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The Neural Circuits that Generate Tics in Gilles de la Tourette Syndrome

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Abstract

Objective—To study neural activity and connectivity within cortico-striato-thalamo-cortical circuits and to reveal circuit-based neural mechanisms that govern tic generation in Tourette syndrome.

Method—We acquired fMRI data from 13 participants with Tourette syndrome and 21 controls during spontaneous or simulated tics. We used independent component analysis with hierarchical partner matching to isolate neural activity within functionally distinct regions of cortico-striato-thalamo-cortical circuits. We used Granger causality to investigate causal interactions among these regions.

Results—We found that the Tourette group exhibited stronger neural activity and interregional causality than controls throughout all portions of the motor pathway including sensorimotor cortex, putamen, pallidum, and substantia nigra. Activity in these areas correlated positively with the severity of tic symptoms. Activity within the Tourette group was stronger during spontaneous tics than during voluntary tics in somatosensory and posterior parietal cortices, putamen, and amygdala/hippocampus complex, suggesting that activity in these regions may represent features of the premonitory urges that generate spontaneous tic behaviors. In contrast, activity was weaker in the Tourette group than in controls within portions of cortico-striato-thalamo-cortical circuits that exert top-down control over motor pathways (caudate and anterior cingulate cortex), and progressively less activity in these regions accompanied more severe tic symptoms, suggesting that faulty activity in these circuits may fail to control tic behaviors or the premonitory urges that generate them.

Conclusions—Our findings taken together suggest that tics are caused by the combined effects of excessive activity in motor pathways and reduced activation in control portions of cortico-striato-thalamo-cortical circuits.

INTRODUCTION

Tourette syndrome is a neuropsychiatric disorder that preferentially affects the face, neck, shoulders, and vocal apparatus to produce involuntary motor and vocal tic behaviors.

Anatomical, functional, and lesion studies suggest that Tourette is caused by a failure of cortico-striato-thalamo-cortical circuits to inhibit the somatosensory urges and associated motor enactments that constitute tic behaviors (1–8). This hypothesis has yet to be verified, however, by studies of isolated neural activity of the functionally distinct regions that compose cortico-striato-thalamo-cortical circuits as Tourette patients tic spontaneously compared with healthy individuals performing similar behaviors voluntarily.

Prior functional imaging studies of Tourette syndrome have attempted to correlate regional brain activity with the temporal occurrence of tics (9,10), but they have not compared activity during spontaneous tics in Tourette patients with activity during similar voluntary behaviors in healthy controls. They also have not assessed causality among brain regions during tics because they could not detect isolated neural activity from each of the functionally distinct regions that compose cortico-striato-thalamo-cortical circuits. One study compared the cross-correlations of brain activity in the primary motor cortex with somatosensory and supplementary motor cortex, and subcortical nuclei, between Tourette patients during tics and controls when simulating tics (11). Group differences were detected only in the supplementary motor area. This limited finding might be attributed to inherent constraints of region-of-interest analyses, which use a pre-determined set of regions rather than those in which activations are found empirically (12).

We therefore acquired fMRI data from 13 Tourette patients as they alternately either allowed their tics to occur spontaneously (*spontaneous tics*) or as they voluntarily produced a single tic-like behavior at a time of their own choosing (*voluntary tics*). We also acquired fMRI data from 21 healthy controls who alternately either produced a practiced tic-like behavior at a time of their own choosing (*self-paced mimicked tics*) or an identical behavior at a time of the experimenter's choosing, as cued by a simple auditory tone (*cue-paced mimicked tics*). This combination of two diagnostic groups performing two tasks each produced four run types of fMRI data. We hypothesized that we would detect greater neural activity within sensorimotor portions of cortico-striato-thalamo-cortical circuits in the Tourette group during spontaneous tics than in controls during self-paced mimicked tics, in direct proportion to the severity of tic symptoms. We also hypothesized that we would detect reduced activity in brain regions thought to exert control over these motor pathways (13).

Despite these strong *a priori* hypotheses, sensorimotor and control portions of cortico-striato-thalamo-cortical circuits involve multiple brain regions, and the precise location of the regions that generate, control, or modulate tic behaviors and premonitory urges in persons with Tourette remains uncertain. We therefore used a data-driven approach – Independent Component Analysis to detect coherent, spatially localized and task-related BOLD activity in each run type of fMRI data. Independent component analysis is a multivariate method for the analysis of fMRI datasets that can separate noise from physiological signals without knowing *a priori* the defining characteristics of the noise and signal or how they are inter-mixed (14,15). Independent component analysis maximizes mutual information within a component while minimizing it between components to identify BOLD activity within brain regions that are functionally distinct and spatially isolated from one another (14, 16, 17). Because BOLD activity is an index of task-related neural activity (18), the regional isolation of BOLD activity using independent component analysis is

thought to identify regions in which neural activity is coherent (i.e., where BOLD signals are mutually phase-coupled) and that therefore constitute either a neural circuit or a portion of one (14,16,17). We applied independent component analysis together with a hierarchical extension of our partner matching algorithm (17) to identify independent components that were reproducible across individuals and across each fMRI run type during the production of tics or tic-like behaviors. To clarify how circuits that generate tics interact with those that control them, we also calculated the Granger causality index (19, 20) as a measure of causal interactions among components of cortico-striato-thalamo-cortical circuits that are known to generate or control motor behaviors (5,21–24).

