Altered Motor Network Recruitment During Finger Tapping in Boys With Tourette Syndrome

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Abstract: In Tourette syndrome (TS), not only the tics but also the findings on deficits in motor performance indicate motor system alterations. But our knowledge about the pathophysiology of the motor system in TS is still limited. To better understand the neuronal correlates of motor performance in TS, 19 treatment-naïve boys [age 12.5 (SD 1.4) years] with TS without comorbid symptomatology were compared to an age-matched healthy control group [$n = 16$; age 12.9 (SD 1.6) years] in regard to brain activation during right-hand index finger tapping by means of functional magnetic resonance imaging. Group differences were found mainly in the left (contralateral) precentral gyrus, which was less activated in boys suffering from TS and in caudate nucleus as well as in medial prefrontal cortex, which was more activated compared to healthy boys. These results show that even in the first years after the onset of the disorder, an altered brain network of motor performance is recruited. These alterations in brain regions frequently associated with TS are probably based on functional changes, which are discussed in terms of early compensatory mechanisms of the motor execution network. *Hum Brain Mapp* 33:666–675, 2012. © 2011 Wiley Periodicals, Inc.

Key words: Tourette syndrome; finger tapping; precentral gyrus; caudate nucleus; functional MRI; boys

INTRODUCTION

Veit Roessner and Matthias Wittfoth contributed equally to this work.

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Tourette syndrome (TS) is a neurodevelopmental disorder characterized by chronic motor and phonic tics [Rothenberger et al., 2007]. In addition to these movement-related core features, TS is often associated with various emotional and cognitive symptoms such as depression, anxiety, obsessions, or attentional difficulties [Freeman, 2007]. This heterogeneous profile of symptoms might be one reason why the etiology and pathophysiology of TS still remain unclear, although it has been the focus of considerable study [Swain et al., 2007].

One line of research in TS is based on the assumption that voluntary movement might be associated with the unwanted

facilitation of competing motor patterns, resulting in tics [Mink, 2003]. In this context, probable basic or tic-related impairment of voluntary motor performance in TS is still a matter of debate, although there is evidence for a reduction of voluntary motor drive in TS [Heise et al., 2008].

Additional evidence for alterations in the motor system in TS stems from performance-monitoring studies. Neuroimaging results showed that patients with TS have enhanced prefrontal activation relative to healthy adults during voluntary movements in executive tasks despite similar performance levels [Baym et al., 2008; Marsh et al., 2007]. This might be explained as related to tic suppression [Mueller et al., 2006] as already reported for the motor readiness potential [O'Connor et al., 2001; Rothenberger, 1990].

The inconsistencies concerning motor performance as well as its underlying brain activation in TS might be due to several methodological differences [Schultz et al., 1998]. First, the validity of most studies in this field is limited either by fairly small sample sizes (i.e., less than 15 participants) and/or by the absence of a control group. Second, most studies did not sufficiently control for the often coexisting attention-deficit hyperactivity disorder (ADHD; [Rothenberger et al., 2007], although there is substantial evidence that children with ADHD show deficits in motor performance compared to unaffected controls [Fliers et al., 2008]. Additionally, ADHD has a greater impact on several neuropsychological parameters compared to TS [Roessner et al., 2007, 2008b], so that ADHD commonly coexisting with TS might have a major impact also on the observed impairment of motor performance. Third, the common inclusion of adult subjects might be problematic, because long-term effects of extensive symptomatic medication exposure cannot be differentiated from etiological factors more specific to TS *per se*. At last, previous studies of voluntary tic suppression have suggested that suppression of tics robustly activates the frontal cortex [Peterson et al., 1998] and that this daily activation may result in a compensatory neuroplastic hypertrophy of frontal cortices (Peterson et al., 2003; Plessen et al., 2004) that helps to regulate activity within those motor circuits, with the consequence of tic reduction [Spessot et al., 2004]. Additionally, the group of adults still suffering from TS represents only a minority of TS patients in view of the high rate of tic remission during late adolescence and early adulthood [Bloch et al., 2006a].

