical participants were collected retrospectively in a previous analysis (Levman et al., 2017). Participants were selected based on a normal MRI examination (assessed by a BCH neuroradiologist) and medical records providing no indication of any neurological problems. Participants with any known disorder were excluded (e.g., autism, cerebral palsy, traumatic brain injury, developmental delay, tuberous sclerosis complex, stroke, neurofibromatosis, epilepsy, and ADHD). Participants with any form of cancer were also excluded in order to avoid data exhibiting growth trajectories that are affected by treatments such as chemotherapy. The same exclusion criteria applied to the TS population was also applied to healthy controls. The neurotypical participants' ages ranged from 0 to 32 years old. This yielded 993 examinations. For the purpose of our study, only neurotypical participants of the same age range as participants with TS were included in the analysis, yielding an average age of 11.2 years and a male to female ratio of 334 to 500 participants. Demographic information on participants is presented in Table 1.

2.2 | MRI data acquisition and preprocessing

Participants were imaged with clinical 3 Tesla MRI scanners (Skyra, Siemens Medical Systems, Erlangen, Germany) at BCH. Examinations with two-dimensional slices not consecutively aligned next to each other were excluded. This yielded T1 structural volumetric imaging examinations accessible through the Children's Research and Integration System (Pienaar et al., 2014). The clinical and retrospective nature of this study resulted in variability in the pulse sequences employed to acquire these volumetric T1 images. A single volumetric MRI was acquired from each imaging session. However, some patients returned for multiple MRI examinations (different imaging sessions) which were included in this study. Although motion correction was not performed, visual assessment was used to exclude examinations with substantial motion artifacts. At BCH, up to three structural

TABLE 1 Demographic information on study participants

Demographic measures and comparative statistics	2.4–7.4 years	7.4–12.4 years	12.4–17.5 years
TS male/female count	7/0	15/5	12/0
Healthy male/female count	90/92	130/180	114/228

MRI examinations are performed per imaging session to compensate for image acquisition challenges, one of which was selected for this study based on image quality. T1 structural examinations were processed by FreeSurfer (Fischl, 2012). If FreeSurfer results substantially failed, they were excluded from the analysis (e.g., FreeSurfer regions of interest [ROIs] that did not align to the MRI and major problems observed with an ROI such as cerebellar segmentation extending far beyond the cerebellum). All brain regions examined were motor regions and included the posterior parietal cortex, premotor cortex, supplementary motor area (SMA), M1, cerebellum, basal ganglia (i.e., caudate, putamen, and pallidum), Broca's area, and primary somatosensory cortex.

2.3 | Statistical analysis

This study included the acquisition of 2893 measurements (cortical thickness, volume, surface area, and surface curvature measurements) for each structural brain MRI examination, as extracted by FreeSurfer (Fischl, 2012). Participants were divided into three age groups: early childhood (2.4–7.4 years old), late childhood (7.4–12.4 years old), and adolescence (12.4–17.5 years). Each type of biomarker measurement considered were evaluated in the following motor regions: the posterior parietal cortex, premotor cortex, SMA, M1, cerebellum, basal ganglia (i.e., caudate, putamen, pallidum), Broca's area, and primary somatosensory cortex. All statistical analyses were performed in MATLAB (R2018a, Natick, MA, USA). Statistical significance was set at $p < 0.05$ adjusted using the Benjamini–Hochberg correction to correct for the effect of performing multiple comparisons and to minimize the false discovery rate (Benjamini & Hochberg, 1995). Statistical testing using

the standard t test (Student, 1908) was used to compare the two groups of samples. To assess effect sizes of all considered biomarkers, Cohen's d statistic (positive/negative values indicate higher/lower average values in the TS population compared with the neurotypical population) was computed in a group-wise manner comparing healthy and TS participants in each age range. We chose to use Cohen's d statistic because it is the most established method to assess effect size. To assess the diagnostic potential of each biomarker, an area under the receiver operating characteristic curve (AUC ROC) analysis was performed for each measurement (Youngstrom, 2014). A multivariable regression model was created to control for secondary effects and is described in the Supporting Information.

3 | RESULTS

Many brain regions demonstrated Benjamini–Hochberg corrected, statistically significant differences in surface curvature and volumetric measurements between participants with TS and neurotypical controls. Leading surface curvature measurements are summarized in Table 2, and leading volume measurements are summarized in Table 3. For ease of comparison, all age groupings and left and right hemisphere results (when available) are presented in Tables 2 and 3, with at least one age group presenting statistically significant differences. The differences in regions identified in Tables 2 and 3 have the potential to be associated with motor tics in TS, as is addressed in detail in Section 4.

