Altered Motor Network Activation and Functional Connectivity in Adult Tourette's Syndrome

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Abstract: Tourette's syndrome (TS) is a developmental neuropsychiatric disorder characterized by motor and vocal tics as well as psychiatric comorbidities. Disturbances of the fronto-striatal-thalamic pathways responsible for motor control and impulse inhibition have been previously described in other studies. Although differences in motor performance are well recognized, imaging data elucidating the neuronal correlates are scarce. Here, we examined 19 adult TS patients (13 men, aged 22–52 years, mean = 34.3 years) and 18 age- and sex-matched controls (13 men, aged 24–57 years, mean = 37.6 years) in a functional magnetic resonance imaging study at 1.5 T. We corrected for possible confounds introduced by tics, motion, and brain-structural differences as well as age, sex, comorbidities, and medication. Patients and controls were asked to perform a sequential finger-tapping task using their right, left, and both hands, respectively. Task performance was monitored by simultaneous MR-compatible video recording. Although behavioral data obtained during scanning did not show significant differences across groups, we observed differential neuronal activation patterns depending on both handedness (dominant vs. nondominant) and tapping frequency in frontal, parietal, and subcortical areas. When controlling for open motor performance, a failure of deactivation in easier task conditions was found in the subgenual cingulate cortex in the TS patients. In addition, performance-related functional connectivity of lower- and higher-order motor networks differed between patients and controls. In summary, although open performance was comparable, patients showed different neuronal networks and connectivity patterns when performing increasingly demanding tasks, further illustrating the impact of the disease on the motor system. *Hum Brain Mapp* 32:2014–2026, 2011. © 2011 Wiley Periodicals, Inc.

Key words: fMRI; motor control; independent component analysis; subgenual cingulate cortex

INTRODUCTION

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Tourette's syndrome (TS) is a developmental neuropsychiatric condition marked predominantly by motor and vocal tics. Its clinical course is characterized by symptoms waxing and waning over time. The onset occurs during childhood, with boys being affected three to four times more often than girls. Comorbidities such as obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), and depression often accompany TS. These comorbidities tend to be the rule rather than the exception and affect 90% of patients when examined in large cohorts [Freeman et al., 2000; Khalifa and von

Knorringer, 2005]. The natural course is usually benign with the majority of patients becoming symptom free to the end of their second decade [Leckman et al., 2006]. Still, up to 30% of patients experience clinically relevant disturbances well into adulthood. Tics are the most prominent feature of the disease and can be extremely disabling, particularly in a social context. Therefore, the neuroanatomy of tics has received particular attention in the neuroimaging research on TS [Bohlhalter et al., 2006; Hampson et al., 2009; Peterson et al., 1998; Stern et al., 2000], highlighting a network of frontal areas, basal ganglia, insula, and cerebellum, compatible with the notion that TS is the result of a failure in network maturation particularly of the fronto-striatal-thalamo-cortical loop [Albin and Mink, 2006].

It is recognized, however, that adult patients also suffer from deficits in the motor domain, namely visuomotor integration, fine-grained motor performance, and executive control [Como, 2001; Channon et al., 2009; Nowak et al., 2005]. Not surprisingly, motor performance in TS deteriorates with increasing task difficulty [Sheppard et al., 2000], also suggesting frontostriatal dysfunction. In particular, sequential movements seem to be clinically impaired [Sweet et al., 1973], with patients relying more heavily on external than internal cues for this type of task [Georgiou et al., 1995]. These findings are in line with recognized functions of the cortico-striato-thalamo-cortical loop [Hallett, 1993].

Although the motor system and its connections (with emphasis on the basal ganglia) has been the focus of structural imaging for quite some time [Plessen et al., 2007, 2009; Sowell et al., 2008], there is surprisingly little functional data on *voluntary*, overt motor performance (as opposed to involuntary motion or mental imagery) in TS with only two previous functional magnetic resonance imaging (fMRI) studies yielding somewhat conflicting results: Biswal et al. found an increase in the number of activated voxels in SMA in a sequential finger-tapping task [Biswal et al., 1998], whereas a second fMRI study [Serrien et al., 2002] reported either no activity or significantly reduced activity when executing a task compared with the resting state in secondary motor areas. The conclusion drawn was that the ongoing activation of secondary motor areas may explain involuntary movements in TS patients. However, both studies differ substantially from each other and from our experiment, potentially explaining some of the differences in results. Biswal et al. examined five controls and five TS patients, for whom disease severity scores were not given. Methodologically, no motion correction or correction for other confounds in the statistical analysis were performed. Finally, they reported a larger (manual) count of activated voxels in the TS patient group in roughly the same anatomical areas as controls, the significance of which is not entirely clear. In the study by Serrien et al., on the other hand, an entirely different task was employed, involving a manipulandum, which had to be lifted rhythmically. Only three TS patients were included in the fMRI section of the study. Thus, only

a single-subject analysis was applicable. Results showed a smaller area of activation in secondary motor areas after correcting for motion, which (in combination with the differences in the given tasks) could contribute to the discrepancy in results vis-à-vis the study by Biswal et al.

