Cortical thickness in provisional and chronic tic disorder

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Abstract

Background: Structural MRI studies have found thinner cortex in Tourette syndrome (TS) than in tic-free controls (TFC) in several cortical regions. Whether this thinning precedes or follows the first tic is unknown. Cortical thickness has not been reported in patients with a tic disorder less than one year in duration (Provisional Tic Disorder, PTD).

Objectives: Compare regional cortical thickness in TS, PTD and TFC.

Methods: T1-weighted brain MRI was acquired in 391 children 5-10 years old: 83 with PTD, 103 with TS, and 205 TFC. FreeSurfer measured cortical thickness in 34 cortical regions in each hemisphere. An ANCOVA compared regional cortical thickness between groups, controlling for age, sex, handedness and intracranial volume and correcting for multiple comparisons with Holm's method.

Results: Brain volume and mean cortical thickness differed significantly among groups (TS < PTD < TFC). That pattern was observed in 34 of 68 cortical regions, including in the subset of highest quality images acquired with prospective motion correction. The typical developmental cortical thinning from age 5.0-11.0 occurred 2–3 times faster in the tic groups. Predicted cortical thickness in the PTD group at tic onset was identical to that of the TFC group, but diminished over the first year to match the TS group at one year after tic onset.

Conclusion: These data from one of the largest imaging studies of tic disorders suggest that the thinner cortex in TS develops after rather than before tics begin. As such, it is

more likely to represent a consequence rather than a cause of tics. We hypothesize that it may reflect earlier maturation of inhibitory circuits because of extended experience suppressing tics.

Introduction

Tourette syndrome and chronic motor or phonic tic disorder (hereinafter, TS) are defined by unwanted, repeated movements and vocalizations (tics) that collectively occur over a period of a year or more without another cause.[1] Tics differ from other movement disorders phenomena in that they are relatively stereotyped but nonrhythmic, can be suppressed with effort for a period of time, and are often preceded by focal or generalized sensory phenomena or an urge to tic.[2]

In vivo structural MRI studies have found thinner precentral and/or postcentral gyrus in TS than in tic-free controls (TFC).[3-8] These gyri contain primary motor cortex (M1) and primary somatosensory cortex (S1). This finding has been taken as supporting a model of tic disorders as characterized by hyperarousal, deficits in sensorimotor gating, and impaired cortical inhibition.[9] However, results were not consistent,[10] and most studies were relatively small. Other cortical regions showing thinning in structural MRI studies of TS include insula and orbital cortex.[11]

Crucially, whether cortical thinning represents a cause or an effect of ticcing is unknown. Chronic ticcing or adaptation to chronic ticcing could result in structural changes to cortical regions.[12] Cortical thinning present when tics begin, or shortly afterwards, would support the interpretation that it contributes to causing tics. To date, however, cortical thickness has not yet been reported in Provisional Tic Disorder (PTD, defined as current tics with no tics present a year or more ago).

To investigate this question, we examined structural MRI data from the New Tics study,[13]

supplemented with data from additional TS and TFC scans on the same MRI scanners. We hypothesized that both TS and PTD would have thinner somatomotor cortex than TFC at the same age.

Methods

MR images from a total of 391 children were analyzed for this study: 83 with PTD, 103 with TS and 205 TFC. A parent or guardian gave informed consent to each child's participation in research. All children with PTD, along with 43 with TS and 26 TFC, were enrolled in the New Tics study. Others had previously given permission to share data with future research studies. For this analysis, diagnosis for all tic patients followed DSM-5 criteria[1] and was confirmed by an experienced Tourette clinician (authors KJB or BLS).

All participants had a T1-weighted MRI of the brain (MP-RAGE sequence) on either a Siemens Trio or Prisma scanner with 0.5-1.0 mm^3 voxels. Sequence details varied, and 217 scans were performed with prospective motion correction (vNavs) to minimize partial volume effect from head motion during scan acquisition (see Supplemental Table A).[14, 15]

If a participant had more than one MP-RAGE image at a given session, the image with the highest *snr_total* value according to MRIQC was used in the analysis.[16] FreeSurfer v. 7.3.2 was used to measure thickness of 34 cortical regions in each hemisphere and to estimate brain volume (eTIV).[17-19] The cortical parcellation by FreeSurfer was visually reviewed for all subjects (original N = 409), and 18 scans with incorrect identification of the cortical ribbon were excluded.