The results indicated various measurements that may aid in understanding the clinical anatomical presentation of the brain in TS. When compared with the neurotypical controls, the participants with TS demonstrated

TABLE 2 Age-dependent analysis—leading surface curvature measurements sorted by effect size (Cohen's d statistic)

Region name	Ages 2.40–7.42 years			Ages 7.42–12.44 years			Ages 12.44–17.46		
	p value	Cohen's d	AUC ROC	p value	Cohen's d	AUC ROC	p value	Cohen's d	AUC ROC
Pars triangularis GausCurve (right)	4.82E-08	2.0291	0.7582	0.2179	0.2614	0.6862	0.8341	−0.0537	0.4308
Pars opercularis GausCurve (right)	1.19E-07	1.9730	0.6668	0.8494	−0.0403	0.3460	0.6004	−0.1342	0.5090
Pars triangularis FoldInd (right)	0.8937	0.0517	0.6754	0.7886	0.0569	0.5677	5.21E-07	1.2638	0.5989
Pars opercularis CurveInd (left)	0.9243	0.0367	0.6421	0.0337	0.4493	0.6990	3.53E-04	0.9076	0.7027

Note: Bolded entries indicate statistically significant differences between TS and control groups with $p < 0.05$ adjusted using the Benjamini–Hochberg correction. GausCurve = Gaussian Curvature, FoldInd = Folding Index, CurveInd = Curvature Index, all computed by FreeSurfer (Fischl, 2012).

TABLE 3 Age-dependent analysis—leading volumetric measurements sorted by effect size (Cohen's *d* statistic)

Region name	Ages 2.40–7.42 years			Ages 7.42–12.44 years			Ages 12.44–17.46		
	<i>p</i> value	Cohen's <i>d</i>	AUC ROC	<i>p</i> value	Cohen's <i>d</i>	AUC ROC	<i>p</i> value	Cohen's <i>d</i>	AUC ROC
Cerebellum cortex (right)	0.3501	0.3609	0.6154	0.4438	0.1626	0.5510	0.0001	0.9763	0.7707
Cerebellum cortex (left)	0.3565	0.3562	0.6122	0.4805	0.1497	0.5466	0.0005	0.8876	0.7635
BA6 gray (left)	0.3752	−0.3425	0.6244	0.4311	0.1671	0.5513	0.0011	0.8277	0.7489
Precentral gyrus gray (right)	0.5779	0.2151	0.5675	0.5635	−0.1226	0.5329	0.0017	0.8006	0.7233
Pallidum (right)	0.3056	0.3956	0.6209	0.0009	0.6996	0.6880	0.5868	0.1393	0.5619
Pallidum (left)	0.4864	0.2690	0.6221	0.0021	0.6482	0.6884	0.2551	0.2914	0.6137

Note: Bolded entries indicate statistically significant differences between TS and control groups with $p < 0.05$ adjusted using the Benjamini–Hochberg correction.

statistically significantly greater surface curvature measurements in the triangular part of the inferior frontal gyrus (pars triangularis) ($d = 2.029$) and the opercular part of the inferior frontal gyrus (pars opercularis) ($d = 1.973$). Statistically significantly greater absolute volumes in the participants with TS, compared with neurotypical controls, were also found in the left (L) and right (R) cerebellar cortex (L: $d = 0.888$, R: $d = 0.976$), the left Brodmann's area (BA) 6 ($d = 0.828$), the right precentral gyrus ($d = 0.801$), and the left and right pallidum (L: $d = 0.648$, R: $d = 0.700$). No statistically significant differences were identified for surface area or cortical thickness measurements.

4 | DISCUSSION

The purpose of the current study was to analyze brain MRI data in an effort to identify differences in regions of motor circuitry between children with TS and neurotypical controls. To confirm previous findings, we investigated brain volume and cortical thickness. In addition, we investigated surface area and surface curvature measurements which have been absent in the literature examining TS. To the best of our knowledge, our study is the first to report increased surface curvature measurements in the pars opercularis and the pars triangularis. These brain regions correspond to BA 45 and BA 44, respectively, and together form Broca's area. We also observed increased volume in the right and left cerebellar cortex, the right and left pallidum, the left BA 6 (i.e., the premotor cortex and SMA), and the right precentral gyrus (i.e., M1) in the TS group. Structural abnormalities in these regions may contribute to the motor and vocal tics associated with TS. It should be noted that a large-scale

meta-analysis of patients with schizophrenia, bipolar disorder, depression, addiction, obsessive–compulsive disorder, and anxiety reported consistent gray matter decreases in the operculum (Goodkind et al., 2015), the same region affected by our observed primary findings of surface curvature abnormalities.