In addition, although the idea of alterations in structural connectivity is now well established (see above), analyses of functional connectivity in TS have gained momentum only recently in terms of a large longitudinal study showing immature and dysfunctional networks governing online adaptive control in children with TS [Church et al., 2009], thus complementing an earlier PET study [Jeffries et al., 2002].

The rationale for our study was as follows: given the behavioral observation of differential motor performance particularly in self-triggered sequential movements in TS and the paucity of functional data, we aimed to elucidate the neural correlates of such a task in a larger group of adult TS patients. Secondly, we tried to answer the question of whether the differential development in functional connectivity observed by Church et al. would continue into adulthood in patients with persisting TS. If this were the case, a delay in maturation of functional connectivity (perhaps mediated by a failure of myelination) could be a pathophysiological correlate of juvenile TS, whereas a subsequent failure of compensation or a premature halt in development could then be a plausible explanation for TS persisting into adulthood.

We used a simple sequential motor task with three conditions (finger tapping right, left and both hands) in an fMRI study to test the following hypotheses:

- (i) voluntary motor performance in adult patients suffering from TS is accompanied by a differential neural activation pattern,
- (ii) increases in tapping frequencies (mirroring higher cognitive effort) lead to differential activations between groups, and
- (iii) functional connectivity of areas related to motor control is altered in persisting adult TS given previous findings in a younger cohort.

MATERIALS AND METHODS

Participants

Patients

Twenty-eight out-patients suffering from TS (age 36 ± 10.8 years; 20 men, 8 women) gave informed consent. Criteria for TS were fulfilled as defined by DSM-IV-TR and ICD-10. Tic severity was measured according to the Yale Global Tic Severity Scale (YGTSS) [Leckman et al., 1989]. A psychiatric assessment according to DSM-IV-TR guidelines as well as a neurological examination was performed by a board-certified specialist (I.N.). Of these, nine had to be excluded from the statistical analysis: eight because of excessive residual motion as indicated by the image analysis software (see

TABLE I. Demographic and medical data of participants

Controls		Tourette's Patients					
Sex	DoB	Sex	DoB	YGTSS-m	YGTSS-v	Comorbidity	Medication
M	1980	F	1984	15	12	—	—
M	1970	M	1962	14	5	—	Tiapride 200 mg
F	1976	F	1959	10	6	—	—
M	1952	M	1960	16	8	—	—
F	1955	M	1965	17	10	—	—
M	1957	F	1972	8	19	—	Pimozide 2 mg
M	1985	F	1977	9	14	OCD, ADHD	Citalopram 20 mg, Methylphenidate 50mg
M	1985	M	1967	14	16	OCD	Amisulpride 200 mg, Tiapride 50 mg
M	1979	M	1957	11	6	—	—
F	1973	M	1981	2	0	—	—
M	1985	M	1985	11	9	—	Escitalopram 10 mg
M	1979	M	1985	14	15	—	—
M	1965	M	1979	12	11	OCD, ADHD	—
F	1962	M	1981	13	13	OCD	Citalopram 20 mg, Tiapride 200mg
M	1964	M	1979	14	0	—	Trimipramine 50 mg
M	1964	F	1983	10	7	—	Aripiprazole 10 mg, Fluoxetine 20 mg
M	1975	M	1987	16	14	—	Ziprasidone 80 mg
F	1980	M	1985	10	12	—	—
		F	1972	12	8	—	—
Range				2–17	0–19		
Average (SD)				12 (3.5)	9.7 (5.1)		

DoB, date of birth; YGTSS-m, Yale Global Tic Severity Score, motor subscore; YGTSS-v, Yale Global Tic Severity Score, vocal subscore; M, male; F, female; OCD, obsessive-compulsive disorder; ADHD, attention deficit hyperactivity disorder; SD, standard deviation.

below) and one for a clinically asymptomatic arachnoid cyst on the left temporal pole evident on structural scanning. The group composition regarding age and sex was the same after exclusion (13 men, 6 women; age 34.3 ± 10.1 years). Of the final group entering analysis, nine patients were on active medication for either tics and/or comorbidities. Two male patients were diagnosed with OCD and ADHD along with TS, two other patients (1 male and 1 female) were diagnosed with OCD as a comorbidity only. None of the TS patients suffered from a depressive episode. Average tic severity scores were 12 (3.5) for the YGTSS-motor and 9.7 (5.1) for the YGTSS-vocal, respectively (SD in brackets). Final demographics, comorbidities, and medication status (current) are given in Table I.