Taken together, it seems worthwhile to examine the functional brain correlates of basic voluntary motor performance associated with “pure” TS following the common recommendation of stricter inclusion criteria [Kassubek et al., 2006; Roessner et al., 2009; Thomalla et al., 2009] in order to elucidate the pathophysiological background of TS *per se*. To minimize confounding factors by *a priori* exclusion and by studying TS as close at its regular onset in childhood as possible, we investigated treatment-naïve boys with “pure” TS. Based on previous functional and structural evidence, studies on fine-motor skills posit a dysfunction of the neural circuits linking the

frontal lobes and the striatum in TS [Bloch et al., 2006b; Singer and Minzer, 2003].

Thus, we hypothesize that treatment-naïve boys with “pure” TS will show brain-activation differences in TS-associated key regions during self-paced finger tapping compared to healthy control boys of the same age and IQ. In particular, we expect differences in the striatum as well as primary and secondary motor areas in which atypical neuronal activity is likely to be reflected. As an additional advantage and in order to be able to generalize our results, we included a rather large sample size of 19 treatment-naïve boys with “pure” TS.

MATERIALS AND METHODS

Subjects

Nineteen treatment-naïve [age 12.5 (SD 1.4) years], right-handed boys with “pure” TS, according to DSM-IV, were sequentially recruited from the outpatient clinic of the Department of Child and Adolescent Psychiatry at the University of Goettingen as well as via the homepage of the German TS Association (for details of recruitment and diagnosing, see [Roessner et al., 2008a]). Children with TS were rated on the TS Severity Scale [Walkup et al., 1992]. Sixteen healthy, right-handed boys [age 12.9 (SD 1.6) years] were recruited as healthy controls from a youth club and school classes in Goettingen (for a detailed description of both groups, see Table I). Broadband psychopathology was screened by parent- and self-rated Strength and Difficulties Questionnaires (SDQ) [Rothenberger and Woerner, 2004], and full-scale IQ was estimated from the similarities, vocabulary, block design, and object assembly subtests of the Wechsler Intelligence Scale for Children-Revised. Right-handedness was assured by the Edinburgh Handedness Inventory [Oldfield, 1971]. All subjects had normal or corrected to normal vision. Informed consent was obtained from all subjects, and their parents participating in this study in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki); the study was approved by the local Ethics Committee.

Task

Participants performed a simple finger-tapping task during functional magnetic resonance imaging (fMRI) measurements, which consisted of dominant right-hand index finger movements. Via a set of MR compatible LCD goggles (Resonance Technology, Northridge, CA), participants viewed a green or a red dot in alternating order. During presentations of the green dot, they had to rhythmically tap onto a rigid board at a frequency of 2 Hz, while resting during red-dot presentations. A short practice session was applied before scanning in order to assure that participants understood the instruction and were able to correctly perform the finger tapping. They performed eight alterations of motor performance

TABLE I. Descriptives

Measure	Healthy control boys	Tourette's syndrome boys ^a	Statistics <i>t</i> -test [<i>t</i> ₍₃₃₎]
	<i>N</i> = 16 ^b Mean (SD)	<i>N</i> = 19 Mean (SD)	
Age (months)	154.6 (19.5)	149.8 (17.2)	0.78, <i>P</i> = 0.44
Estimated total IQ	106.3 (10.7)	106.1 (13.7)	0.07, <i>P</i> = 0.95
TS Severity Scale ^b	—	1.9 (1.4)	—
Age at onset of first tics (months) ^c	—	83.5 (20.3)	—
Duration of tics (months) ^c	—	66.3 (26.6)	—
SDQ			
Parent rated			
Total problems 6	5.1 (3.9)	9.7 (6.3)	2.4, <i>P</i> = 0.02
Emotional symptoms 1	0.8 (1.0)	1.8 (2.1)	1.7, <i>P</i> = 0.09
Conduct problems 2	0.7 (0.8)	2.1 (1.9)	2.5, <i>P</i> = 0.02
Hyperactivity 3	3.3 (2.2)	4.2 (2.5)	1.1, <i>P</i> = 0.28
Peer problems 4	0.4 (0.7)	2.3 (3.4)	2.2, <i>P</i> = 0.04
Prosocial behavior 5	8.3 (1.1)	7.4 (2.2)	-1.5, <i>P</i> = 0.16
Self-rated			
Total problems 6	7.4 (4.0)	9.9 (5.6)	1.5, <i>P</i> = 0.15
Emotional symptoms 1	1.0 (1.2)	2.1 (1.6)	2.2, <i>P</i> = 0.04
Conduct problems 2	1.6 (1.1)	1.8 (1.5)	0.5, <i>P</i> = 0.63
Hyperactivity 3	3.6 (1.9)	3.6 (2.6)	<0.1, <i>P</i> = 0.98
Peer problems 4	1.3 (1.3)	2.4 (2.3)	1.7, <i>P</i> = 0.09
Prosocial behavior 5	7.9 (1.2)	7.9 (1.8)	<0.1, <i>P</i> = 0.97