METHOD

Participants

Thirteen participants with Tourette and 21 age-matched healthy participants were scanned (Table 1; Supplemental Materials). Controls could not have prior psychiatric illness; Tourette patients could not have lifetime illness other than OCD or ADHD. Tourette participants were required to have a right facial tic to ensure a comparable location of neural generator for at least one tic across participants and to ensure comparability of behavior during spontaneous and mimicked tics. Patients who had large-amplitude excursion tics were excluded to minimize motion artifact. All Tourette participants reported premonitory urges. Assessments included the Schedule for Tourette and Other Behavioral Syndromes (25), Yale Global Tic Severity Scale (26), Yale-Brown Obsessive-Compulsive Scale (27), and ADHD rating scale (28). Written informed consent was obtained from all participants, and the study was approved by our Institutional Review Boards.

Experimental Design

The Supplemental Materials provide more details of study design and its rationale. Each diagnostic group underwent two types of scanning runs that were unique to each group and that were event-related in design. In the Tourette group, one run type (*spontaneous tics*) consisted of allowing all tics to occur spontaneously and naturally, without forcing or inhibiting them. The other run type (*voluntary tics*) consisted of performing a voluntary movement that emulated a right-sided facial tic at a rate that eliminated the premonitory urge normally preceding that tic, thereby eliminating the need to perform the spontaneous tic. For the control group, both run types consisted of voluntary movements emulating a single right-sided facial tic, but in one run type (*self-paced mimicked tics*) these movements were self-paced, and in the other (*cue-paced mimicked tics*) they were prompted by an auditory cue at the same rate as their self-paced mimicked tics. Pacing with a sensory cue was included in control participants because tics are usually performed in response to an internal cue (the premonitory urge); the auditory cue was included to control in part for this cue-driven feature of tics.

Image Acquisition

Imaging was performed on a GE 1.5T Signa Scanner (Milwaukee, WI). Functional images consisted of 10 axial slices acquired using a gradient-recalled single-shot echo-planar pulse sequence with repetition time=1200ms, echo time=60msec, flip angle=60°, matrix=128×64,

FOV=40×20cm, providing an in-plane resolution of 3.125×3.125mm, with 102 images acquired per run type. We acquired four run types of fMRI data corresponding to the two conditions for the two groups.

Image Analysis

Standard fMRI data preprocessing procedures included slice-timing and motion correction, spatial normalization, and smoothing. We performed independent component analysis on the preprocessed run types, using information criteria to determine the number of sets of independent components to generate. We used hierarchical partner-matching, an extension of our previously validated partner-matching algorithm (17), to identify task-related independent components that were reproducible across participants and run types. Briefly, partner-matching uses a measure of spatial similarity (Tanimoto distance) to find independent components that “match” across all participants and run types (17). This procedure identifies corresponding components across participants, given that components never perfectly align across participants. Our hierarchical extension of partner-matching determines automatically the optimal number of components to generate for each participant and each run type. First, it uses information criteria to estimate the lower and upper bounds of the numbers of independent components to generate. It then samples from this space of possible components (from the lower to the upper bound, in increments of 10) to determine the optimal number of components to generate for each participant and run type. It then combines the matched components and uses partner-matching to identify those independent components that are most reproducible across participants, diagnostic groups, and run type (i.e., task), independent of the choice of the number of independent components that were generated. We used Granger causality to analyze causal influences across the regions identified by these components (Supplemental Materials).

RESULTS

Reproducible Independent Components

Independent component analysis generated 12 different sets of independent components for each run type within each participant. Hierarchical partner-matching applied to these 12 sets of components identified 15 clusters of independent components that were significantly reproducible in their spatial patterns across participants, diagnostic groups, and run types. We used the general linear model under SPM to perform a one-sample t-test on each of the 15 clusters, covarying for age and sex, to generate 15 random-effect, independent component maps (Table 2, Fig. 1). Each of the 15 maps represented neural activity in regions that should be functionally interconnected to perform similar functions (16,17).