All patients had normal or corrected-to-normal vision and no hearing loss and reported strong right-hand preference as assessed by the Edinburgh Handedness Questionnaire (Oldfield, 1971) (laterality index controls mean 97.4, SD 4.5, range 90–100, patients 96.9, SD 4.8, range 90–100). We did not seek to deliberately exclude patients with comorbidities, given their high prevalence in TS. This approach has also been successfully used previously [Church et al., 2009; Hampson et al., 2009; Sowell et al., 2008] and has been explicitly recommended for use in structural imaging [Plessen et al., 2007].

Controls

Eighteen healthy control subjects matched for age and sex (37.5 ± 10.7 years, 13 men, 5 women) with no history of neurological or psychiatric disease as assessed by an expert, with normal or corrected-to-normal vision and no hearing loss, gave written informed consent. All control subjects also were tested for strong right-hand preference using the Edinburgh Handedness Inventory.

To ascertain equality in terms of age across groups, this feature was tested using the two-sample Student's *t* test using "R" software. Results of the *t* test showed no differences across groups for the feature "age" ($P = 0.34$). Furthermore, the feature "sex" did not account for any of the following as tested for by the Wilcoxon rank-sum test (P values in brackets): tapping frequency (0.28), YGTSS-motor (0.64), YGTSS-vocal (0.55), comorbidity with ADHD (0.52) or OCD (0.85), and medication (0.81).

The study was conducted according to the Declaration of Helsinki and approved by the local ethics committee according to local standard operating procedures

Study Design – Task

Patients and controls were asked to lie in the scanner and to touch their fingers with their thumbs sequentially

in the following order: right hand only (condition R), left hand only (condition L), and both hands simultaneously (condition B). Each task was performed for 32 s and was repeated three times in sequential order (R, L, B). A baseline period of 32 s rest followed each task. Instructions for starting and stopping the task were given by brief verbal commands over the MR scanner intercom system. Subjects and patients were instructed to perform the task as quickly and as accurately as possible, having had time to practice the task beforehand.

Performance was monitored using a specifically adapted whole body MR-compatible video system [Neuner et al., 2007]. In particular, accuracy, frequency of tapping and overt tics were recorded. Video tapes were analyzed by a trained staff member under the supervision of a board-certified neurologist and psychiatrist (I.N.).

Behavioral Data

Measured tapping frequencies were subjected to a two-sample *t* test to detect possible discrepancies in performance across groups. In addition, we performed repeated Wilcoxon rank-sum tests with “sex” as the explanatory variable and “frequency”, “comorbidity”, “medication”, “YGTSS-motor,” and “YGTSS-verbal” as dependent variables to exclude an influence of sex on those scores. Finally, we performed a multiple linear regression of “age”, “YGTSS-motor,” and “YGTSS-vocal” against tapping frequencies. All calculations were performed using “R” software (<http://cran.r-project.org>).

Functional Imaging - Acquisition

A Siemens Sonata 1.5-T whole body scanner with echo planar imaging (EPI) capability was used for the acquisition of functional MR images. Standard sequence parameters were used: Gradient-echo EPI, TE = 60 ms, TR = 3200 ms, flip angle = 90°, 30 axial slices of 4 mm thickness, 0.4 interslice gap, matrix = 64 × 64, field of view (FOV) = 200 mm, in-plane resolution = 3.125 × 3.125 mm. The 30 slices covered the brain from the vertex to the brainstem just below the cerebellum and were parallel to the anterior and the posterior commissure (AC-PC line) as determined by a midsagittal scout image. For all subjects, additional high-resolution anatomical images were acquired using a 3D MP-RAGE sequence with the following parameters: TE = 3.93 ms, TR = 2200 ms, flip angle = 15°, inversion time (TI) = 1200 ms, 176 sagittal slices of 1.0 mm thickness, matrix = 200 × 256, FOV = 256 mm, resolution = 1.0 × 1.0 × 1.0 mm.

Functional Imaging – First-Level Image Analysis

fMRI data processing was performed using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library). The following pre-statistics processing was applied after discarding the first three vol-

umes to allow for magnetic field saturation: motion correction using MCFLIRT [Jenkinson et al., 2002]; slice-timing correction using Fourier-space time-series phase-shifting; nonbrain removal using BET [Smith, 2002]; spatial smoothing using a Gaussian kernel of 6.0 mm (full width – half maximum); grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor and high-pass temporal filtering adapted to the frequency of the task (Gaussian-weighted least-squares straight line fitting, with sigma = 100.0 s, equalling ca. 0.005 Hz). In addition, sharp and brief in-volume motion was detected based on outliers in the sum of squared changes after the motion correction using the “fsl_motion_outliers”-script supplied with FSL. On the basis of this data, a confound matrix was created, removing the effect of these time points from the analysis in the final design matrix. Thus, effects depending on both subject position and subject velocity were removed as a first-order approximation, leaving autocorrelations intact and adjusting the degrees of freedom accordingly. Subjects exceeding a mean displacement of 0.4 mm were discarded.