Whole-brain effects of diagnosis were tested by a general linear model (hereinafter GLM) controlling for age, sex, handedness, and scanner. This analysis was done with estimated intracranial volume (eTIV) as the dependent variable, but to ensure robustness, it was repeated with eTIV replaced by mean cortical thickness and by total gray plus white matter volume (GM+WM).

Based on prior studies, we specified one *a priori* regional hypothesis; namely, that sensorimotor cortex would be thinner in children with tics. We tested this hypothesis by defining M1S1 in each participant as the average of bilateral mean precentral thickness (M1) and bilateral mean postcentral thickness (S1). An ANCOVA compared M1S1 between groups, controlling for age, sex, handedness and eTIV.

We also examined all 34 cortical regions in each hemisphere, with a GLM controlling for age, sex, handedness, scanner and eTIV. The effect of interest was a trend TS < PTD < TFC or in the opposite direction. Multiple comparisons correction used Holm's method with a family-wise Type I error (FWE) rate of .05 as the criterion for significance.[20]

Exploratory analyses included the following. Cortical thickness in regions with a significant diagnosis-related trend was tested for correlation with YGTSS total tic score (TTS), available for $N = 202$, after accounting for age and sex. After predicting cortical thickness in significant regions based on the age and sex of the child using the ANCOVA model in the TFC group, the prediction error for children with tics (observed – predicted) was plotted against duration of illness (measured as days between tic onset and the scan), available for $N = 157$ including all PTD participants. The date of tic onset was estimated

carefully as described in detail elsewhere.[21] We also tested for correlations of regional thickness among cortical regions. Finally, we used a principal components analysis (PCA) and a support vector machine (SVM) approach to assess how much diagnosis-related information was contained in the collection of all regional data, beyond what can be explained by effects in any single cortical region. The SVM included all the regional cortical thickness data in addition to age, sex, handedness, scanner and eTIV.

Results

Effects of age, sex, handedness and scanner

Brain volume showed essentially the same results whether measured with eTIV or GM+WM. Older children have larger brains, boys have larger brains, and brain volume was smaller in scans from the Trio than in the prospective motion-corrected Prisma scans. As for mean cortical thickness, older children have thinner cortex ($p = 3.7 \times 10^{-8}$) and boys have thinner cortex than girls ($p = .0003$). Handedness, scanner, and the age × sex interaction were not statistically significant.

