

Neural correlates of tic severity and cognitive control in children with Tourette syndrome

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Tourette syndrome (TS) is a neurodevelopmental disorder characterized by involuntary motor and phonic tics. It is hypothesized that excess dopamine leads to an imbalance in the pathways through the basal ganglia, resulting in unchecked movements via thalamic disinhibition. It has been unclear whether TS is associated with cognitive control deficits as well as pure motor control deficits, or whether cognitive deficits are associated with the presence of comorbid conditions. Furthermore, little is known about the neural underpinnings of TS in childhood, prior to the long-term effects of medication on brain function. Here, children with TS and typically developing children performed a cognitive control task during event-related fMRI data acquisition. The study included 18 native English-speaking 7–13-year-old children with TS ($M = 10.42$; 15 males), and 19 healthy, age-matched native English-speaking volunteers ($M = 10.33$; 11 males). The task involved three separate manipulations of cognitive control. Behaviourally, higher tic severity was correlated with slower task performance on the most demanding task conditions. Neurally, higher tic severity was associated with enhanced activation of dopaminergic nuclei (substantia nigra/ventral tegmental area) and cortical, striatal and thalamic regions in the direct pathway. Heightened tic severity was also associated with greater engagement of the subthalamic nucleus area, suggestive of a compensatory mechanism. Overall, patients engaged left prefrontal cortex more strongly than typicals during task performance. These data suggest that children aged 7–13 unmedicated for TS exhibit increased activation in the direct pathway through the basal ganglia, as well as increased compensatory activation in prefrontal cortex and the subthalamic nucleus.

Keywords: frontal; striatal; paediatric; brain imaging; disorder

Abbreviations: ADHD = attention deficit disorder; fMRI = functional magnetic resonance imaging; OCD = obsessive-compulsive disorder; PFC = prefrontal cortex; TS = Tourette syndrome

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Introduction

Tourette syndrome (TS) is characterized by the expression of tics, or involuntary movements, such as sudden gestures or facial movements, and vocalizations, such as throat-clearing or utterances. The diagnostic criteria require the expression of involuntary tics defined as sudden, rapid, recurrent, non-rhythmic, stereotyped motor movements and vocalizations (APA, 1994). Both the expression of tics, and the effort expended in suppressing them, result in marked disturbance in the individual's daily functioning. Pure cases of TS are the exception rather than the rule; common comorbidities include obsessive-compulsive

disorder (OCD) and attention deficit disorder (ADHD), as well as mood disorders, other anxiety disorders and conduct disorders (Comings *et al.*, 1990; Leckman, 1993). The heredity and genetic underpinnings of TS and associated disorders are a subject of active investigation (e.g. Pauls and Leckman, 1986; Pauls, 2003; Curtis *et al.*, 2004; Abelson *et al.*, 2005).

TS has been associated with a deficit in executive function or cognitive control—i.e. the set of cognitive processes that allow an individual to produce meaningful, goal-directed behaviour by selecting relevant thoughts and actions. In particular, deficits have been observed in

inhibitory control and cognitive flexibility, two components of cognitive control (Bornstein and Baker, 1991; Johannes *et al.*, 2001; Watkins *et al.*, 2005). However, these studies do not conclusively demonstrate the presence of a cognitive control deficit, for several reasons. First, studies have not always considered the comorbidity profiles of TS patients. Some researchers have found that TS patients who do not additionally have OCD or another comorbid neurological disorder like ADHD are not impaired on tests of executive function (Ozonoff *et al.*, 1998; Como, 2001; Verte *et al.*, 2005). Second, it is a challenge to find medication-naïve patients—especially adults. Third, patients (especially adults, perhaps) are likely to engage in compensatory strategies that diminish their deficits. Indeed, one study found evidence for *enhanced* performance on a cognitive control task in patients with TS (Mueller *et al.*, 2006). Fourth, it may be that some cognitive control processes are impaired, whereas others are intact. As such, it is important to determine which cognitive control processes, if any, are deficient in TS.

Widely characterized as a frontostriatal disorder, TS is believed to involve abnormalities in the neural brain structures that are important for cognitive control: prefrontal cortex (PFC) and the striatum (Albin and Mink, 2006). Clues regarding frontostriatal abnormalities in TS—or, more specifically, a disruption in cortico-striatal-thalamic-cortical circuitry (CSTC; Butler *et al.*, 2006)—come primarily from anatomical studies in adults and children (Gerard and Peterson, 2003; Pringsheim *et al.*, 2003; Frey and Albin, 2006; Ludolph *et al.*, 2006), positron emission tomography studies, primarily in adults (Chase *et al.*, 1984; Baxter and Guze, 1992; Ernst *et al.*, 1999; Gilbert *et al.*, 2006), magnetic resonance spectroscopy (DeVito *et al.*, 2005), and neuroscientific research on non-human animals (Saka and Graybiel, 2003). Recent studies have shown promise for the use of deep brain stimulation of several components of the basal ganglia in the treatment of patients with severe TS (Mink *et al.*, 2006).

Peterson and colleagues (2003) conducted volumetric analyses in a large sample, and showed reduced caudate nucleus volumes in both children and adults with TS. Notably, smaller bilateral caudate volumes in childhood have been shown to be predictive of tic severity and obsessive compulsive symptoms in adulthood (Bloch *et al.*, 2005). Additionally, other anatomical studies have shown larger volumes among patients in ventral putamen (Ludolph *et al.*, 2006), midbrain, potentially including dopaminergic nuclei (Garraux *et al.*, 2006), and thalamus (Lee *et al.*, 2006). In contrast, smaller volumes in patients with TS have been found in the hippocampus (Lee *et al.*, 2006). With respect to PFC volumes, the data have been more mixed (Peterson *et al.*, 2001; Fredericksen *et al.*, 2002). Based on the pattern of findings for PFC volumes in children and adults with TS relative to controls, it has been hypothesized that children who learn to effectively suppress their tics during development show increased growth of

PFC, resulting in an amelioration of symptoms later in life (Gerard and Peterson, 2003).

Consistent with the anatomical findings, functional magnetic resonance imaging (fMRI) studies of TS have pointed to abnormalities in frontostriatal function (e.g. Peterson *et al.*, 2003; Frey and Albin, 2006; Marsh *et al.*, 2007). Disturbances in projections from PFC to the caudate nucleus or from caudate to other basal ganglia structures are thought to be responsible for the inability to suppress tics (Gerard and Peterson, 2003). To date, only a few studies have examined brain activation of TS patients—either adults or children—during performance of a cognitive task (Johannes *et al.*, 2001; Hershey *et al.*, 2004; Serrien *et al.*, 2005; Marsh *et al.*, 2007) that is unrelated to tic generation or suppression (Stern *et al.*, 2000; Bohlhalter *et al.*, 2006).