A time-series statistical analysis was performed using FILM and local autocorrelation correction [Woolrich et al., 2001] was applied. Regressors coding actual tapping onset as detected by the video analysis were convolved with a double-gamma basis function imitating the shape of the hemodynamic response function (HRF). Further regressors comprised the six motion correction parameters, the movement outliers detected by the “sum of squared changes” analysis, and tic onset times and durations as recorded by the video system, if present. The latter regressor was also convolved with the HRF.

The following contrasts were computed for each subject:

- (i) Conditions R, L, and B > baseline, respectively, and
- (ii) Condition B > (0.5*[condition R] + 0.5*[condition L])

While the contrasts in (i) detected neuronal correlates relating to actual motor performance, contrast (ii) aimed at highlighting the motor control components involved in coordinating bimanual tapping but not directly related to open motor output (and being fully balanced for the latter). Contrast parameter estimates were carried up to a higher-level analysis. Functional data were coregistered onto their structural high-resolution counterparts and then transformed into standard MNI space using FLIRT [Jenkinson and Smith, 2001; Jenkinson et al., 2002].

Functional Imaging – Second-Level Image Analysis

Statistics were performed using FEAT stages 1 and 2 in a mixed-effects model. We calculated the group mean for each of the lower-level Z-statistics (R, L, B and (B > [0.5*R + 0.5*L])). In addition, demeaned behavioral data (frequency of in-scanner finger tapping = *f*(Patients) and

$f(\text{Controls})$, respectively) were added to the design matrix as covariates of interest. We calculated the following higher-level contrasts for each of the lower-level statistical maps:

- (1) Patients > Controls
- (2) Controls > Patients
- (3) $f(\text{Patients}) > f(\text{Controls})$
- (4) $f(\text{Controls}) > f(\text{Patients})$

While the first two contrasts estimated global group-specific differences in BOLD signal, the last two contrasts compared changes relating to an increase in tapping frequencies across groups. This was motivated by the assumption that neuronal patterns would differ as task complexity increased.

Demeaned age, YGTSS scores, and comorbidities (OCD and/or ADHD as yes/no, respectively), as well as current medication status (yes/no) and sex, were entered as covariates of no interest to account for their respective variances. Resulting whole brain Z-statistics were thresholded using cluster-thresholding methods (Keith, 2003) as implemented in FSL ($Z \geq 2.0$, corrected cluster $P \leq 0.05$).

Functional Imaging - Correction for Structural Nuisance Variables

It has been shown previously that differences in brain structure can lead to systematic errors and pseudo-activations in the data not attributable to metabolic but to structural changes [Oakes et al., 2007]. Because many of the recognized structural changes in TS actually affect the motor system [Plessen et al., 2009], we incorporated voxel-based morphometric (VBM) data into the GLM, thus reducing the probability of structure-related false-positive activations. VBM data were generated using subjects' high-resolution structural MRIs following the method described by Oakes et al. [2007] in a fully automated fashion using FSL software. The resulting subject-specific voxel-wise regressors were fed into the second-level design matrix as covariates of no interest.

Functional Imaging - Functional Connectivity

Group differences in connectivity were analyzed using MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components), Version 3.09, and a subsequent dual regression analysis as previously described [Filippini et al., 2009]. After standard pre-statistical processing (including motion correction, brain extraction, spatial smoothing (FWHM 8 mm) and high-pass temporal filtering (sigma 100 s/0.005 Hz), functional data were coregistered into standard MNI space via the individuals' structural scans. Preprocessed data were concatenated temporally and then decomposed into spatially independent maps representative of the whole study sam-

ple using probabilistic principal component analysis with automatic estimation of the number of dimensions [Beckmann and Smith, 2004]. An underestimation of the dimensionality would lead to the discarding of valuable information and result in suboptimal signal extraction. Overestimation, however, would result in a large number of spurious components due to an unrestrained estimation and a factorization which would over-fit the data, impairing later inference indications and dramatically increasing computational costs. Within the probabilistic Principle Component Analysis (PCA) framework, it has been demonstrated, however, that the number of source processes can be inferred from the covariance matrix of the observations using a Bayesian framework that approximates the posterior distribution of the model order, taking account of the limited amount of data and the particular structure of fMRI noise.

Estimated component maps were thresholded with a mixture-model probability of $P > 0.5$ by fitting a mixture model to the histogram of intensity values. Voxels with a Z-score > 6 belonging to the respective maps were plotted on a standard MNI-152 brain. The first three components relating to known motor functions and/or motor control were selected on a neuroanatomical basis using cytoarchitectonic probability maps as a reference [Eickhoff et al., 2005]: component (1) right primary somatosensory cortex (BA4), SMA (mesial BA6), left cerebellum; component (2) left primary somatosensory cortex (BA4), SMA (mesial BA6), right cerebellum; and component (3) pre-SMA, ventral prefrontal cortex (BA44/45) and inferior parietal cortex bilaterally. To further validate our selection, first principal eigenvectors (calculated from all pertaining time courses of this map, variance normalized) were correlated with the time course of the task. Spearman's rank rho was calculated and tested for significance.