Comparing Activity across Diagnostic Groups

General linear modeling compared activity between the Tourette and control groups while covarying for age and sex in each of the 15 clusters of independent components. Generally, neural activity was significantly stronger in the Tourette participants during spontaneous tics than in controls during the production of self-paced mimicked tics (Fig. 1), and activity in each region in the Tourette group correlated positively with tic severity (Fig. 2). A listing of regions for which this was true, together with significant correlations with current tic

severity (in parentheses), includes: primary motor cortex ($r=0.82$, $p<0.001$); primary somatosensory cortex; posterior parietal cortex ($r=0.81$, $p<0.01$); supplementary motor area ($r=0.74$, $p<0.01$); premotor area; left prefrontal cortex ($r=0.75$, $p<0.01$); both globus pallida ($r=0.71$, $p<0.01$); both putamen; each hemi-thalamus ($r=0.72$, $p<0.01$); substantia nigra ($r=0.74$, $p<0.01$); amygdala/hippocampus complex; and cerebellar lobules IV–V ($r=0.86$, $p<0.01$). In a small number of regions, activity was weaker in the Tourette group and correlated inversely with tic severity (Fig 2). These include anterior cingulate cortex ($r=-0.87$, $p<0.001$), both caudate nuclei ($r=-0.90$, $p<0.001$), and parietal operculum ($r=-0.80$, $p<0.01$). We detected nearly identical group differences when comparing neural activity in Tourette participants during voluntary tics with activity in controls during cue-paced mimicked tics, except that groups did not differ in activity of parietal operculum, and caudate activity did not correlate significantly with tic severity (Table 2). All these group differences were unchanged when covarying for medication, OCD, and ADHD in the Tourette participants.

Comparing Activity across Tasks within Each Diagnostic Group

We performed a paired t-test assessing within-subject differences in each of the 15 clusters across the two tasks, but within each group. This comparison in controls during self-paced versus cue-paced mimicked tics assessed whether pacing with a cue generated significant differences in activity compared with a self-generated behavior. We detected no significant differences in component activity across the two tasks in healthy controls. We also compared activity in Tourette participants during spontaneous tics versus activity during voluntary tics (Fig. 3) to identify activity uniquely associated with the generation of spontaneous tics. We detected significantly stronger activity during spontaneous tics within primary somatosensory and posterior parietal cortices, putamen, and the amygdala/hippocampus complex, compared with activity during voluntary tics.

Granger Causality Interactions among Cortico-Striato-Thalamo-Cortical Circuit Components

Granger causality indices assessed the causal interactions between the time courses of independent components involved in motor generation or control: primary motor and somatosensory cortices, supplementary motor and premotor areas, putamen, caudate, pallidum, thalamus, substantia nigra, and prefrontal cortex (Fig. 4)(21,22,24). This analysis produced two types of causality indices for each run type: $GCI_{A \rightarrow B}$ (influence of region A on B), and $GCI_{A \rightarrow B|C}$ (influence of region A on B through region C), where C was activity in the thalamus when assessing causal influences from basal ganglia to cortices. The Wilcoxon rank test was used to compare $GCI_{A \rightarrow B}$ and $GCI_{A \rightarrow B|C}$ for all connections defined by the motor circuit (Fig. 4), comparing each of them within and across diagnostic groups for the four run types (Supplemental Materials). Causal influences were stronger in the Tourette group during spontaneous tics than in controls during self-paced mimicked tics in connections from premotor to supplementary motor area [0.031 (0.024–0.088) vs. 0.008 (0.004–0.034), $p<0.01$] and vice-versa [0.023 (0.009–0.067) vs. 0.011 (0.004–0.018), $p<0.05$]; from primary somatosensory to primary motor cortex [0.071 (0.021–0.146) vs. 0.012 (0.004–0.067), $p<0.05$]; from substantia nigra to caudate [0.069 (0.041–0.112) vs. 0.015 (0.006–0.043), $p<0.01$] and putamen [0.028 (0.020–0.056) vs. 0.011 (0.005–0.023),

$p < 0.05$]; and from pallidum to supplementary motor area via thalamus [0.066 (0.034–0.100) vs. 0.022 (0.014–0.045), $p < 0.05$].

Causal influences were stronger in the Tourette group during voluntary tics than in controls during cue-paced mimicked tics in connections from prefrontal to premotor [0.028 (0.015–0.054) vs. 0.008 (0.002–0.023), $p < 0.05$] and supplementary motor cortex [0.037 (0.019–0.072) vs. 0.012 (0.004–0.019), $p < 0.01$]; from premotor to supplementary motor area [0.046 (0.024–0.162) vs. 0.006 (0.002–0.036), $p < 0.05$]; from premotor to primary motor cortex [0.069 (0.041–0.176) vs. 0.024 (0.002–0.043), $p < 0.01$]; from primary somatosensory cortex to putamen [0.065 (0.015–0.152) vs. 0.015 (0.007–0.042), $p < 0.05$]; from pallidum to thalamus [0.049 (0.016–0.070) vs. 0.019 (0.010–0.042), $p < 0.05$]; from substantia nigra to caudate [0.064 (0.025–0.073) vs. 0.016 (0.005–0.026), $p < 0.01$]. We compared but did not detect significant differences in the causal influences between run types within each of the normal and Tourette groups.

We also calculated the Spearman's rank correlation ρ between causality indices and symptom severity in the Tourette group. During spontaneous tics, we detected a positive correlation in connections between primary motor cortex and putamen ($\rho = 0.60$, $p < 0.05$). During voluntary tics, we detected positive correlations in connections from premotor to primary motor cortex ($\rho = 0.69$, $p < 0.05$), from primary somatosensory to primary motor cortex ($\rho = 0.61$, $p < 0.05$), from pallidum to supplementary motor area via thalamus ($\rho = 0.66$, $p < 0.05$), and from pallidum to primary motor cortex via thalamus ($\rho = 0.80$, $p < 0.01$).