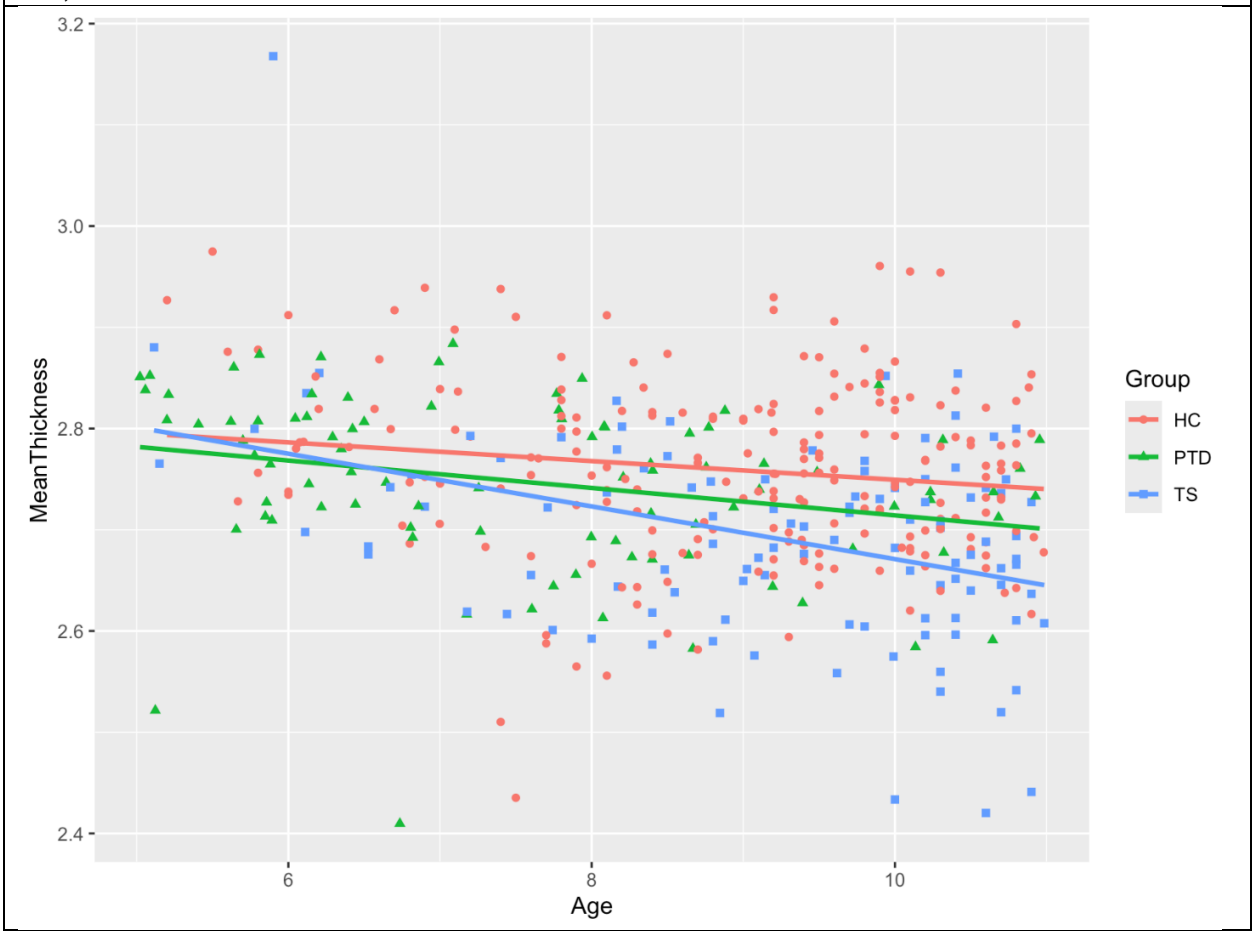
Global effects of diagnosis

Controlling for age, sex, handedness and scanner, whole brain volume differed significantly by diagnosis (TS < PTD < TFC, $p < .00001$). Post-hoc comparisons found TS < TFC $p = .0001$, PTD < TFC, $p = .09$. For eTIV, factor and covariate p values included PTD diagnosis .0016, TS diagnosis .0001, age 1.6×10^{-7}, sex 4.5×10^{-22}, handedness .09, and scanner 9.0×10^{-6}. Results were roughly similar for total gray and white matter volume, including PTD diagnosis $p = .0070$, TS diagnosis $p = 2.6 \times 10^{-5}$.

Mean left or right cortical thickness also differed significantly by diagnosis (TS < PTD < TS), controlling for age, sex, handedness and scanner, whether or not eTIV was included as an additional covariate (left, p = .08 for PTD, .0001 for TS; right, .10 for PTD, .0001 for TS). Mean left hemisphere cortex was about 1.4% thinner in TS (mean 2.87 mm) than in TFC (mean 2.91 mm), with PTD intermediate (mean 2.89 mm), only 0.6% thinner than in TFC.

All three groups had similar cortical thickness at age 5, but children with tics experienced faster cortical thinning than those without the tics. The slopes of cortical thinning as the children grow older are ranked TS < PTD < TFC < zero (Figure 1). The slope seen in typical development is nearly doubled in PTD and tripled in TS. This result still holds when sex, handedness and eTIV are included in the model.

Figure 1. Mean whole-brain cortical thickness decreases with age from 5 to < 11 years old, and does so faster in children with tics.



A priori hypothesis

Controlling for age, sex, handedness, scanner and brain volume, M1S1 differed significantly among groups (p<.0001). It is smaller in TS than in controls (LSE = –.05, p=.0003), and nonsignificantly smaller in PTD (least squares difference LSE = –.01, p=.36 vs TFC). The difference is all explained by precentral gyrus (M1), p_{FWE} = .0116 left, NS right; postcentral gyrus did not differ significantly.