Dual regression analysis was then performed as follows: selected components were spatially regressed against the individual fMRI data sets to identify matrices describing subject and map-specific time courses. These time courses were used to estimate the respective spatial map for each subject (temporal regression). Finally, all these maps were tested voxel-wise for statistically significant group differences using nonparametric permutation testing with 5,000 permutations [Nichols and Holmes, 2002]. Again, group membership and tapping frequencies were entered as independent variables into the analysis. Contrasts were the same as in the functional imaging analysis. A corrected cluster significance level of $P \leq 0.05$ TFCE [threshold-free cluster estimation [Smith and Nichols, 2009]] was chosen for permutation testing.

RESULTS

Behavioral Analysis: Data Do Not Differ Across Groups

Although patients experienced an average of 20.1 tics (range 0–58, SD 16.5) during the whole measurement,

tapping frequencies did not differ across groups in Welch's t test (group mean Controls: 1.84/s, group mean TS: 1.77/s, $t(28.317) = 0.4032$, $P = 0.69$). Fewer tics were registered during task performance than during rest periods. In addition, it was found that the age factor, along with YGTSS-motor and YGTSS-vocal factors, had no impact on task performance using multiple linear regression ($F(3,33)$: 0.009142, $P = 0.9988$; single P values were 0.994, 0.945, and 0.973, respectively).

Functional Imaging Analysis: Differences in Functional Imaging Increase With Task Demands

Condition "R"

Contrasting TS > Controls did not show a differential pattern of activation at the threshold chosen. On the other hand, we observed brainstem and cerebellar signals in contrast 2, indicating higher neuronal activation in controls than in patients during right-handed tapping (Fig. 1A and Table II for coordinates). The absolute maximum and the majority of remaining local maxima were localized within the left corticospinal tract as referenced by cytoarchitectonic probability maps, but spread to right cerebellar structures too.

The interaction contrasts of group and performance (contrast 3 and 4) did not reveal any significant activation for right-handed tapping.

Condition "L"

Comparing patients with controls, a differential network of activation spreading from the posterior cingulate cortex (PCC) over the precuneus and bilateral parietal cortices into the right angular gyrus was observed. In addition, frontal activation with a focus on the left dorsolateral prefrontal cortex was noted (Fig. 1B; Table II). The opposite contrast 2 did not reveal any significant differences. Turning to performance-related activation patterns (contrasts 3 and 4), we observed no patient- or control-specific activations.

Condition "B"

Comparing mean activation images for bimanual tapping of healthy adults with patients and vice versa, no differential activations were observed. Contrast 3, however, testing for performance-related differences in the TS patients as opposed to controls, detected a single frontopolar cluster of activation, anterior of and slightly overlapping with left BA45 (Fig. 1C; Table II). No significant activations could be observed in contrast 4.

Condition "B > ([0.5*R] + [0.5*L])"

This contrast aimed at detecting activation related to the "motor-control" related aspects of bimanual tapping while

Figure 1.

Differential functional activations induced by the motor task. (A) Contrast 2 (Controls > Patients), highlighting left corticospinal tract superior to the pyramidal decussation and right cerebellum in condition "R". (B) Network of activation evoked by tapping with the nondominant hand in Tourette's syndrome patients (contrast 1, Patients > Controls, condition "L") with activations in PCC, right parietal cortex, and left prefrontal cortex. (C) Left prefrontal cortex activation elicited by increasing bimanual tapping frequencies in patients as opposed to controls (contrast 3, $f(\text{Patients}) > f(\text{Controls})$, condition "B"). (D) Left panel: Tapping the cognitive domain of a motor act by subtracting conditions "R" and "L" from "B" and then comparing across groups: specific activation of ACC in healthy controls (contrast 2, Controls > Patients, condition "B > ([0.5*R] + [0.5*L])"). All images comply with radiological convention and are thresholded at $P < 0.05$, cluster corrected. Color coding: $2.3 < z < 4.8$ Right panel: Averaged parameter estimates for the activated voxels in panel D show a selective activation of the anterior cingulate cortex for condition B in the control group (dark grey) only, whereas patients (light grey) recruit this area for all conditions, yielding a positive interaction term. Error bars: standard error.

being fully controlled for all motor aspects of task execution itself even on the intrasubject level. On the group level, activation along the anterior cingulate cortex (ACC) could be detected in the healthy control group only when compared with the patient group (Fig. 1D, left panel, $P < 0.05$ cluster corrected for multiple comparisons, Table II).