^aTics in arm or hand: no tics in arm or hand *n* = 4; tics in arm only *n* = 3; tics in hand only *n* = 3; tics in arm and hand *n* = 9.

^bExclusion criteria were head movements during functional measurements of more than 4 mm or 4° during a functional run. On this basis, six participants [five boys with Tourette syndrome (age 139.6; SD 21.1 months) and one healthy control boy (age 134 months)] were not included in our analyses.

^cTSSS, Tourette's Syndrome Severity Scale (Walkup et al., 1992).

(12 s) and resting periods (18 s). Including an initial rest block, total scanning time was 4 min and 18 s. Movement execution was monitored online by the experimenter. No mirror movements could be observed.

Magnetic Resonance Imaging

Magnetic resonance imaging was carried out at 3 T (Magnetom Trio, Siemens Healthcare, Erlangen, Germany) using the standard eight channel-phased array head coil. T1-weighted high-resolution anatomical images were acquired for each participant (3D Turbo FLASH, repetition time 1,950 ms, inversion time 1,100 ms, echo time 3.92 ms, and flip angle 12°). For blood oxygenation level dependent (BOLD) fMRI, a T2*-weighted gradient-echo echo-planar-imaging technique was used, recording 22 sections of 4-mm thickness with an in-plane resolution of 2 × 2 mm² every 2 s (TE 36 ms, flip angle 70°, and matrix size 96 × 128).

fMRI Data Analysis

Functional magnetic resonance imaging (fMRI) data were processed using BrainVoyager QX (Brain Innovation, Maastricht, The Netherlands) including slice scan time and three-dimensional head movement correction, linear trend removal, and high-pass filtering with three cycles/unit in

time course. For group analysis, functional data were transformed into Talairach space [Talairach and Tournoux, 1988] and smoothed with a Gaussian filter with full width at half maximum = 5 mm. The data were analyzed voxel-wise by means of the general linear model, using a deconvolution of the block design with a two-gamma function in order to model the hemodynamic response. Random effects analyses were separately computed using the first-level single subject contrasts (tapping versus rest) for each group (TS and healthy controls). To directly compare brain-activation differences of TS boys and healthy control children, between-group differences were assessed by an analysis of variance (ANOVA) based on the whole-brain level. To correct for multiple comparisons the cluster-level statistical threshold estimation at a corrected *P* < 0.05 was applied [Forman et al., 1995] resulting in cluster sizes of 108 mm³ for the main effects (tapping versus rest) per subject group and 243 mm³ for the between-group differences. For visualization, activations were projected onto the inflated representations of the MNI brain.

RESULTS

Sample Description

As shown in Table I, the two groups did not differ in age and estimated total IQ. In the SDQ, there were no

group differences in the self-rated form, except for emotional symptoms, but parents reported more total problems, conduct problems, as well as peer problems in boys with TS. All group means were clearly within the normal range [Woerner et al., 2004], and group means of specific instruments (ADHD: Fremdbeurteilungsbogen Hyperkinetische Störung (FBB-HKS) [Erhart et al., 2008]; OCD: Leyton Obsessional Inventory-Child Version (LOI-CV) [Berg et al., 1988]) to detect disorders commonly coexisting with TS like ADHD and OCD were within the lower normal range confirming “pure” TS in all affected boys. Furthermore, there were no group differences concerning these specific instruments.

fMRI Results

Within-group activations

During right-hand index finger tapping, healthy control children showed a left primary sensorimotor cortex activity that was contralateral to the executing hand, along with the activity in the ipsilateral cerebellum. Additionally, the bilateral basal ganglia, the insula, supplementary motor area (SMA), and right-sided inferior parietal lobule (IPL) were activated by finger tapping (Table II and Fig. 1).