DISCUSSION

We isolated neural activity within independent components representing portions of cortico-striato-thalamo-cortical circuits that participate in planning, controlling, and executing motor behaviors, including primary motor, supplementary motor, premotor, and somatosensory cortex; putamen, caudate, pallidum, thalamus, and substantia nigra; and prefrontal cortex (21,24,29). We detected these components during the expression of spontaneous tics in the Tourette group and during the voluntary imitation of a facial tic in both the Tourette and control groups. Activity in the Tourette group was greater during spontaneous tics than in controls during self-paced mimicked tics in most sensorimotor portions of cortico-striato-thalamo-cortical loops. Moreover, activity within these regions correlated positively with the severity of tics in the Tourette group, indicating that increasing activity within sensorimotor portions of these loops accompanied more severe tic behaviors. These findings demonstrate that tics engage the same neural circuits that support the expression of normal voluntary motor behaviors in healthy individuals. More severe tic symptoms simply produce more activity in these motor circuits.

Analyses of Granger causality demonstrated that the activity within sensorimotor pathways in the Tourette group during the spontaneous generation of tics follows a chain of causal influences within the pathways that have long been postulated in the generation of movement: from premotor to supplementary motor area, from primary somatosensory to primary motor cortex, from pallidum via thalamus to supplementary motor area, and from substantia nigra to the striatum. These measures of causal influence were stronger in the

Tourette group than in controls, suggesting an enhanced functional coupling of activity between successive nodes in this circuit in Tourette. Furthermore, the top-down causal influence from primary motor cortex to putamen during spontaneous tics and the bottom-up influence from the pallidum to primary motor cortex via the thalamus during voluntary tics correlated positively with tic severity, confirming that a stronger generation of tics may be caused by a greater interaction between motor cortices and striatum.

Activity in the anterior cingulate, parietal operculum, and caudate, in contrast, was significantly less in the Tourette group during spontaneous tics than in controls voluntarily mimicking tics, with less activity in each of these regions in the Tourette group accompanying more severe symptoms. The anterior cingulate and caudate represent cognitive control portions of cortico-striato-thalamo-cortical loops (23,30) that can modulate activity in sensorimotor portions of the striatum via striato-nigro-striatal (31) and striato-thalamo-striatal circuits (32). Activity in the anterior cingulate and caudate are known to increase during the successful and willful suppression of tic behaviors (33), with greater caudate activation accompanying fewer tic symptoms. Reduced activity in the anterior cingulate and caudate during spontaneous tics in the Tourette group therefore likely represented deficient engagement of circuits that inhibit either tic behaviors or the sensorimotor urges that produce them. These findings remained significant when comparing activity during spontaneous tics in the Tourette group with activity during cue-paced mimicked tics in controls, demonstrating that group differences were not simply the consequence of spontaneous tics being generated by cues (the premonitory urge). Thus our findings suggest that tics are caused by the combined effects of excessive activity in motor pathways and reduced activity in control portions of cortico-striato-thalamo-cortical circuits, consistent with recent evidence of abnormal development of control regions in Tourette patients (34).

The Tourette group exhibited greater activity in the putamen, somatosensory cortices (including primary somatosensory cortex and parietal operculum), and amygdala/hippocampus complex during the spontaneous generation of tics than during the voluntary imitation of tics, a contrast designed to help identify regions that contribute to the generation of spontaneous tics. Conceptually, spontaneous tics should differ from voluntary tics in the presence of (a) a “tic generator” during spontaneous tics, (b) premonitory urges associated with spontaneous tics (with the urges themselves possibly being the tic generators), or (c) volitional control during voluntary tics. Differences in neural activity between spontaneous and voluntary tics could derive from any of these three sources. Given the intense sensory and emotional salience of the premonitory urge in the subjective experience of Tourette patients (35,36), however, the differences in activity that we detected in primarily sensory and emotional pathways seem most likely to derive from intense sensory and emotional experiences associated with premonitory urges in the Tourette group. Therefore, we suspect that greater activity in somatosensory cortices likely represented the sensory features of those urges, whereas greater activity in the amygdala/hippocampus complex likely represented either the emotional discomfort associated with the urges before the tic or the relief experienced following the tic. The stronger Granger causality index from primary somatosensory to primary motor cortex during spontaneous tics in the Tourette group than in

controls during self-paced mimicked tics furthermore suggests that activity in sensory cortices from these premonitory urges causally influenced activity in motor pathways.

Greater activity in the amygdala in the Tourette group can have alternative explanations. The emotional experiences signaled by the amygdala can influence motor pathways via projections to the ventral striatum, which in turn influences motor areas in the dorsal striatum (31). These pathways are similar to those implicated in addictive behaviors (37) which, like the tics of Tourette, have compulsory qualities.