TABLE II. Coordinates of functional activations from the conventional GLM analysis in standard MNI space

	<i>x</i>	<i>y</i>	<i>z</i>	Cluster size	Z-score	Anatomy
Condition R						
Control > Tourette	−10	−22	−24	607	4.46	Left corticospinal tract
Condition L						
Tourette > Control	2	−50	10	960	4.81	Right posterior cingulate gyrus
	−28	−84	34	955	4.60	Left lateral occipital cortex
	−10	−58	62	791	4.70	Left precuneus/superior parietal lobule
	−30	26	50	612	4.58	Left middle frontal gyrus
	54	−48	34	421	4.11	Right angular gyrus
Condition B						
Tourette > Control	−52	42	10	417	4.62	Left frontal pole/anterior part of BA 45
B-(0.5*R+0.5*L)						
Control > Tourette	−6	36	−8	399	4.41	Paracingulate gyrus/anterior left cingulate gyrus

Peak voxel coordinates for each cluster found are given in millimeters with their respective Z-scores.
BA, Brodmann area.

Inspection of the parameter estimates revealed that this was due to the continuous activation of this area in TS during all three conditions, as opposed to a selective activation here for the “difficult” condition in the control group (Fig. 1D, right panel).

Apart from that, no Tourette-specific activations could be seen. Correlating task performance with group-specific activations did not show any significant differences.

Performance-Related Patterns of Functional Connectivity Distinguish TS Patients From Controls

Independent component analysis (ICA) yielded a total of 46 components. The first 10 components made up 68.51% of all the explained variance and included primary motor, somatosensory, and auditory components, as well as components related to motion and physiological noise (data not shown). Of these, the first three components were actually related to motor control and were selected for further analysis (Fig. 2A–C; Table III). Correlation with the task time-course was highly significant for all three selected components ($P < 0.0001$). Spearman’s rank rho was 0.68 for component 1, 0.64 for component 2 and 0.31 for component 3.

Component 1

This component comprising of primary right-sided sensorimotor areas, SMA (BA6 as defined by cytoarchitectonic probability maps) and the left cerebellum most probably reflected left-hand tapping. When testing for absolute group differences, no significant clusters could be identified. However, when connectivity patterns were related to

performance, increased connectivity with a right temporal region (posterior part of superior temporal gyrus, $x = 70$, $y = -30$, $z = 20$) was observed solely in the patient group (Fig. 3A). This differential pattern was significant.

Component 2

Here, coherent activation patterns in the left-hemispheric primary sensorimotor areas, SMA (BA6) and right-sided cerebellar activations were presumably evoked by right-handed tapping. Comparing absolute and performance-related connectivity maps did not yield significant differences in either direction.

Component 3

This component included mesial premotor activations in the paracingulate gyrus/anterior cingulate gyrus, just anterior to that seen in components 1 and 2, associated with activations in the posterior division of supramarginal gyrus bilaterally as well as bilateral frontal operculum (BA44/45). No absolute differences in connectivity were observed across groups. When we analyzed performance-related connectivity patterns, however, significantly stronger associations of this component with a cluster of right frontopolar activation ($x = 38$, $y = 60$, $z = -10$) could be shown, indicating the significantly higher connectivity of this map with increasing tapping frequencies for TS patients (Fig. 3B).

DISCUSSION

Using fMRI followed by multi-modal data analysis, we show profound differences in motor-task-related neuronal

Figure 2.

Results of data-driven independent component analysis. **(A)** Component 1, including right primary sensory and motor cortices along with SMA and left cerebellum, most probably pertaining to left-hand motor activity. **(B)** Component 2, mirroring component 1 by encompassing left primary sensorimotor cor-

tex, SMA, and right cerebellum, probably reflecting right-hand motor activity. **(C)** Component three with symmetrical activation of BA44/45, angular gyrus, and pre-SMA. All maps are thresholded with a mixture-modelling $P < 0.5$. Color coding A+B: $6 < z < 32$. Color coding C: $6 < z < 10$.

activation patterns between adult patients suffering from TS and matched controls. These differences included changes in standard functional imaging as well as changes in functional connectivity as measured by a data-driven ICA approach.