The first fMRI study involving children with TS was recently published by Marsh and colleagues (2007). In this study, children and adults with TS and healthy volunteers performed a Stroop task during fMRI data acquisition. The patients and typicals did not differ in terms of performance on this cognitive control task, but did differ in terms of brain activation patterns. Among patients, stronger behavioural Stroop interference effects were associated with increased activation of dorsolateral PFC (DLPFC) and ventrolateral PFC (VLPFC), lenticular nucleus, thalamus and mesial PFC. In contrast, healthy individuals exhibited increased activation in right VLPFC with better performance on their task. Interestingly, within the patient group, greater tic severity was associated with increased activation in DLPFC, possibly reflecting an ineffectual compensatory mechanism (Marsh *et al.*, 2007). While this prior study does offer insight into the mechanisms of cognitive control across children and adults with TS, it did not examine the whole brain, leaving open the possibility that there may be additional regions important for compensation. Furthermore, as many of the patients (in particular the children) were medicated, it remains unclear whether the differential patterns of activation observed between groups were attributable to Tourette syndrome itself or to changes in brain structure/function as a result of medication.

A number of lines of evidence point to dysfunctional dopamine neurotransmission in TS (Pringsheim *et al.*, 2003; Albin and Mink, 2006). In particular, medications that block dopamine receptors are used to control tics, and a variety of anatomical measures point to abnormal dopaminergic function in TS (Albin and Mink, 2006). It is hypothesized that excess dopamine leads to an imbalance of activity in the direct and indirect pathways through the basal ganglia, resulting in involuntary movements via disinhibition of the motor thalamus (Albin and Mink, 2006). However, the precise nature of the dopamine dysfunction in TS is not yet understood. Some of the brain differences between adults with and without TS, such as decreased availability of D2 receptors in those with TS (Gilbert *et al.*, 2006), may be indicative of compensatory

mechanisms counteracting the underlying disorder. Indeed, some of the differences observed between adults with and without TS may be a result of long-term use of medications, and/or the long-term consequences of voluntary and/or involuntary recruitment of compensatory brain circuits.

Several studies have found evidence of compensatory mechanisms in adults with TS: i.e. enhanced prefrontal activation in TS patients relative to healthy adults, despite similar performance levels (Johannes *et al.*, 2001; Hershey *et al.*, 2004). Intriguingly, as noted previously, one study showed enhanced cognitive control in adults with TS, possibly as a result of years of tic suppression (Mueller *et al.*, 2006). If the compensatory developmental hypothesis of Gerard and Peterson (2003) summarized above is correct, it would emphasize the point that it is imperative to diagnose TS as early as possible, so as to provide children with coping strategies that could lead to beneficial long-term brain plasticity and a better long-term prognosis. These studies provide a strong rationale for characterizing brain anomalies—both anatomical and functional—in paediatric patients as well as in adults.

In our event-related fMRI study, we sought to test for differences between unmedicated children with TS and age-matched typically developing children (referred to here as typical) in terms of performance and brain activation associated with a cognitive control task. We devised a task (Fig. 1A) that included manipulations of three separate aspects of cognitive control: (i) task-switching, or the ability to properly update the currently relevant task information; (ii) response selection, or the ability to ignore competing information to select between response options and (iii) rule representation, or the ability to retrieve and use currently relevant response contingencies. By including three separate manipulations, we could assess whether children with TS were impaired on one or more of these facets of cognitive control, and examine the neural correlates of task performance. Based on the few behavioural studies of cognitive control that have been conducted in children with TS, we predicted that this group would have difficulty switching between tasks and selecting between competing response alternatives.

The task was intended to be challenging, but not overly difficult, for children aged 7–13 (Fig. 1A). Prior to MRI scanning, participants were taught stimulus-response (S-R) mappings based on 'Direction' and 'Color' rules. On Direction trials, participants were to press a left button in response to a leftward pointing stimulus, and to press a right button for a rightward pointing stimulus. On Color trials, participants were to press a left button in response to a red stimulus, and a right button in response to a blue stimulus, or vice versa.

The task-switching manipulation compared trials in which the rule was different from that of the previous trial (Switch) to those in which the rule was the same as that of the previous trial (Repeat). Demands on task-switching

were intentionally minimized on this task by the fact that participants had multiple seconds to prepare for an upcoming trial, and that they were explicitly given the rule at the start of each new trial. Nonetheless, we expected that children would have greater difficulty when switching from one rule to the other than when employing the same rule as on the preceding trial. Based on prior behavioural research (Watkins *et al.*, 2005), we predicted that children with TS would exhibit magnified behavioural costs for Switch versus Repeat trials relative to typical children.

Finally, the response selection manipulation compared Incongruent and Congruent trials, in which the two potentially relevant features of a stimulus—its colour and orientation—were associated with different responses or the same response. Based on the prior behavioural research described previously, we predicted that children with TS would exhibit magnified behavioural costs for incongruent versus congruent trials compared with typical children.

The rule manipulation contrasted arbitrary S-R mappings (the Color rule), and non-arbitrary mappings (the Direction rule). Demands on rule representation were minimal on this task, in that the currently relevant rule was explicitly indicated on each trial. However, we still expected that the Color rule would tax rule representation more strongly than the Direction rule, because it relied on newly learned S-R associations. We did not have any predictions regarding group differences in terms of rule representation, but sought to test whether children with TS would exhibit magnified behavioural costs for Color versus Direction trials relative to typical children.

In terms of brain imaging analyses, we sought to test for signs of hyperdopaminergic transmission in patients with TS, as indexed by increased activity in the substantia nigra (SN) and/or ventral tegmental area (VTA), dopaminergic nuclei with neuromodulatory effects on widespread regions of the brain. These nuclei are located sufficiently close to one another that they are difficult to distinguish from one another (Aron *et al.*, 2004). Thus, rather than attempting to examine the SN and VTA independently from one another, we sought to test whether the SN/VTA area would be more strongly engaged by patients with TS.

With respect to the relationship between brain activation and performance in TS, we entertained three possible outcomes: namely, that unmedicated children with TS would (i) exhibit a deficit in cognitive control, associated with specific differences in brain activation relative to typical; (ii) exhibit no cognitive control deficits and no differences in task-related brain activation, after taking into account other comorbidities, in particular ADHD or (iii) exhibit no deficits in performance on a cognitive control task, but exhibit enhanced brain activation relative to typical, suggestive of the engagement of compensatory neural mechanisms.