The Tourette group had greater neural activity than controls within the substantia nigra during the performance of spontaneous and voluntary tics. Causal influences of the nigra on the caudate were also stronger in the Tourette group during spontaneous tics than in controls during the performance of both self-paced and cue-paced mimicked tics. The pars compacta of the substantia nigra contains dopaminergic neurons that project to the striatum, and excessive striatal dopaminergic activity has long been suspected to play a role in Tourette (38). Our findings may therefore reflect overactive nigrostriatal dopaminergic activity in Tourette.

Our findings permit a detailed understanding of the circuit-based disturbances that together generate tics. They suggest that increased activity in primary somatosensory cortex, putamen, and amygdala/hippocampus may represent activity associated with the premonitory urge and act as a trigger for tic behaviors. They also indicate that primary sensory cortex exerts a causal influence on putamen that is greater in the Tourette group than in controls, presumably within the projection from sensory cortex to putamen that is known to be glutamatergic and excitatory. Findings furthermore suggest that increased activity in the putamen in the Tourette group exerts an increased causal influence on the pallidum, a projection that is inhibitory (GABAergic). The pallidum sends an inhibitory projection to the thalamus, and the thalamus in turn sends an excitatory projection to the motor cortex, a pathway that our data indicate overall has a stronger causal influence in the Tourette group than in controls. The stronger inhibitory influence of the putamen on the pallidum would therefore ultimately disinhibit thalamic excitation of the cortex, which should increase the production of tics, consistent with dysfunction that has long been postulated in the direct pathway of cortico-striato-thalamo-cortical circuits in Tourette (5). Finally, our findings indicate that the putative trigger from the premonitory sensory urge and the excess activity in motor portions of cortico-striato-thalamo-cortical circuits combines with reduced activity in the anterior cingulate and caudate, the putative control portions of these circuits, to yield disinhibited and poorly regulated motor activity in proportion to tic severity.

Our study has several limitations, including small sample size, inclusion of medicated patients and comorbid illnesses, and absence of adults with remitted symptoms. A follow-up study with a larger sample would help to assess more rigorously any possible effects of medications and comorbid illnesses. Our study, like others before it, was unable to control stringently for the strength, duration, or pacing of tics across conditions or groups (although visually the behaviors were indistinguishable across conditions and groups). Finally, our partner-matching technique detects independent components that are reproducible and can

be compared across conditions and groups; it does not permit identification of components unique to a condition or group.

Nevertheless, this is the first time to our knowledge that neural activity in all major components of a cortico-striato-thalamo-cortical circuit has been detected using an analysis of BOLD signals. Comparing activity in this circuit during a pathological involuntary behavior (spontaneous tics) with activity during a similar normal voluntary behavior (voluntary or mimicked tics) across patient and control groups allowed us to demonstrate that tics engage the same motor circuit as do normal voluntary behaviors. This comparison also permitted us to identify the somatosensory cortices, putamen, and amygdala/hippocampal complex as regions that likely subserve the experience of premonitory sensory urges and their associated emotional content. Finally, the comparison also allowed us to show that tics likely arise as a combined consequence of this sensory trigger, its contributions to the excessive activity in motor pathways, and faulty regulation from the anterior cingulate cortex and caudate nucleus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Albin RL, Mink JW. Recent advances in Tourette syndrome research. *Trends Neurosci.* 2006; 29:175–182. [PubMed: 16430974]
2. Groenewegen HJ, van den Heuvel OA, Cath DC, et al. Does an imbalance between the dorsal and ventral striatopallidal systems play a role in Tourette's syndrome? A neuronal circuit approach. *Brain Dev.* 2003; 25:S3–S14. [PubMed: 14980365]
3. Mink JW. Neurobiology of basal ganglia circuits in Tourette syndrome: faulty inhibition of unwanted motor patterns? *Adv Neurol.* 2001; 85:113–122. [PubMed: 11530421]
4. Mink JW. Basal ganglia dysfunction in Tourette's syndrome: a new hypothesis. *Pediatr Neurol.* 2001; 25:190–198. [PubMed: 11587872]
5. Mink JW. Neurobiology of basal ganglia and Tourette syndrome: basal ganglia circuits and thalamocortical outputs. *Adv Neurol.* 2006; 99:89–98. [PubMed: 16536354]
6. Peterson BS. Neuroimaging studies of Tourette syndrome: a decade of progress. *Adv Neurol.* 2001; 85:179–196. [PubMed: 11530427]
7. Peterson BS, Thomas P, Kane MJ, et al. Basal Ganglia volumes in patients with Gilles de la Tourette syndrome. *Arch Gen Psychiatry.* 2003; 60:415–424. [PubMed: 12695320]
8. Ziemann U, Paulus W, Rothenberger A. Decreased motor inhibition in Tourette's disorder: evidence from transcranial magnetic stimulation. *Am J Psychiatry.* 1997; 154:1277–1284. [PubMed: 9286189]
9. Baym CL, Corbett BA, Wright SB, et al. Neural correlates of tic severity and cognitive control in children with Tourette syndrome. *Brain.* 2008; 131:165–179. [PubMed: 18056159]