Similar to the healthy controls in boys with TS, functional magnetic resonance imaging (fMRI) revealed activations in the primary sensorimotor cortex on the left side, also with ipsilateral cerebellar signal increases. In the patient group, we found the SMA cluster to extend into the pre-SMA. In the right hemisphere, a signal increase in the cingulate motor area was observed. Boys with TS showed additional deactivations in the right primary sensorimotor cortex and in the right dorsal premotor region.

Between-group activations

During right-hand index finger tapping, healthy control boys showed stronger activation compared to boys with TS in the left, that is, contralateral precentral gyrus as well as in the right, that is, ipsilateral superior and IPLs (Table III and Fig. 2). Additionally, stronger activation was found in the right middle temporal and middle frontal gyrus.

Conversely, the only two regions in which boys with TS showed significantly more activation compared to healthy control children were the left caudate nucleus and the right medial frontal gyrus.

DISCUSSION

To shed light on possible functional differences related to simple right unilateral finger tapping, we conducted an fMRI study comparing functional activations of treatment-naïve boys suffering from “pure” TS compared to age-, gender-, and IQ-matched healthy control children. Despite the fact that there have been some reports on voluntary fine motor function in TS [Biswal et al., 1998; Bornstein, 1990;

Bornstein et al., 1991; Fattapposta et al., 2005; Hagin et al., 1982; Schultz et al., 1998], our study has the advantage of fairly large sample of patients at an early disease stage without comorbid symptomatology. Although usual clusters of motor activation patterns reported in finger-tapping studies were similar in both groups [Witt et al., 2008], that is, contralateral primary sensorimotor cortex, supplementary motor areas, and ipsilateral cerebellum), this study also found BOLD signal *differences* between both groups. By using whole-brain between-group analyses, in boys with “pure” TS *lower* magnitude of activation was found in the contralateral precentral gyrus and in right parietal lobules, whereas *higher* magnitude of activation could be observed in the left caudate nucleus and in the right medial frontal gyrus.

Precentral Gyrus

Our finding that the left, that is, contralateral precentral gyrus was activated to a lesser extent in boys with TS suggests that TS patients might use a different neuronal recruitment strategy to execute simple motor tasks compared to the control children. This view is supported by Heise et al. [2008] who found a decreased voluntary motor drive in children with TS and a recent study with adult patients suffering from TS [Heise et al., 2010]. The latter proposed a model of deficient motor inhibition at rest, which leads to a higher probability of tics while an increased inhibition during motor preparation is thought to reflect a compensatory mechanism to gain control over motorcortical excitability. Note that this view differs from that of a previous study [Orth and Rothwell, 2009], which reported not steeper but shallower recruitment curves in TS leading to their conclusion of overall reduction of cortical excitability. At least to some extent, those conflicting results might reflect different samples of patients ([Heise et al., 2010]: 11 TS patients without comorbid symptomatology versus Orth and Rothwell [2009]: 29 TS patients of which 38% had comorbidities) emphasizing once more the importance to account for TS-associated ADHD and/or OCD.

Motor network alterations are also supported by the observation of ipsilateral motor area deactivation only in boys with TS during right-hand index finger tapping compared to rest, although this result did not survive our rigorous multiple-testing corrections on the group level. However, both the deactivation of the ipsilateral motor area only in the TS boys (within-group contrast) as well as the reduced recruitment of contralateral precentral gyrus in TS compared to healthy boys adds to the view of a different functional organization of their motor execution network. In addition, boys with TS seem to have thinner sensorimotor cortices [Fahim et al., 2009] and the degree of cortical thinning in TS being proportional to tic severity [Sowell et al., 2008].