Whole-cortex analysis

Numerous cortical regions showed diagnosis-related differences in thickness, correcting for age, sex, handedness, scanner and brain volume (Table 1). All were thinner in TS than in PTD and TFC.

Table 1. FWE-corrected *p* values for cortical regions with a TS < PTD < TFC trend.
LHem = left hemisphere. RHem = right hemisphere. ".0000" means <.00005.

region	*p* (LHem)	*p* (RHem)
caudal middle frontal	.0000	.0009
pars opercularis	.0001	.0054
banks of superior temporal sulcus	.0001	
superior temporal	.0001	.0001
middle temporal	.0002	.0102
superior frontal	.0005	.0028
insula	.0007	
fusiform	.0009	.0000
inferior parietal	.0013	
inferior temporal	.0027	
pars triangularis	.0066	
precentral	.0116	
lateral orbitofrontal	.0193	
supramarginal	.0287	.0489
pars orbitalis	.0319	.0388
medial orbitofrontal		.0404
rostral anterior cingulate		.0409

Figure 2. Cortical regions showing a significant trend TS < PTD < TFC.
A capital X indicates a region with $p_{FWE} < .001$, and a lower-case x indicates $.05 < p_{FWE} < .001$, for the left hemisphere, which underlies them. The italic, serif *x* marks two regions that are only significant on the right hemisphere. The black rectangles mark the approximate location of the FreeSurfer "banks of superior temporal sulcus" region. The underlying figure is from ref. [22], © Klein and Tourville, 2012, released under a Creative Commons Attribution License.

These regions cover the lateral and inferior temporal lobe and most of the lateral frontal lobe, plus the rostral anterior cingulate and the medial orbitofrontal cortex (yellow markers in Figure 2).

The PCA showed that 33.4% of the variance was explained by the first principal component alone, with subsequent components individually contributing little additional information. The first 4 PCs explain just over half of the total variance. The tic groups are not well separated by the first few PCs. In the SVM analysis, age, sex, handedness, scanner

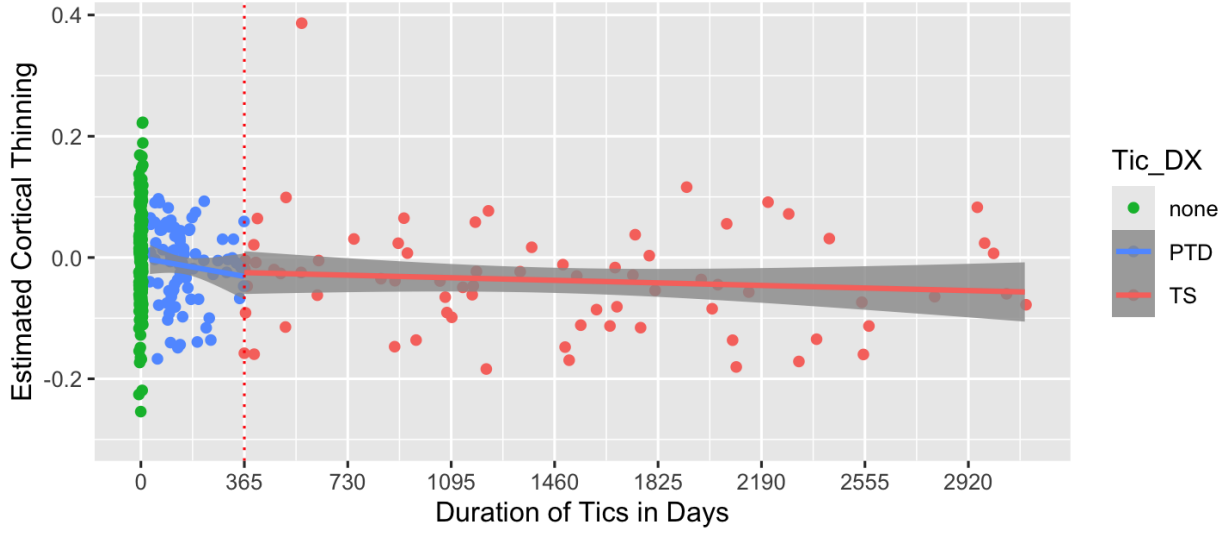
and eTIV left a diagnostic group misclassification rate of 41%, but adding all the cortical thickness data reduced the misclassification rate to 17%. One third of this improvement can be achieved using only mean cortical thickness.