10. Bohlhalter S, Goldfine A, Matteson S, et al. Neural correlates of tic generation in Tourette syndrome: an event-related functional MRI study. *Brain*. 2006; 129:2029–2037. [PubMed: 16520330]
11. Hampson M, Tokoglu F, King RA, et al. Brain areas coactivating with motor cortex during chronic motor tics and intentional movements. *Biol Psychiatry*. 2009; 65:594–599. [PubMed: 19111281]
12. Poldrack RA. Region of interest analysis for fMRI. *Soc Cogn Affect Neurosci*. 2007; 2:67–70. [PubMed: 18985121]
13. Marsh, R.; Gorman, D.; Royal, J., et al. Tourette Syndrome and Obsessive-Compulsive Disorder: Disturbances in the Maturation of Frontostriatal Systems. In: Ernst, M.; Rumsey, J., editors. *Neuroimaging in Developmental Clinical Neuroscience*. Cambridge: Cambridge University; 2008. p. 200-217.
14. Jung TP, Makeig S, McKeown MJ, et al. Imaging brain dynamics using independent component analysis. *Proc of IEEE*. 2001; 89:1107–1122.
15. McKeown MJ, Makeig S, Brown GG, et al. Analysis of fMRI data by blind separation into independent spatial components. *Hum Brain Mapp*. 1998; 6:160–188. [PubMed: 9673671]
16. van de Ven VG, Formisano E, Prvulovic D, et al. Functional connectivity as revealed by spatial independent component analysis of fMRI measurements during rest. *Hum Brain Mapp*. 2004; 22:165–178. [PubMed: 15195284]
17. Wang Z, Peterson BS. Partner-matching for the automated identification of reproducible ICA components from fMRI datasets: algorithm and validation. *Hum Brain Mapp*. 2008; 29:875–893. [PubMed: 18058813]
18. Fox MD, Snyder AZ, Zacks JM, et al. Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nat Neurosci*. 2006; 9:23–25. [PubMed: 16341210]
19. Chen Y, Rangarajan G, Feng J, et al. Analyzing multiple nonlinear time series with extended Granger causality. *Physics letters A*. 2004; 324:26–35.
20. Granger CWJ. Investigating causal relations by econometric models and cross-spectral methods. *Econometrica*. 1969; 37:424–438.
21. Carlson, NR. Control of movement, in *Physiology of Behavior*. Needham Heights, MA: Allyn and Bacon; 1998. p. 224-251.
22. Eccles, JC. The Understanding of the Brain. New York: McGraw-Hill Book Company; 1977. The control of movement by the brain; p. 106-145.
23. Middleton FA, Strick PL. Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res Brain Res Rev*. 2000; 31:236–250. [PubMed: 10719151]
24. Passingham, RE.; Ramnani, N.; Rowe, JB. The motor system, in *Human Brain Function*. San Diego, CA: Elsevier Academic Press; 2004. p. 5-32.
25. Pauls, DL.; Hurst, CR. Schedule for Tourette and Other Behavioral Syndromes. New Haven, Conn: Yale University Child Study Center; 1996.
26. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry*. 1989; 28:566–573. [PubMed: 2768151]
27. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry*. 1989; 46:1006–1011. [PubMed: 2684084]
28. Barkley RA, DuPaul GJ, McMurray MB. Attention deficit disorder with and without hyperactivity: clinical response to three dose levels of methylphenidate. *Pediatrics*. 1991; 87:519–531. [PubMed: 2011430]
29. D'Ardenne K, McClure SM, Nystrom LE, et al. BOLD responses reflecting dopaminergic signals in the human ventral tegmental area. *Science*. 2008; 319:1264–1267. [PubMed: 18309087]
30. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain*. 1995; 118(Pt 1):279–306. [PubMed: 7895011]
31. Haber SN. The primate basal ganglia: parallel and integrative networks. *J Chem Neuroanat*. 2003; 26:317–330. [PubMed: 14729134]

32. de las Heras S, Mengual E, Gimenez-Amaya JM. Double retrograde tracer study of the thalamostriatal projections to the cat caudate nucleus. *Synapse*. 1999; 32:80–92. [PubMed: 10231128]
33. Peterson BS, Skudlarski P, Anderson AW, et al. A functional magnetic resonance imaging study of tic suppression in Tourette syndrome. *Arch Gen Psychiatry*. 1998; 55:326–333. [PubMed: 9554428]
34. Church JA, Fair DA, Dosenbach NU, et al. Control networks in paediatric Tourette syndrome show immature and anomalous patterns of functional connectivity. *Brain*. 2009; 132:225–238. [PubMed: 18952678]
35. Bliss J. Sensory experiences of Gilles de la Tourette syndrome. *Arch Gen Psychiatry*. 1980; 37:1343–1347. [PubMed: 6934713]
36. Cohen AJ, Leckman JF. Sensory phenomena associated with Gilles de la Tourette's syndrome. *J Clin Psychiatry*. 1992; 53:319–323. [PubMed: 1517194]
37. Belin D, Everitt BJ. Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. *Neuron*. 2008; 57:432–441. [PubMed: 18255035]
38. Steeves TD, Fox SH. Neurobiological basis of serotonin-dopamine antagonists in the treatment of Gilles de la Tourette syndrome. *Prog Brain Res*. 2008; 172:495–513. [PubMed: 18772048]