A pathway between right inferior frontal cortex (IFC) and the right subthalamic nucleus (STN) has recently been characterized in humans (Aron *et al.*, 2007). Through this

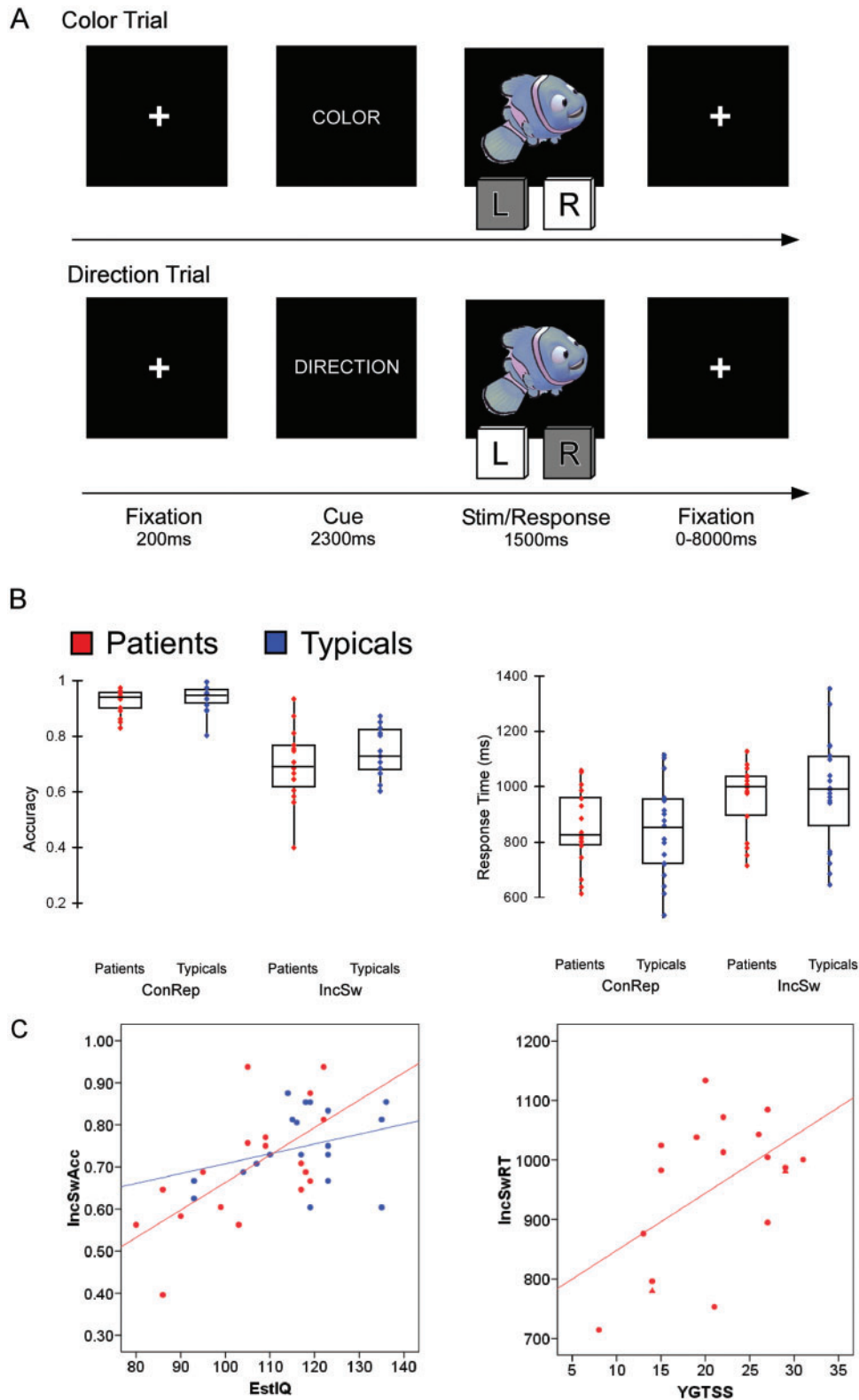


Fig. 1 Task design and behavioural data. **(A)** Participants were instructed to respond with a left or right button press to each stimulus, based on the relevant rule for that trial (Color or Direction). Variable ITIs (2–8 s) were interleaved between each trial. **(B)** Box-and-whisker plots of accuracy and RT showing min/max/first quartile/third quartile/median divided by activation for ConRep and IncSw, and by group. **(C)** Behavioural correlations between estimated IQ and accuracy on IncSw trials, separately for patients and typicals and between tic severity and RT on IncSw trials for the patients only. RTs are reported for correct trials only. Medication naive patients are indicated with circle markers. Patients previously medicated for ADHD symptoms are indicated with triangle markers.

and/or other *hyperdirect* pathways to the basal ganglia, motor inhibition could proceed rapidly, bypassing the inhibitory *indirect* pathway through the basal ganglia (Mink, 2001; Aron and Poldrack, 2006). We hypothesized that patients with TS might compensate for weakened basal ganglia control via increased engagement of a hyperdirect pathway. Thus, we sought to test the prediction that children with TS would engage the STN more strongly than typical. Such a pattern would be consistent with a compensatory mechanism; in contrast, stronger STN activation in typical than in patients with TS would be consistent with diminished activity in the indirect pathway through the basal ganglia, resulting from increased dopamine transmission and stimulation of D2 receptors (Mink, 2001). Like the SN/VTA, the STN is a small nucleus; however, relying on coordinates from prior fMRI studies (Aron *et al.*, 2004, 2007; Aron and Poldrack, 2006), we sought to test our theoretically motivated prediction that there would be group differences in the STN area.

Materials and Methods

Inclusion and exclusion criteria

Children aged 7–13 with TS and healthy age-matched controls were recruited for participation in this study, and were compensated financially for their involvement. Children with serious neurological, psychiatric or medical conditions, other than TS with or without comorbid ADHD or OCD, or with an estimated IQ below 75 were not included in the study. Rather than considering OCD and ADHD as exclusion criteria for the patients, we included scores on standard measures of OCD and ADHD as continuous variables in multiple regression analyses of performance and brain activation. Children who had taken medication to treat tics were excluded from the study.

Participants

The study included 18 native English-speaking 7–13-year-old children with TS ($M=10.42$; 15 males, 3 females), and 19 healthy, age-matched native English-speaking volunteers ($M=10.33$; 11 males, 8 females). Children in the two groups did not differ in age ($P=0.996$). Although the two groups had different proportions of males and females, two-sample *t*-tests revealed no significant performance differences between males and females (all $P>0.05$). Three patients and one typical child included in the study were left-handed. One patient had a history of epilepsy, but was not an outlier relative to the other patients on any of our other measures.