Effects of illness severity or duration

Mean TTS was higher in TS than in PTD (20.0 ± 7.0 *vs.* 16.9 ± 5.6, $p = .001$, two tails). Cortical thickness did not correlate significantly with YGTSS total tic score (TTS) across the entire tic group, but differed significantly between the PTD and TS groups. This finding held either with or without correction for age, sex and scanner.

Cortical thickness in the PTD group was examined in terms of its deviation from the expected values from the TFC group for each child's age and sex (blue dots between 0 and 365 days after tic onset in Figure 3). Cortical thickness at tic onset was identical to that of the TFC group (*i.e.*, the *y*-intercept of the linear fit in the PTD group was .000), but diminished over the first year to match the TS group at one year after tic onset (the TS group is shown in red dots in Figure 3).

Figure 3. Cortical thickness in the M1S1 region compared to the predicted value based on age and sex compared to the TFC group, plotted by days after tic onset (PTD in blue between 0 and 365 days, TS in red after 365 days). The TFC group is plotted in green at time = 0.



Discussion

In vivo structural MRI studies have found thinning of primary motor or somatosensory cortex in TS.[3-5, 8, 23] These findings have been taken as supporting a model that characterizes tic disorders as involving hyperarousal, deficits in sensorimotor gating, and impaired cortical inhibition.[9] Other structural MRI studies have found reduced cortical thickness or volume in insula or orbital prefrontal cortex, which comprise part of the brain's social decision-making network, dysfunction in which is hypothesized to explain important features of TS.[6, 24-27]

However, these studies left three important questions in their wake. First, results were only partially replicated across studies. Given the variability, one is left with the question of which cortical areas are truly thinner in tic patients? Second, among various

differences in these studies, some studied children and others adults. When does cortical thinning develop relative to age, or relative to the onset of ticcing? Third, most prior reports discuss the results as explaining the existence or characteristics of tics, though the cross-sectional association of cortical thinning with diagnosis does not imply that the thinning causes or mediates the appearance of tics. The present study helps resolve these questions by virtue of a sample size more than 3 times larger than any of these previous studies and, importantly, including for the first time a large sample of children with tics for less than a year.

First, our results confirm many of these earlier findings and suggest that in fact numerous cortical regions are thinner in TS. Likely the differences in specific regions previous studies identified reflects in part Type II errors that the larger sample minimizes. Second, thinning appears not to be present at tic onset but to progress over the first year to match that of TS participants at one year's duration. At the same age, cortical thinning is greater in magnitude in chronic than in recent-onset tics. Such results suggest not lesions causing tics but cortical thinning that develops over time with tics. What might explain this result? One possibility is suggested by the observation that from age 5 to 10, cortex *thins* with age even in TFC. Several large studies find the same pattern, while others have reported that thinning starts around age 8.[28-31] In that light, cortical thinning in TS may represent not a lesion but rather faster maturation than is evident in children without tics. Possibly this early maturation could reflect experience inhibiting tics. Structural correlates of such inhibition would be expected to develop gradually over time after the onset of tics, and to develop to a greater extent than in children without tics, who do not

experience the same nearly constant need to suppress tics. This is in fact the pattern observed in the PTD group in the present study. This model may explain why in other studies thinning in various cortical regions has correlated with greater tic severity.[4, 5, 24] Fahim et al showed that progressive cortical thinning regions continued from ages 10 to 25 years, though in 3 of 4 regions, extrapolating from linear regression in each group suggested that the thinning in TS would slow over that age interval so as to match the thickness of the TFC group by age 20–30.[5] This result would fit the clinical observation that tics generally improve from approximately 10 to 25 years. In the early inhibitory maturation model above, these results would be interpreted as reflecting decreased need to suppress tics over that time interval, plus the eventual development in TFC of inhibitory control for non-tic behavior.