Functional Imaging Reveals Multilevel Affection of the Motor System in TS

Our data seem to imply that the motor system in TS is affected on several levels both anatomically and functionally: regarding the low-level condition “R” (i.e., dominant hand tapping), we show an increase in blood flow in cerebellar and brain-stem structures along the (left) corticospinal tract in the control population. On a structural level, left midbrain has been previously identified as significant in TS, in terms of increased midbrain grey matter den-

sities, including midbrain reticular nuclei [Garraux et al., 2006]. Recent structural findings also point to changes in the white matter of the corticospinal tract [Neuner et al., 2010]. Although in principle our signal in this contrast could therefore be derived from structural differences only, we took particular care to correct for that possibility (see Methods section). Considering the cerebellar part of the activation, it has been shown that the cerebellum is activated by increases in tapping frequency [Sadato et al., 1996]. However, behavioral differences are not a plausible explanation for this activation: first, no behavioral differences could be detected between groups, and second, correlation with frequency did not show any related group differences in the functional data. Thus, our data on right-handed sequential tapping seem to support changes in midbrain and cerebellum function as structural changes previously described in other studies of TS,

TABLE III. Characteristics of the first three identified ICA components

	<i>x</i>	<i>y</i>	<i>z</i>	Z-score	Anatomy
Component 1	42	-22	60	32,4	Right primary somatosensory cortex BA1 R/primary motor cortex BA4a
	2	-6	56	10,7	Right mesial premotor cortex BA6
	-18	-50	-24	15,6	Left cerebellum, anterior lobe
Component 2	-38	-24	60	37,2	Left primary motor cortex BA4a
	-2	-8	54	11,5	Left mesial premotor cortex BA6
	18	-54	-20	14,7	Right cerebellum, anterior lobe
Component 3	2	14	48	10,7	Right mesial premotor cortex BA6
	-52	42	10	7,9	Left orbitofrontal cortex BA44/45
	46	18	-2	6,15	Right orbitofrontal cortex BA44/45
	-58	-46	34	7,2	Left supramarginal gyrus, posterior part
	62	-42	36	6,8	Right supramarginal gyrus, posterior part

Peak voxel coordinates in millimeters are given in standard MNI space along with the maximum Z-score at this coordinate. All maps were thresholded at a mixture-modelling $P > 0.5$ as a whole. BA, Brodmann area.

complementing previously known cortical changes in activation [Serrien et al., 2002].

Increasing Task Demands Lead to an Increase in Areas Related to Motor Control

When tasks demands increase, as in conditions “L” and “B” (signifying tapping with the nondominant hand and both hands, respectively), an increase in cortical BOLD signals encompassing the PCC and precuneus, the parietal cortices and left prefrontal cortex occurred for the TS group, partially in a frequency-dependent manner (condition “B”, left prefrontal cortex).

The integrity of the precuneus/PCC function has been shown to be essential for self-referential processes and introspection [Lou et al., 2005]. As such, it is seen as an essential component of the so-called default mode network

(DMN) during resting state analyses [Chen et al., 2008; Damoiseaux et al., 2006; Raichle and Snyder, 2007]. Activations in these areas are usually anti-correlated with cognitively demanding tasks [Cavanna and Trimble, 2006]. Therefore, the activation of the precuneus/PCC in an overt voluntary motion task could imply a failure of deactivating the DMN during task execution. This would be compatible with the notion of disturbed DMN connectivity in a multitude of conditions [Cauda et al., 2009; Rombouts et al., 2005; Sorg et al., 2007; Zhang et al., 2007]. On the other hand, it is known from studies on the macaque monkey that the precuneus is tightly interconnected with superior parietal cortices as well as with the prefrontal cortex [Cavada and Goldman-Rakic, 1989; Selemon and Goldman-Rakic, 1988]. In humans, these areas are judged to be part of a network responsible for online adaptive control [Dosenbach et al., 2007] and to be differentially connected

Figure 3.

Altered connectivity patterns in Tourette's syndrome. (A) Difference in connectivity of component 1 (red) with right superior temporal gyrus, posterior part (blue) in Tourette's syndrome with increasing tapping speed. (B) Tourette-specific, frequency-

related connectivity of component 3 (red) with right prefrontal cortex (blue). Both differential connectivity patterns are significant at $P < 0.05$ TFCE, corrected for multiple comparisons. Color coding: red: $6 < z < 10$; blue: $0.05 > P > 0$.

in pediatric TS [Church et al., 2009]. Thus, precuneus/PCC activation during a task could reflect the possible integration of these areas into the action monitoring network described above.

Increasing task demands (nondominant hand, higher tapping frequencies) could furthermore explain the differential prefrontal activation seen in conditions “L” and “B”, given the well-known role of the prefrontal cortex in monitoring conflicting task-related sensory feedback [Fink et al., 1999] and executive control in motor tasks in general [Tanji and Hoshi, 2008]. Again, this functional finding complements structural data, implying prefrontal changes in TS [Müller-Vahl et al., 2009; Peterson et al., 2001; Plessen et al., 2009]. In terms of functional connectivity, differential coactivation of the right superior temporal gyrus (STG) was observed in the TS patients when testing for performance-related connectivity in the left-hand ICA map. The superior temporal gyrus (right) has previously been implied in the occurrence of tics in TS [Stern et al., 2000], illustrating the fact that tic and motor-related networks are interwoven.