Medication status

Sixteen out of 18 patients were medication-naïve, as per parental reports. The other two children had taken atomoxetine (brand name StratteraTM) to treat ADHD symptoms. One child had ended treatment approximately 1 month prior to testing; the other had been off atomoxetine for 40 h prior to testing. Behavioural and fMRI analyses performed with and without these two children indicated that they were not outliers.

Excluded participants

Apart from the 37 participants included in the study, eight additional participants were excluded from the final analysis. Five patients and one typical were excluded on the basis of excessive head motion during scanning (greater than 5 mm within a run), one patient on the basis of poor task performance, and one typical on the basis of low estimated IQ.

Recruitment and screening

Children with TS were recruited via the Tourette Syndrome Association based in the United States, clinical referrals, local advertisements, physician referrals and through the University of California at Davis. The diagnosis of TS was based on DSM-IV criteria (APA, 1994) and established by: (i) a previous diagnosis of TS by a psychologist, psychiatrist, neurologist or behavioural paediatrician; (ii) clinical judgment (B.A.C.) and (iii) confirmation of the presence of motor and phonic tics by the Yale Global Tic Severity Scale (YGTSS). The parents of all the participants also completed a semi-structured interview, the Diagnostic Interview Schedule for Children (DISC; Shaffer *et al.*, 2000) to determine the extent of symptomatology across other related disorders (e.g. OCD, ADHD, anxiety).

Typically developing children were recruited through area schools, fliers and recreational centres. Following initial contact, potential participants were screened via parent interview for the absence of neurodevelopmental disorders. Individuals with a history of serious physical illness (e.g. endocrine, cardiovascular or neurological disorders) were excluded from enrollment in the study. The groups were not matched on the basis of intellectual functioning (Table 1). After thorough explanation of the study was completed, informed written consent was obtained from parents and verbal assent was obtained from all research subjects prior to inclusion in the study. This study was approved by the Institutional Review Board of the University of California at Davis.

Psychological assessments

Each child underwent an extensive clinical evaluation prior to scanning by, or under the supervision of, paediatric neuropsychologist (B.A.C.). Diagnostic testing was completed following informed consent procedures on the first of two visits. The *Wechsler Abbreviated Intelligence Scale* (WASI; Wechsler, 1999) was used as an estimate of IQ. This measure was administered to all participants, unless an IQ score from a more comprehensive measure had been recently completed (<2 years). Children with a score of <75 on the WASI were excluded from the study.

On the first visit, each child completed a psychological assessment that included 15 subsections of the DISC (Shaffer *et al.*, 2000), the YGTSS (Leckman *et al.*, 1998), and the Child Yale-Brown Obsession and Compulsion Scale (CY-BOCS; Scahill *et al.*, 1997). Additionally, parents were given the following measures to complete at home, prior to the scanning visit: the Behavior Rating Inventory of Executive Function (BRIEF; Gioia *et al.*, 2000), Conners' Parent Rating Scale-Revised (Short) (CPRS-R:S; Conners, 2001), Child Behavior Checklist (CBCL; Achenbach and Rescorla, 2001), Social Communication Questionnaire (SCQ; Rutter *et al.*, 2003), Multidimensional Anxiety Scale for Children (MASC; March, 1999) and Parenting Stress Index (PSI; Abidin, 1995). More details regarding each of the assessments are provided

Table 1 Results of psychological assessments

Test	Measure of	TS patients	Typicals	P-value
YGTSS	Tic severity	21 (7)	0 (0)	2.14E-10
BRIEF	Executive dysfunction	61 (11)	43 (4)	2.08E-06
Conners'	ADHD	59 (11)	46 (3)	0.0002
CY-BOCS	OCD	8 (7)	0 (1)	0.0003
CBCL	Behavioural problems	57 (10)	42 (7)	0.0003
SCQ	Social communication problems	8 (5)	2 (2)	0.0005
MASC	Anxiety	54 (10)	42 (8)	0.001
WASI	Estimated IQ	106 (14)	117 (12)	0.01

Table of mean scores for assessment results, ordered from most to least significant difference between groups. P-values indicate level of significance of unpaired comparisons between groups. Standard deviations are reported in parentheses. Test results are ordered from most to least significant effect.

in the Supplementary Material. Questionnaires filled out at home were properly and entirely completed for 29/37 participants (14 patients and 15 typical); for the remaining participants, 1–4 of the questionnaires could not be scored.

Nemo task

Participants were instructed on a trial-by-trial basis to use one of two visually presented rule cues ('Color' or 'Direction') to determine the appropriate response for a given target stimulus (Fig. 1A). The target stimuli were cartoons from the Disney movie 'Finding Nemo'; the colour and orientation of these stimuli were manipulated in Adobe Photoshop CS2. Participants were taught the relevant stimulus-response (S-R) mappings for the two rules prior to scanning (Fig. 1A). On Direction trials, participants were to press a left button in response to a leftward pointing stimulus, and a right button for a rightward pointing stimulus. On Color trials, half of the participants were taught that a red stimulus indicated a left-button press and a blue stimulus indicated a right-button press, and half were taught the reverse S-R mapping. Participants used the index and middle fingers of their right hand to respond.

Experimental design

The experimental task followed a 3×2 factorial design, enabling the assessment of independent contributions of rule difficulty, task-switching and interference suppression. The rule difficulty manipulation contrasted arbitrary S-R mappings learned on the day of testing (Color) with previously learned S-R mappings (Direction). The task-switching manipulation compared trials involving a rule switch relative to the prior trial (Switch) with those in which the rule was the same as on the previous trial (Repeat). The interference suppression manipulation compared trials in which two features of a stimulus were associated during training with different responses (Incongruent) or the same response (Congruent).

Timing parameters

On each trial of the event-related fMRI paradigm, a fixation cross appeared for 200 ms, followed by an instructional cue ('Color' or 'Direction') for 2300 ms, and a target stimulus for 1500 ms (Fig. 1A). Color and Direction trials were pseudorandomly ordered throughout a scan, with variable intertrial intervals

(ITIs) interspersed between them. The order of trial type presentation and jittered fixation was determined using Optseq2, an optimizing program designed to allow for maximal efficiency in deconvolving trials from each condition and baseline activation (Dale, 1999). Jittered fixation lasted from 2 to 8 s and was interspersed throughout the functional runs.