Caudate Nucleus

In line with the findings of neuronal density differences in the basal ganglia and thus an alteration of functional

TABLE II. Statistically significant areas of main effects of finger tapping, corrected at $P < 0.05$

Brain regions	Side	Brodmann's area	Controls				Tourette			
			Coordinates (Talairach)			Max. <i>t</i> -value	Coordinates (Talairach)			Max. <i>t</i> -value
			X	Y	Z		X	Y	Z	
Frontal										
Middle frontal gyrus	R	10	39	47	10	5.2				
Superior frontal gyrus	L/R	6					0	11	49	6.0
Precentral gyrus	L	4	-36	-19	52	14.5	-36	-19	55	23.3
	R	4	30	-25	58	-5.0	33	-16	40	-5.6
Precentral gyrus	R	6	21	-19	64	-5.2				
Precentral gyrus	L	44	-48	-1	10	7.4				
Cingulate gyrus	L	24	-6	-4	43	6.8	-3	5	37	5.7
	R	24					3	-10	31	5.9
Cingulate gyrus	R	32					6	20	34	5.1
Medial frontal gyrus	L	6	-9	-7	55	7.8	-6	-10	52	6.3
Insula	L	13	-42	-19	19	8.1	-39	8	13	6.6
	R	13					42	8	7	5.0
Insula	L	13	-36	2	10	8.0				
	R	13	39	5	4	7.6	36	-13	22	-5.0
Anterior insula	L	13	-30	23	7	5.6				
	R	13	27	17	13	5.5				
Subcortical										
Lentiform nucleus	L		-24	2	4	9.1	-27	5	1	8.6
	R		18	2	13	6.6				
Caudate nucleus	L						-18	14	19	7.1
	R						15	11	19	5.3
Thalamus	L		-15	-19	10	10.4	-15	-16	10	6.0
Temporal										
Superior temporal gyrus	R	41	48	-34	13	5.6				
Parietal										
Postcentral gyrus	R	3	21	-37	58	-5.7	21	-28	55	-7.1
Inferior parietal lobule	R	40	54	-37	50	5.5				
Inferior parietal lobule	L	40	-45	-28	25	7.0				
	R	40	48	-34	46	8.6				
Precuneus	R	7	21	-52	40	5.2				
Occipital										
Fusiform gyrus	R	19/ 37	42	-40	-14	4.8	36	-73	-11	4.6
Inferior occipital gyrus	L	18	-33	-85	-8	5.8	-24	-88	-5	5.3
	R	18	24	-88	-14	9.0				
Lingual gyrus	L	18	-18	-94	11	6.1				
	R	18	15	-94	-11	4.9	18	-82	-5	5.7
Cerebellum	L						-39	-64	-20	5.5
	R		12	-43	-14	9.6	15	-40	-14	6.7

dynamics of cortico-striato-thalamic circuitry in TS [Kalanithi et al., 2005; Kataoka et al., 2010], we found increased left caudate nucleus activity in boys suffering from TS compared to controls during simple right-hand finger tapping. However, the greater recruitment of the left caudate nucleus in boys with TS does reflect altered but not necessarily impaired execution of motor plans, because there was no performance deficit in a prescanning practice session. Most likely, these different functional dynamics reflect the consequence of functional disorder-related compensatory processes [Fair et al., 2009].

On the basis of the fronto-striato-thalamo-cortical circuits [Albin and Mink, 2006] and the two primary input nuclei of the basal ganglia, previous research suggests that the caudate is associated with both cognitive [Chang et al., 2007; Crottaz-Herbette et al., 2004] and emotional [Delgado et al., 2004] processing, and the putamen with motor function [Cummings, 1993]. One might wonder why our findings of enhanced recruitment of caudate nucleus in such a simple finger-tapping task in children suffering from TS compared to healthy controls can fit in this frame. However, a recent study conducted to elucidate fronto-striato-thalamo-cortical circuit function found consistently

Figure 1.

fMRI results for each group. BOLD responses to right-hand finger tapping of the control group (left) and of boys suffering from Tourette syndrome (right) are shown for the main effect “finger tapping vs. rest.” Statistical maps are projected onto inflated Montreal Neurological Institute cortical surfaces.