Limitations

Children with different tic diagnoses were not balanced across scanners. However, this imbalance does not explain our key results. The children with PTD were more likely to be scanned on the Prisma, which was associated with thicker cortex, yet they had thinner cortex than did tic-free controls. Additionally, the GLM included a factor for scanner.

Head movement during scan acquisition can lead to apparent artifactual thinning of the cortex.[32-35] The finding that cortex was thinner if measured on the Trio than on the Prisma, all other factors being equal, is consistent with this known artifact. In this setting it is natural to wonder whether the presence during the scan of tics that moved the head created artifactual results. Again, however, this concern does not affect our key results.

The Prisma vNav scans, which minimize movement-related effects on structural MRI,[15] show the same differences by diagnostic group. Although tics are more severe in the TS group (at least outside of the scanner), cortical thinning did not differ significantly by diagnosis. Finally, tics are suppressible, and most of the children in these studies had practice holding still, including training in a mock scanner. Thus tics on the day of the scan do not necessarily imply that tics that caused head movement were present during the scan acquisition.

Conclusion

In conclusion, the brain is slightly smaller in children age 5-10 who have TS than in tic-free controls, and less so in children the same age with tics for less than a year (TS < PTD $\lesssim$ TFC). The cortex is overall thinner in the same pattern (TS < PTD $\lesssim$ TFC). Numerous cortical regions contribute to this pattern, with mean cortical thickness supplying a meaningful fraction of the total pattern, yet thickness in numerous regions contains information relevant to diagnosis. Overall, these data suggest that the thinner primary motor cortex in TS develops beginning at tic onset and gradually progresses over the first 8 years after tic onset. As such, thinning of M_1 (and of other cortical regions) is more likely to represent a consequence than a cause of tics. The data are consistent with the hypothesis that over time, chronic tic suppression affects brain structure in the same direction as does growth and maturation over this age range.

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Supplemental Table A

Acquisition details, by diagnostic group, for all MRI scans used in this analysis.

Scanner	Sequence	Head Coil	TR (ms)	TE (ms)	TI (ms)	Voxel Size (mm)	TS	PTD	TFC
Siemens Prisma, 166038	tfl3d1_16ns\tfl_mgh_epinav_ABCD	32-channel	2500	2.9	1070	1x1x1	18	0	0
Siemens Prisma, 67064	tfl3d1_16ns\tfl	64-channel	2400	2.22	1000	0.8x0.8x0.8	0	4	0
	tfl3d1_16ns\tfl_mgh_epinav_ABCD	20-channel	2500	2.9	1070	1x1x1	0	0	54
	tfl3d1_16ns\tfl_mgh_epinav_ABCD	64-channel	2500	2.9	1070	1x1x1	40	59	35
Siemens Trio, 35177	tfl3d1_16ns\tfl	12-channel	2200	2.34	1000	1x1x1	14	20	1
	tfl3d1_16ns\tfl	12-channel	2400	3.08	1000	1x1x1	15	0	30
	tfl3d1_16ns\tfl	12-channel	2400	3.12	1000	1x1x1	3	0	14
	tfl3d1_16ns\tfl	12-channel	2400	3.13	1000	1x1x1	7	0	4
	tfl3d1_16ns\tfl	12-channel	2400	3.14	1000	1x1x1	3	0	11
	tfl3d1_16ns\tfl	12-channel	2400	3.17	1000	1x1x1	1	0	2
	tfl3d1_16ns\tfl_mgh_epinav_ABCD	12-channel	2530	1.74	1000	1x1x1	0	0	3
	tfl3d1_16ns\tfl_mgh_epinav_ABCD	12-channel	2530	1.74	1070	1x1x1	2	0	3
	tfl3d1_16ns\tfl_mgh_epinav_ABCD	12-channel	2530	1.74	1100	1x1x1	0	0	1
	tfl3d1_16ns\tfl_mgh_epinav_ABCD	12-channel	2530	1.74	1200	1x1x1	0	0	2
Siemens Trio, 35248	tfl3d1_16ns\tfl	12-channel	1900	2.92	1100	0.8x0.8x0.8	0	0	2
	tfl3d1_16ns\tfl	12-channel	1900	2.92	1100	1x1x1	0	0	25
	tfl3d1_16ns\tfl	12-channel	2400	3.16	1000	1x1x1	0	0	18