Experimental procedure

Prior to MRI scanning, children were introduced to the scanner environment through the use of a mock scanner. They were asked to lie down in the mock scanner, listen to prerecorded sounds of the pulse sequences, and practice lying still and making button presses. After participants were familiarized with the scanning procedure, they learned S-R mappings for the Color and Direction rules, and practiced applying them both on paper and in a 3 min computerized session. During this training session, participants provided 1 ml saliva samples at 20 min intervals following initial exposure to the mock scanner as part of a study on the biological response to stress in patients with TS.

MRI data acquisition

Imaging was performed using an 8-channel phased-array coil on a 3-Tesla Siemens Trio MRI scanner (Siemens Medical Solutions, Erlangen, Germany) at the University of California at Davis Imaging Research Center (Sacramento, CA). Participants viewed visual stimuli on a projection screen using an angled mirror and responded using a button box in the right hand.

After acquisition of a T2 localizer scan, four functional runs were collected, each 4.5 min long (TR = 2000 ms, TE = 25 ms, 34 axial slices, no interslice-gap, $3.4 \times 3.4 \times 4 \text{ mm}^3$ voxels, flip angle = 90° , field of view = 220 mm, 135 volumes per run). A gradient-echo echo-planar pulse Prospective Acquisition Correction (3D-PACE) sequence was used to minimize motion artifacts during fMRI data acquisition. The 3D-PACE sequence prospectively adjusts scan parameters throughout a run on the basis of real-time assessment of head motion (Siemens Medical Solutions; Thesen *et al.*, 2000). Four volumes from the start of each functional scan were removed from analysis to account for magnetic field equilibration. Following the functional scans, high-resolution T1 MPRAGE anatomical images were acquired.

Across the four functional scans, participants completed 48 trials of each of the following conditions: Congruent Repetition

(ConRep), Congruent Switch (ConSw), Incongruent Repetition (IncRep) and Incongruent Switch (IncSw) trials. For each of these conditions, an equal number of trials involved the Color rule and the Direction rule. Each scan included six trials of each of the eight resulting trial types. The order of the functional scans was counterbalanced across subjects.

Image preprocessing

Data were analysed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK). Functional volumes from each participant were corrected for interleaved slice acquisition, and were translated using a rigid-body motion correction. Functional volumes were normalized to an EPI template using a 12-parameter affine transformation, and resampled to $3 \times 3 \times 4 \text{ mm}^3$ voxels. The SPM EPI template has been validated for use in normalization of brain volumes for children aged ≥ 6 (Burgund *et al.*, 2002; Kang *et al.*, 2003). Finally, functional volumes were smoothed using an 8 mm full-width at half maximum isotropic Gaussian kernel.

To examine individual movement, we computed root mean square (RMS) values for translation for each participant across scans for typicals ($M=0.291$; range=0.317) and patients ($M=0.398$; range=0.567). As expected, patients exhibited more head movement than typicals ($t=2.82$, $P<0.009$). However, multiple steps were taken to ensure that the fMRI data were not compromised by excessive head motion, as noted above. First, we used a 3D-PACE prospective acquisition sequence during data acquisition, so as to minimize the impact of head motion on our results. Secondly, we excluded participants for whom head motion was greater than 5 mm within a run. Finally, we included motion regressors as covariates of no interest in the analysis of individual subjects' data.

Single-subject fMRI analyses

Statistical analyses were performed using the general linear model in SPM2. fMRI time-series data were modeled as a series of events, time-locked to the onset of each trial, and were convolved with a canonical hemodynamic response function. The resulting functions were used as covariates in a general linear model, along with a basis set of cosine functions that high-pass filtered the data, as well as a covariate for session effects. Six motion regressors (indicating amount of translation and rotation in the x , y and z dimensions for each 2 s TR) were included in the analysis as covariates of no interest. The least-squares parameter estimates of height of the best-fitting synthetic hemodynamic response function for each condition were used in pair-wise contrasts, and the resulting contrast images, computed on a subject-by-subject basis, were submitted to group analyses. Incorrect trials were modeled separately, and were not included in the fMRI analyses.

Group fMRI analyses

Several analytic approaches were used to characterize differences in brain activation between children with and without TS. First, voxel-based two-sample t -tests were used to directly compare the groups. Second, voxel-based multiple regression analyses were used to assess the effects of various factors both within and across groups. For these two types of analyses, we limited the search space to regions for which we had specific predictions: lateral PFC,

basal ganglia and thalamus. Voxel-based analyses were restricted to voxels within two anatomical masks created in the MarsBar toolbox for SPM2 (Brett *et al.*, 2002): a lateral prefrontal mask including 4816 voxels (bilateral B.A. 6, 8, 9, 10, 44, 45, 46, 47), and a subcortical mask including 1475 voxels (bilateral caudate, putamen, globus pallidus and thalamus). We report results for contiguous clusters of 5 or more voxels within one of these masks meeting an uncorrected threshold of $P<0.005$. At this threshold, ≤ 1 cluster would be expected by chance alone within either the prefrontal or subcortical mask.

Region-of-interest (ROI) analyses were performed to further characterize the activation profile across all four task conditions for regions of *a priori* interest. ROIs in lateral PFC were defined functionally from a voxel-based t -test (patients > typicals for all correct trials > baseline). ROIs in SN/VTA and nucleus accumbens were defined functionally from a voxel-based multiple regression analysis used to identify activations positively correlated with YGTSS. For basal ganglia structures and the thalamus, we used anatomical ROIs from the MarsBar toolbox. Mean parameter estimates for a given ROI were computed for each participant and condition, and were submitted to repeated measures ANOVAs and post-hoc comparisons. For anatomical ROIs, both left- and right-sided regions (e.g. left and right putamen) were submitted to analysis, and hemisphere was included as a within-subject variable.

In total, eight different regions from lateral PFC, basal ganglia and the thalamus were submitted to ROI analyses (Table 2). Taking into account this number of ROIs, the corrected statistical threshold would be $P<0.00625$ with an alpha of 0.05. None of our ROI-based results met correction for multiple comparisons. However, the pattern of results observed in these ROIs were highly consistent with our predictions, and are featured here as initial findings regarding the neural mechanisms of cognitive control in unmedicated children with TS.