Taking these findings together, changes in functional activation along a gradient of difficulty could mirror neural compensatory mechanisms involving cortical areas implied in cognitive control. We postulate that these cortical compensatory mechanisms could make up for the clear impairments in striatal loops, thus enabling a population of quite severely affected individuals to perform comparably with a healthy control population. We acknowledge of course that it is always very difficult to disentangle changes caused by diverse factors such as primary pathology, compensation, or adaptation.

Subgenual ACC Fails to Modulate With Increasing Task Demands, and Functional Connectivity of Higher-Order Motor Networks Is Altered in TS

When examining all aspects of open motor performance by subtracting both conditions “R” and “L” from condition “B”, significant group differences occur in the BOLD signal of the control group in the subgenual ACC. The parameter estimates indicate that this is due to a continuous activation of this region during all conditions R, L, and B in patients, whereas controls selectively activated this area during the bimanual tapping condition. Considering that ACC is a critical node in online action monitoring [Posner and Dehaene, 1994] and conflict detection [Carter et al., 1998; Rushworth et al., 2004], this seems to imply that in TS there is a particular need for the recruitment of this area even in cognitively less demanding motor tasks.

To explain this, converging evidence points to a dysfunctional ACC in TS: it has been shown that ACC dopamine levels are decreased in TS [Gilbert et al., 2006]. In addition, ACC activation in a task involving cognitive control can be abolished by lesioning the subthalamic nucleus

[Schroeder et al., 2002], accompanied by an activation decrease in the ventral striatum. Ventral striatum has recently been shown to be functionally connected to ACC [Di Martino et al., 2008], thus closing the “ACC loop” as proposed by Alexander et al. [1990]. Increased BOLD signal in ACC could therefore be seen as a correlate of compensatory mechanisms attempting to rectify disturbed striatal input. Thus, we feel that our data is in line with converging evidence indicating alterations in the cortico-striato-thalamo-cortical circuits with a focus on the subgenual cingulate cortex.

Our data-driven approach using ICA also identified a highly task-related, higher-order motor network, including a mesial prefrontal area anterior to that seen in the primary-motor related components, potentially equalling pre-SMA, the putative analogue of the macaque area F6 [Geyer, 2004]. Highly correlated activation can be observed in posterior parietal cortices bilaterally, consistent with anatomical connections described between F6 and posterior parietal areas PG and PFG [Geyer et al., 2000]. In addition, bilateral activation in prefrontal/opercular areas (BA44/45) is evident on this map. Prefrontal connections to pre-SMA have also been described in the macaque, and BA44 has been shown to be essential in initiating movements [Nishitani and Hari, 2000] and encoding sequential actions [Clerget et al., 2009] or sequences in general [Bahlmann et al., 2009]. Thus, prefrontal areas together with the pre-SMA and parietal cortex seem to form a higher-order motor network in our data. The connectivity of this network was differentially modulated by an increase in tapping frequency (Fig. 3B): in the TS patients, an increase of tapping frequency was accompanied by additional connectivity to a cluster of right prefrontal activation. Previously, the prefrontal cortex has been associated with a number of aspects of cognitive control [Tanji and Hoshi, 2008] and attention [Marklund et al., 2007]. Frontopolar cortex in particular has been linked with global functioning in a verbal fluency task in schizophrenia [Takizawa et al., 2008]. Although we cannot make any statements concerning the direction of this influence, it could be argued that with increasing tapping speed, additional prefrontal input to the motor network detected by the ICA analysis is necessary to keep performance up in TS. Further studies using rapid-TR phase-shift fMRI, MEG or coupled EEG-fMRI using mathematical models using directionality such as Granger Causality or Dynamic Causal Modelling could help elucidate this issue.

Finally, although we did not perform a longitudinal study ourselves, it could be argued that our results extend the developmental trajectory of failing maturation in cortical networks in children and adolescents as described by Church et al. [2009] into adulthood. Delayed, but effectively complete, maturation of cortical network connectivity could thus be postulated to represent the pathophysiological basis of TS remitting once adulthood has been reached, whereas an incomplete and prematurely blocked process of maturation could lead to persisting TS even in older patients.

Performing longitudinal studies with an extended age range should help to verify this hypothesis.

CONCLUSION

Using fMRI followed by multi-modal data analysis techniques in a sequential finger-tapping motor paradigm involving uni- and bimanual tapping, we detected profound alterations in the human motor system in TS, ranging from changes in midbrain and cerebellar activations in low-level conditions up to alterations in the functional connectivity of higher-order networks and altered functional activations in conditions of increased task complexity. Areas known to be involved in TS on a structural level were affected on a functional level in our study. However, by building structural information into our analyses, we ensured that our results were not affected by these changes. Our data complement previous structural data on the motor system in TS by demonstrating corresponding functional changes in higher-order cortical motor systems, in particular, dysfunctional subgenual ACC. Longitudinal studies and interventional studies are needed to evaluate whether these changes are static or dynamic in nature, and whether they can be modulated by pharmacological or behavioral interventions.

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