Figure 1. Comparisons of Neural Activity between Tourette Patients and Normal Controls

The first set of 3 columns (labeled “NC”) displays the random-effect group activity maps detected from 21 normal controls who generated *self-paced mimicked tics*. The first column is an axial view, the second is a coronal view, and the third is a parasagittal view. The second set of 3 columns (labeled “TS”) display the corresponding group activity maps detected from the 13 participants with Tourette who generated *spontaneous tics*. The third set of 3 columns (labeled “TS vs. NC”) displays t-contrast maps comparing the group activity maps from the control and Tourette groups shown in the first and second sets of columns. Each row within the first or second sets of columns displays one group activity map that was generated by applying a one-sample t-test to 1 of the 15 clusters of independent components. Each number at the left side of each row indicates that the group activity map on that row corresponds to a numbered cluster of independent components listed in Table I. Any 2 group activity maps within the same row across the first and second columns are significantly similar to one another in their spatial configurations. The figures show that compared with normal controls, the Tourette participants had stronger activity, as evidenced by the color red in the TS vs. NC columns, within primary motor cortex (M1), primary somatosensory cortex (S1), posterior parietal cortex (PPC), supplementary motor area (SMA), premotor area (PMA), left prefrontal cortex (PFC), pallidum, putamen,

thalamus, substantia nigra (SN), amygdala/Hippocampal complex, and cerebellar lobules IV–V. Compared with normal controls, the Tourette participants had weaker activity, as evidenced by the color blue in the TS vs. NC columns, within parietal operculum (PO), caudate, and anterior cingulate cortex (ACC).

Figure 2. Correlations of BOLD Activity with Tic Severity

Each panel is labeled by the name of the location of significant activity identified in the specific group activity map. The upper portion of each panel displays the correlation map produced by calculating at every voxel across the 12 Tourette participants for whom we had tic severity scores the correlation coefficient between tic severity and the z-score for each of the 15 clusters of independent components when generating *spontaneous tics*. We obtained 15 component maps, but 4 of those 15 had no voxels containing significant correlations with tic severity, and thus we display only the remaining 11 maps that did contain significant correlations. The lower portion of each panel shows the corresponding scatter-plot for the correlation of tic severity with the z-scores of that activity map averaged across voxels in the

identified cluster. Neural activity correlated significantly with severity scores in primary motor cortex (M1) ($r=0.82$, $p<0.001$); posterior parietal cortex (PPC) ($r=0.81$, $p<0.01$); supplementary motor area (SMA) ($r=0.74$, $p<0.01$); parietal operculum (PO) ($r=-0.80$, $p<0.01$, inversely correlated); left prefrontal cortex (PFC) ($r=0.75$, $p<0.01$); caudate ($r=-0.90$, $p<0.001$, inversely correlated); pallidum ($r=0.71$, $p<0.01$); thalamus ($r=0.72$, $p<0.01$); substantia nigra (SN) ($r=0.74$, $p<0.01$); anterior cingulate cortex (ACC) ($r=-0.87$, $p<0.001$, inversely correlated); cerebellum lobules IV–V ($r=0.86$, $p<0.01$).

Figure 3. Comparison of BOLD Activity for Spontaneous and Voluntary Tics in Tourette Participants

The first set of 3 columns displays the random-effect group activity maps detected from the 13 Tourette participants as they generated *spontaneous tics*. The second set of 3 columns displays the random-effect group activity maps detected in the same 13 participants when generating *voluntary tics*. The third set of columns displays the t-contrast maps that compare activity when generating *voluntary tics* with activity when generating *spontaneous tics*. Regions containing significant ($p < 0.05$) differences were left primary somatosensory cortex (S1), posterior parietal cortex (PPC), putamen, and amygdala. In each instance, activity during spontaneous tics was greater than during voluntary tics.

Figure 4. Motor Circuits That Are Hypothesized to Generate or to Control Tics

Shown here are volume renderings (generated using in-house JAVA3D-based volume rendering software) of the maps of independent components representing activity in motor pathways, including premotor area (PMA), supplementary motor area (SMA), primary motor cortex (M1), primary sensory cortex (S1), caudate, putamen, pallidum, substantia nigra (SN), thalamus, and prefrontal cortex (PFC), overlaid on a high-resolution anatomical template. Structures are color coded (and some are represented in the two hemispheres). The connections indicate the hypothesized directions of effective connectivity between regions based on previously published preclinical studies (21, 22, 24). Red arrows indicate the connection from cortices to basal ganglia, blue arrows indicate the connection from basal ganglia to cortices via thalamus, and green arrows indicate the connection between regions within cortices or basal ganglia.