Results

Psychological assessments

The TS group differed from the typical group in terms of tic severity, as measured by YGTSS. Indeed, this was the factor that most prominently distinguished the two groups (Table 1). However, the groups differed in other ways as well. Listed in order from strongest to weakest group differences, the TS group also scored higher on a parental assessment of executive dysfunction (BRIEF), Attention Deficit Hyperactivity symptoms (Conners'), Obsessive-Compulsive symptoms (CY-BOCS), behavioural problems (CBCL), social communication problems (SCQ) and anxiety levels (MASC). Although the patients with TS in our sample were high-functioning (mean estimated IQ score \pm SD: 106 ± 14), they had lower estimated IQ scores than our sample of typicals. Indicative of the fact that TS takes a toll on the family rather than merely the individual, parents of children with TS scored higher on a parental stress index than parents of typical children (mean \pm SD for parents of patients versus typicals: 76 ± 21 versus 57 ± 16 ; $P<0.004$).

Because of the strong prevalence of obsessive-compulsive and attention-deficit symptoms in patients with TS, and

Table 2 Results of multiple regression analyses conducted on ROIs

Region	ConRep		IncSw	
	TS	Ctrl	TS	Ctrl
Bilateral caudate	–	–	–	–
Bilateral globus pallidus	–	–	–	–
Bilateral putamen	–	–	YGTSS $R^2 = 0.27$, $P < 0.04$	–
Bilateral thalamus	–	–	YGTSS $R^2 = 0.32$, $P < 0.02$	–
Bilateral SN/VTA	–	–	YGTSS $R^2 = 0.39$, $P < 0.009$ BRIEF R^2 change = 0.177, $P < 0.033$	EstIQ $R^2 = 0.34$, $P < 0.017$
Right STN	–	–	YGTSS $R^2 = 0.32$, $P < 0.02$	EstIQ $R^2 = 0.36$, $P < 0.011$
Left STN	–	–	–	EstIQ $R^2 = 0.46$, $P < 0.003$
Nucleus Accumbens	–	–	YGTSS $R^2 = 0.39$, $P < 0.007$	–

Estimated IQ, YGTSS, CY-BOCS, Conners', MASC, BRIEF and age were included as independent variables. All correlations were in the positive direction. No hemispheric differences were observed in the regions noted as bilateral; average R^2 - and P -values are reported for variables that account for a significant portion of the between-subject variance of activation for an ROI ($P < 0.05$).

because these symptoms are not always severe enough to meet full diagnostic criteria for OCD or ADHD, we purposefully used continuous measures of ADHD and OCD rather than categorical ones. However, using conservative cut-offs (t -score ≥ 70 for the Conners' and raw score ≥ 8 for the CY-BOCS), seven patients scored in the clinical range for TS + OCD, one for TS + ADHD and two for TS + OCD + ADHD. The remaining eight patients and all typical participants scored in the normal range on both the Conners' and CY-BOCS.

Task performance

Repeated-measures ANOVAs were performed on accuracy and response time (RT) data from the Nemo task. We examined the between-subjects effect of Group (Patients, Typical), and the within-subjects effects of Congruency (Congruent, Incongruent), Switching (Switch, Repeat) and Rule (Color, Direction).

Effects of task manipulations on performance across all participants

Across groups, accuracy and RTs were affected by each of the three task manipulations (Fig. 1B). Children performed worse when they had to switch from one rule to another (Switch versus Repetition trials; accuracy: $F_{1,35} = 71$, $P < 0.001$; RTs: $F_{1,35} = 48$, $P < 0.001$). Additionally, performance was worse when the irrelevant dimension of the stimulus was associated with the opposite response from the relevant dimension (Incongruent > Congruent trials; accuracy: $F_{1,35} = 83$, $P < 0.001$; RTs: $F_{1,35} = 30$, $P < 0.001$). Finally, performance was worse for the arbitrary rule than for the non-arbitrary one (Color > Direction trials; accuracy: $F_{1,35} = 43$, $P < 0.001$; RTs: $F_{1,35} = 39$, $P < 0.001$). Significant interactions of Congruency \times Switching ($F_{1,35} = 18$, $P < 0.001$) and Congruency \times Rule ($F_{1,35} = 24$, $P < 0.001$) were observed in terms of accuracy. In terms of RTs, there was a significant interaction of Congruency \times Rule ($F_{1,35} = 13$, $P = 0.001$). These results indicate that the congruency manipulation

placed increased demands on both task-switching and rule representation.

Taken as a whole, the two groups did not differ significantly from one another in performance (accuracy: $F_{1,35} = 1.6$, $P = 0.21$, RTs: $F_{1,35} < 1$, $P = 0.99$), and there were no significant interactions involving Group. However, because our TS group exhibited a range of tic severity, from mild to marked (total YGTSS scores ranged from 8 to 31), we sought to examine more closely the relationship between tic severity and task performance.

Multiple regression analyses of behavioural performance

We performed stepwise multiple regression analyses to examine the effects on performance of age, estimated IQ and total scores on the YGTSS, BRIEF, Conners', MASC and CY-BOCS. These regression analyses were performed separately for accuracy and RTs on the more difficult condition in each of the three task manipulations: Incongruent, Color and Switch trials. Taking into account the number of whole-brain regressions computed (fourteen), the corrected statistical significance was $P = 0.0036$ with an alpha of 0.05. Correlations that met correction for multiple comparisons are noted with an asterisk (*). Given the dearth of behavioural data on cognitive control paradigms for unmedicated children with TS, correlations that did not meet correction for multiple comparisons are also listed below.

Across all children, accuracy was positively correlated with IQ for Incongruent trials ($R = 0.50$; $P < 0.003^*$), Switch trials ($R = 0.46$; $P < 0.006$), and Color trials ($R = 0.37$; $P < 0.03$) (Fig. 1C). Additionally, Switch accuracy was correlated with age (R^2 change = 0.13; $P < 0.02$). A stronger correlation between accuracy and estimated IQ across the entire group was observed for IncSw trials ($R = 0.54$; $P < 0.0001^*$) than for ConRep trials ($R = 0.282$; $P < 0.05$). RTs were positively correlated with Age for Incongruent trials ($R = 0.40$; $P < 0.02$), and for Switch trials ($R = 0.35$; $P < 0.05$), but not