TABLE III. Regions with significant group differences evoked by finger tapping, corrected at $P < 0.05$

Brain region	Brodmann area	Coordinates (Talairach)			Max <i>t</i> -value
		<i>x</i>	<i>y</i>	<i>z</i>	
Controls > Tourette					
Right middle temporal gyrus	22	51	−46	1	4.2
Right middle frontal gyrus	46	45	20	19	4.4
Right inferior parietal lobule	40	39	−34	40	4.3
Right superior parietal lobule	7	33	−46	46	3.7
Right precuneus	7	15	−61	46	3.3
Left precentral gyrus	6	−15	−19	64	4.0
Tourette > Controls					
Right medial frontal gyrus	9	15	32	31	4.3
Left caudate	—	−12	17	19	4.3

caudate activity even during motor tasks, thereby challenging this simple dichotomy [Lee et al., 2010]. Finally, the involvement of the caudate nucleus in motor task seems to be connected to task complexity [Lehericy et al., 2006], thus providing an argument for the view that the greater activation magnitude in TS represents higher motor performance effort. On the background of the above-mentioned view of an abnormally disinhibited level of intracortical inhibition during motor performance [Heise et al., 2010], the additional recruitment of the caudate nucleus may play an important role to implement motor

control through fronto-striato-thalamo-cortical pathways, which result in comparable behavioral performance and efficiency.

This view is supported by studies, which found volumetric alterations in TS [Plessen et al., 2009; Sowell et al., 2008], in particular in the caudate nucleus [Peterson et al., 2003]. Caudate nucleus activity, together with the higher magnitude of activation in the right medial frontal cortex, might reflect the presence of hypoplasia across motor-related parts of the cortico-striatal-thalamo-cortical circuits. The importance of the interplay between frontal

Figure 2.

Activation results for the group comparison (Controls vs. TS). Results reveal greater finger tapping-related activity in controls compared to patients in the left precentral gyrus, right parietal, middle frontal, and middle temporal regions (shown in yellow and orange color), whereas patients show greater activity in the

right medial frontal gyrus (shown in blue color) and the left caudate (as can be seen on the right side on an axial brain slice) (Abbreviations: PCG: precentral gyrus; SPL: superior parietal lobule; IPL: inferior parietal lobule; MTG: middle temporal gyrus; MFG: right middle frontal gyrus).

cortex and basal ganglia as a regulatory mechanism to maintain control over motor-related processes has recently been reported [Mazzone et al., 2010].

Additionally, we also observed decreased magnitude of activation in the right parietal, temporal, and middle frontal cortices in TS. This part of the parietal lobule has been hypothesized to be especially relevant for the integration of visual and somatosensory information and the retrieval of movement representations [Danckert et al., 2002], while more recent theoretical approaches associate the posterior parietal cortex with movement intention and awareness [Desmurget and Sirigu, 2009].

Limitations

Our findings must be interpreted in light of several limitations. First, it is important to mention that during concentration on finger tapping, TS boys might have actively or automatically suppressed their tics. Thus, we (and all other fMRI studies on TS) cannot be sure how this might have confounded the results. Second, by comparing the realignment parameters of both groups, two movement-related range values showed significant differences. However, in contrast to pure cognitive or emotional experimental paradigms, the investigation of motion-related activation has shown to evoke very reliable brain activation. Therefore, differences in only two realignment parameters should have very little influence on our findings of brain activation differences. Third, we conclude that the found functional alterations probably represent the neural correlates of early compensatory mechanisms of the motor execution network in response to primary disease-related processes. Although, some studies [Georgiou et al., 1997; Lavoie et al., 2007; Roessner et al., 2008] and our prescanning practice session found no performance differences between patients suffering from TS and healthy controls in regard to motor performance; on the basis of our results alone, we cannot decide whether activation differences between both groups reflect functional compensatory mechanisms or a primary disease process, because performance data were not obtained, which might have shown that patients performed the finger-tapping task differently.

CONCLUSION

This study provides evidence for a differentially altered neuronal recruitment strategy of a complex motor network in TS. Thus, it allows for a better understanding of both kinds of movements, that is, tics versus voluntary actions, and to optimize behavioral treatments. The validity of the findings is underlined by the advantage of investigating young boys with “pure” TS, that is, without any comorbid symptomatology without a history of treatment and very young age including minimization of long-term compensatory changes due to daily tic performance and/or suppression. It will be a predominant aim in future research to

further disentangle the impact of different compensatory and comorbid aspects of TS.

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