Table I

Demographic and Clinical Characteristics of Subjects

Subjects			
Characteristic	Tourette Syndrome (n = 13)	Healthy Controls (n = 21)	Test Statistic
Age, y	33.5 (13.3)	32.5 (11.1)	$t_{32} = 0.41$; $p = 0.68$
Sex, M:F	8:5	12:9	$\chi^2 = 0.06$; $p = 0.80$
YGTSS score			
motor+phonic current	24.1 (10.1), range: 11–39		
motor+phonic worst ever	33.1 (6.8), range: 26–44		
Comorbidity #(%)			
OCD	6	0	
ADHD	2	0	
OCD/ADHD	1	0	
No comorbid illnesses	6	N/A	
Medication #			
SSRI's	4	0	
α -adrenergic agonists	1	0	
Benzodiazepines	1	0	
Medication free	7	21	

Abbreviations: ADHD, Attention-deficit/hyperactivity disorder; OCD, Obsessive-compulsive disorder; OCD/ADHD, obsessive-compulsive disorder and attention-deficit/hyperactivity disorder; YGTSS, Yale Global Tic Severity Scale; SSRIs, selective serotonin reuptake inhibitors

* Values are mean (SD) unless otherwise specified

* YGTSS scores were available in 12 of the 13 participants with Tourette Syndrome

Table 2

Locations for, and Between-Run-Type Comparisons of, the 15 Independent Component Maps

IC #	Talairach Coordinates and T-scores		Functional Anatomy	Comparisons Between Run Types				Correlation with Severity (TS only I_1)	
	Left hemisphere	Right hemisphere		TS spont vs. NC self- I_1	TS spont vs. TS vol	TS vol vs. NC cue- I_1	TS spont vs. TS vol	NC self- vs. NC cue-	TS spont
1	(-45, -19, 47), T=14.02	(42, -16, 44), T=6.73	Primary Motor Cortex (M1), BA4	Increased	Increased	Increased	NS ²	NS	r=-0.82, p<0.001
2	(-48, -19, 38), T=11.11	(57, -13, 41), T=11.14	Primary Somatosensory Cortex (S1), BA3b	Increased	Increased	Increased	Increased	NS	NS
3	(-36, -61, 47), T=10.90	(35, -58, 56), T=5.59	Posterior Parietal Cortex (PPC)	Increased	Increased	Increased	Increased	NS	r=-0.81, p<0.001
4	(0, 2, 50), T=9.17	R (0, -25, 56), T=7.11	Supplementary Motor Cortex (SMA), BA6	Increased	Increased	Increased	NS	NS	r=-0.74, p<0.01
5	(-51, -1, 44), T=8.77	(48, -4, 44), T=5.3	Premotor Area (PMA), BA6	Increased	Increased	Increased	NS	NS	NS
6	(-60, -16, 23), T=9.74	(63, -13, 17), T=13.24	Parietal Operculum (PO), S2, BA40	Decreased	NS	NS	NS	NS	r=-0.80, p<0.01
7	(-30, 47, 5), T=21.37		Left Prefrontal Cortex, BA45	Increased	Increased	Increased	NS	NS	r=-0.75, p<0.01
8	(-6, 11, 8), T=24.69	(6, 8, 5), T=24.24	Bilateral Caudate Nuclei	Decreased	Decreased	Decreased	NS	NS	r=-0.90, p<0.001
9	(-15, -7, 5), T=9.84	(18, -4, 11), T=7.24	Bilateral Pallidum	Increased	Increased	Increased	NS	NS	r=-0.71, p<0.01
10	(-27, -4, 2), T=8.32	(24, 2, 2), T=8.33	Bilateral Putamen	Increased	Increased	Increased	Increased	NS	NS
11	(-3, -19, 14), T=13.21	(9, -25, 14), T=14.63	Bilateral Thalamus	Increased	Increased	Increased	NS	NS	r=-0.72, p<0.01
12	(-9, -16, -8), T=8.45	(8, -18, -9), T=6.42	Substantia Nigra (SN)	Increased	Increased	Increased	NS	NS	r=-0.74, p<0.01
13	(-21, -16, -7), T=11.16	(27, -10, -10), T=7.31	Amygdala/Hippocampal complex	Increased	Increased	Increased	Increased	NS	NS
14	(0, 35, 23), T=25.22		Anterior Cingulate Cortex (ACC), BA24	Decreased	Decreased	Decreased	NS	NS	r=-0.87, p<0.001
15	L(-6, -52, -7), T=9.12	(9, 46, -10), T=7.13	Cerebellum IV-V	Increased	Increased	Increased	NS	NS	r=-0.86, p<0.01

Notes:

- 1 TS= Tourette syndrome; NC=normal control; TS spont = TS spontaneous tics; TS volunt = TS voluntary tics; NC self- = NC Self-paced Mimicked Tics; NC cue- = NC Cue-paced Mimicked Tics.
- 2 NS = Not Significant.