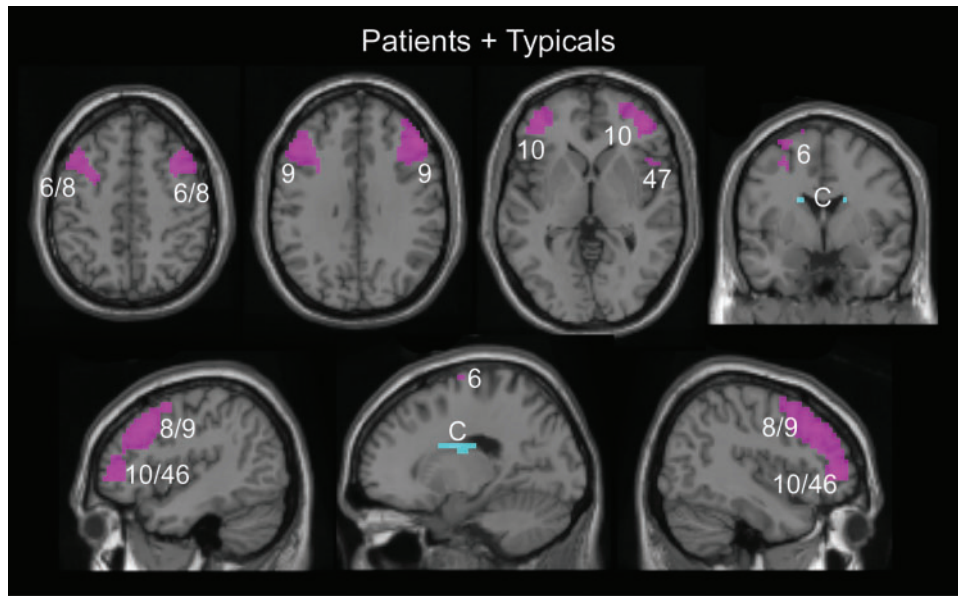


Fig. 2 Voxel-based activation across all correct trials relative to fixation, shown across all participants ($P < 0.005$, 5-voxel extent, within lateral prefrontal and subcortical masks). Regions within the lateral PFC mask are shown in magenta and regions within the subcortical mask are shown in cyan. Top row: axial slices for z-coordinates of +48, +32 and 0, and coronal slice for y-coordinate of -1 . Lower row: sagittal slices for x-coordinates of -42 , -17 and $+42$. Numbers correspond to approximate Brodmann areas. C = Caudate nucleus.

for Color trials ($P > 0.05$). Thus, performance on Incongruent and Switch trials, but not Color trials, was correlated with IQ and age across the whole group.

Focusing on the patient group only, we again found that accuracy was positively correlated with IQ for Incongruent trials ($R = 0.55$; $P < 0.023$), and Switch trials ($R = 0.61$; $P < 0.009$), but not for Color trials (all $P > 0.05$). RTs were positively correlated with tic severity (as measured by YGTSS) across the TS group for Incongruent trials ($R = 0.51$; $P < 0.037$) and Switch trials ($R = 0.52$; $P < 0.04$), but not for Color trials ($P > 0.05$) (Fig. 1C). The strongest correlation between task performance and YGTSS was observed for the IncSw trials ($R = 0.53$, $P < 0.02$); a slightly weaker correlation was observed for ConRep trials ($R = 0.42$, $P < 0.04$).

The remaining variables (age, MASC, CY-BOCS, Conners' and BRIEF) were not significantly correlated with RTs for the TS group (all $P > 0.05$). This latter finding does not necessarily mean that performance on this task is correlated with TS but not with other disorders, such as ADHD or OCD; rather, it is likely to be related to the fact that we recruited children with a primary diagnosis of TS. The exclusion of the two participants who had been medicated for ADHD symptoms only slightly weakened the behavioural correlations with YGTSS for Incongruent trials ($R = 0.44$) and Switch trials ($R = 0.45$). In summary, we found that (i) overall, better performance on the Incongruent and Switch trials was associated with higher IQ and older ages and (ii) children with TS who responded most slowly on Incongruent and Switch trials tended to have the highest tic severity.

fMRI results

Task-related activation across groups

As a first pass, we conducted voxel-based contrasts within our anatomical masks to identify regions in lateral PFC, basal ganglia and/or thalamus that were generally engaged during task performance across the two groups, collapsing across conditions (Fig. 2). For correctly performed trials relative to fixation, clusters of activation included bilateral middle and inferior frontal gyri (BA 6, 8, 9, 10 and 46), and bilateral caudate nucleus.

Comparisons between patients and controls

Voxel-based two-sample t -tests were performed to identify regions in PFC, basal ganglia and/or thalamus that were engaged differentially by the two groups. No regions were engaged more strongly by typicals than patients. As predicted, greater activation for patients than typicals was observed in lateral PFC. Two small clusters were located in left middle frontal gyrus (MFG; BA 8, 46) and left superior frontal gyrus (SFG; BA 9).

Follow-up ROI analyses revealed that the left SFG cluster was engaged relative to baseline by patients but not typicals, in a manner that was insensitive to our task manipulations (all $P > 0.13$). In contrast, the left MFG cluster exhibited significant effects of both switching ($F_{1,35} = 5.4$, $P = 0.027$) and rule ($F_{1,35} = 4.3$, $P = 0.046$) (Fig. 3). Thus, patients exhibited overall greater activation in two focal regions of PFC, one of which was specifically associated with rule representation and task-switching.

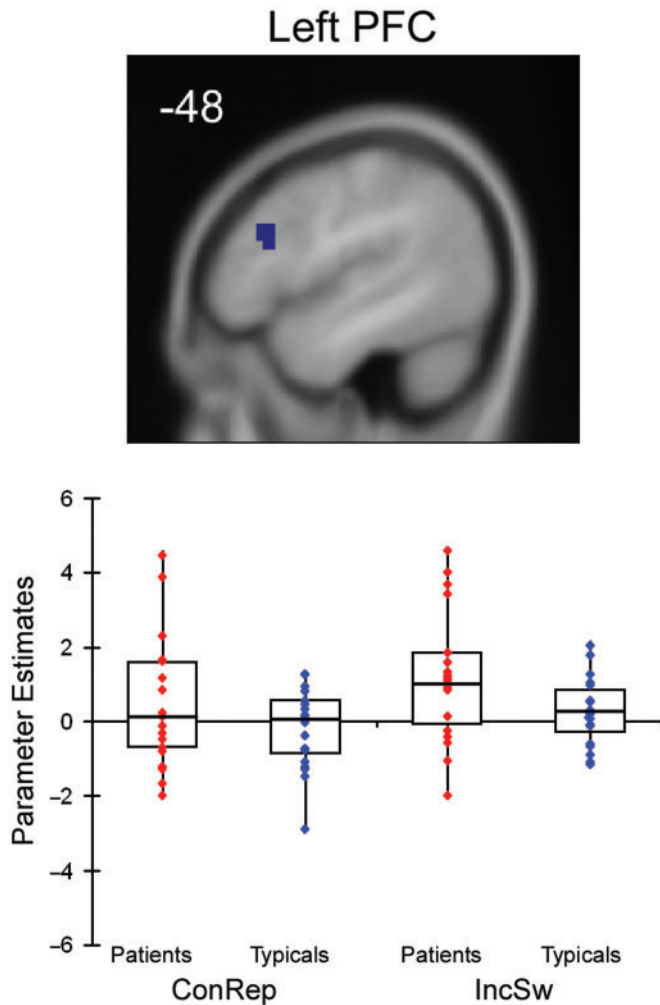


Fig. 3 Lateral prefrontal ROI (BA 8/46; $-48, 23, 24$; 16 contiguous voxels) derived from all correct trials $>$ fixation for patients $>$ typicals. Box-and-whisker plot showing min/max/first quartile/third quartile/median divided by activation for ConRep and IncSw, and by group.