The results from our study indicated a statistically significant difference in surface curvature in our TS cohort when compared with a neurotypical group. More specifically, the TS group displayed increased surface curvature in the pars opercularis and the pars triangularis; together, they make up Broca's area. Broca's area is important for speech production (Papoutsis et al., 2009). More specifically, Broca's area plays a role in resolving competing interactions during language production as word selection is determined by choosing the word with the highest level of activation compared with other activated words (Schnur et al., 2009). Schnur et al. (2009) suggested that damage to Broca's area may give rise to the hesitant multiword speech evident in those with Broca's aphasia. It is possible that our abnormal surface curvature findings in TS are associated with vocal tics prevalent in the condition. From a developmental neuroscience perspective, it is possible that surface curvature abnormalities may be the result pruning irregularities, with pruning near the surface of the cortex resulting in tissue removal, which potentially directly affects measurements of curvature on the surface of the recently pruned tissue.

Surface curvature abnormalities in Broca's area appear most prominent in the right hemisphere of our TS participants. Although the left hemisphere is typically thought of as the superior language processor, current evidence suggests that the right hemisphere also plays a significant role in language processing

(Lindell, 2006). Research suggests that the right hemisphere plays a greater role in involuntary or nonpropositional speech that does not require the generation or processing of new ideas (e.g., counting and reciting days of the week) (Lindell, 2006). Given the involuntary nature of vocal tics, one may classify the tics as a form of nonpropositional speech potentially associated with abnormalities of the right hemisphere of Broca's area in patients with TS.

Due to the retrospective clinical and complete cross sectional design of this experiment, there was an imbalance in the ratio of males to females in the TS and neurotypical cohorts. A multivariable regression model was employed (see Supporting Information) to control for the effects of age and gender, which revealed lower *p* values for the MVR model adjusted comparisons, implying that age and gender are not likely to be the cause of our primary findings. Additionally, it should be noted that the previously studied neurotypical cohort (Levman et al., 2017) did not exhibit statistically significant gender-based differences in the primary surface curvature measurements (Levman et al., 2017) being reported on in this study, further implying that our primary findings are not the result of gender differences.

We performed a retrospective MRI study investigating volume, surface curvature, surface area, and cortical thickness in children with TS. Our main finding is the increased surface curvature in Broca's area in children with TS, which has yet to be reported in the literature. We also observed increased volumes in the cerebellar cortex, pallidum, premotor cortex, SMA, and M1 in children with TS. These findings confirm that structural abnormalities are present in the motor circuitry of children with TS, are detectable clinically, and may contribute to the production of motor tics. Additional discussion of our extensive findings is available in the Supporting Information. Our volumetric findings support the hypothesis that the CSPTC circuits are abnormal in TS and suggest that the cortex (i.e., premotor cortex, SMA, and M1) and the pallidum may be the brain regions exhibiting the largest differences in TS relative to neurotypical patients. Abnormalities of these regions may be a major factor in the production of motor tics. We did not identify any brain differences with respect to cortical thickness or surface area. Future studies should be conducted controlling for comorbidities and medication states in order to increase the validity of literature findings. Furthermore, future studies should obtain increased patient information such as tic severity and frequency in order to help identify a more direct relationship between structural brain abnormalities and motor tics in TS. Finally, future studies could assess the regions identified herein for their potential involvement in non-TS tic disorders.

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CONFLICT OF INTEREST

JL is the owner of Time Will Tell Technologies, Inc. The authors have no relevant conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Conception of the study: Jacob Levman, Bernadette McCann, and Emi Takahashi. *Data collection:* Jacob Levman and Emi Takahashi. *Analysis:* Jacob Levman, Bernadette McCann, Tadashi Shiohama, Emi Takahashi, and Melanie Lam. *Manuscript editing:* Jacob Levman, Bernadette McCann, Tadashi Shiohama, Emi Takahashi, and Melanie Lam. *Software analytics:* Prahar Ijner. *Supervision:* Jacob Levman, Emi Takahashi, and Melanie Lam.

DATA AVAILABILITY STATEMENT

The data used in this analysis are from Boston Children's Hospital and are not publicly available.

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