Regions exhibiting correlations with tic severity within the patient group

Because the patient group varied considerably in terms of tic severity, we sought to identify brain regions in PFC, basal ganglia and/or thalamus for which level of activation on the challenging Incongruent Switch trials was either positively or negatively correlated with tic severity. To this end, a multiple regression analysis was performed in SPM, including YGTSS scores as the covariate of interest, and Age and Incongruent Switch accuracy as covariates of no interest. No regions were observed for the negative correlation with YGTSS. In contrast, several regions within our anatomical masks were engaged more strongly as a function of higher tic severity, including premotor cortex (bilateral BA 6), superior frontal gyrus (left BA 9, right BA 8), inferior frontal gyrus pars triangularis (right BA 45), middle frontal gyrus (left BA 9, right BA 8, 46),

bilateral thalamus and putamen, and right nucleus accumbens (Fig. 4; Supplementary Table 1). The SN/VTA, an *a priori* predicted region that was not included in the mask of subcortical regions created with Marsbar, also exhibited a positive correlation with YGTSS. These findings indicate that patients with more severe TS symptoms exhibited heightened task-related activation in a number of regions in the CSTC loop.

To test whether the regions identified as showing a positive correlation with YGTSS could have been correlated instead with ADHD or OCD symptoms, an additional multiple regression analysis was performed on the fMRI data, including YGTSS, Conners', CY-BOCS and IncSw accuracy as regressors. In effect, none of the activations identified as being associated with tic severity could be attributed to either OCD or ADHD severity. Further, the exclusion of the two children who had been medicated for ADHD symptoms did not change the set of regions found to be correlated with YGTSS.

ROIs in SN/VTA and nucleus accumbens

As noted previously, we sought evidence suggestive of elevated dopaminergic activity in patients relative to controls. To this end, ROI analyses were performed to further characterize the activation profile and group differences in the nucleus accumbens and SN/VTA area, as identified from the positive correlation with YGTSS (Fig. 5). To isolate the SN/VTA area from a larger cluster of activation, we masked the cluster with 5 mm spheres centered on MNI coordinates of $\pm 9, -24, -8$. Because these regions were identified from a positive correlation of IncSw $>$ fixation brain activation with YGTSS among patients, multiple regression analyses were performed to determine whether additional behavioural variables modulated activation in either the patient or typical group (Table 2). The following variables were included in the regression analyses: YGTSS, CY-BOCS, Conners' and BRIEF, as well as three additional covariates of no interest: MASC, estimated IQ and age.

In addition to being correlated with YGTSS, activation in bilateral SN/VTA on IncSw trials was also correlated across patients with scores on the BRIEF, a parental-report measure of executive dysfunction, such that patients with higher scores—indicative of *worse* executive function—engaged this region more strongly (right: R^2 change = 0.186, $P < 0.02$; left: R^2 change = 0.17, $P < 0.05$; Fig. 5). Although SN/VTA activation was positively correlated with both YGTSS and BRIEF, scores on these two questionnaires were not correlated with one another ($R^2 = 0.009$). For typicals, by contrast, greater SN/VTA activation was associated with higher IQ (right: $R^2 = 0.39$; $P < 0.01$, left: $R^2 = 0.29$, $P < 0.03$). Thus, greater SN/VTA activation was associated with greater tic severity and executive dysfunction in the patient group, but higher intellectual functioning in the typical group. In contrast to SN/VTA, nucleus accumbens

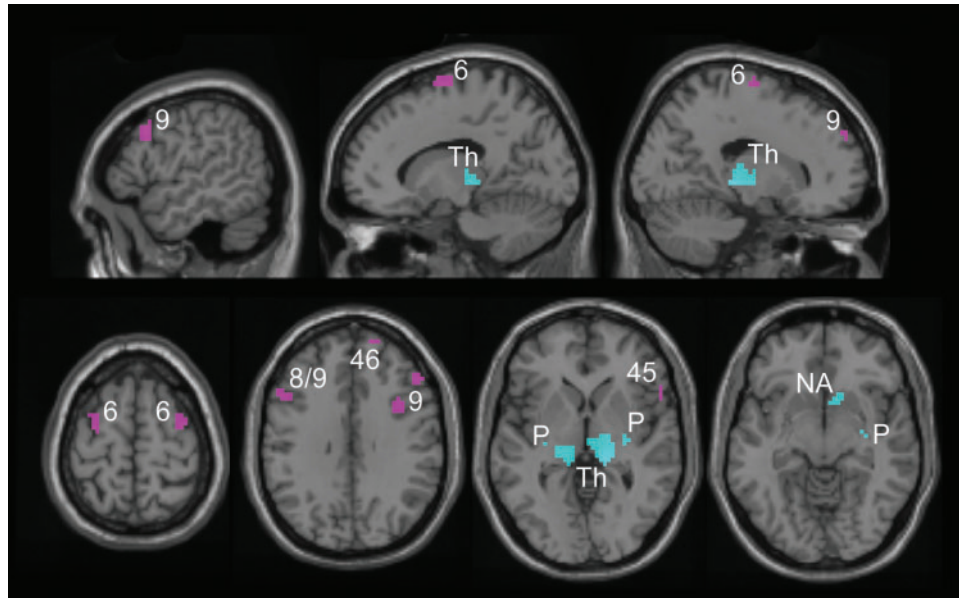


Fig. 4 Regions correlated with tic severity (YGTSS) for patients during performance of IncSw trials (covariates of no interest: IncSw accuracy and age). Clusters of activation within the lateral prefrontal mask are shown in magenta, and clusters within the subcortical mask are shown in cyan. Within the masks, clusters are shown if they met a statistical threshold of $P < 0.005$ with a 5-voxel extent. Top row: sagittal slices for x-coordinates of -52 , -14 and $+18$. Lower row: axial slices for z-coordinates of $+64$, $+32$, 0 and -8 . Numbers correspond to approximate Brodmann areas. Th = thalamus; P = putamen; NA = nucleus accumbens.

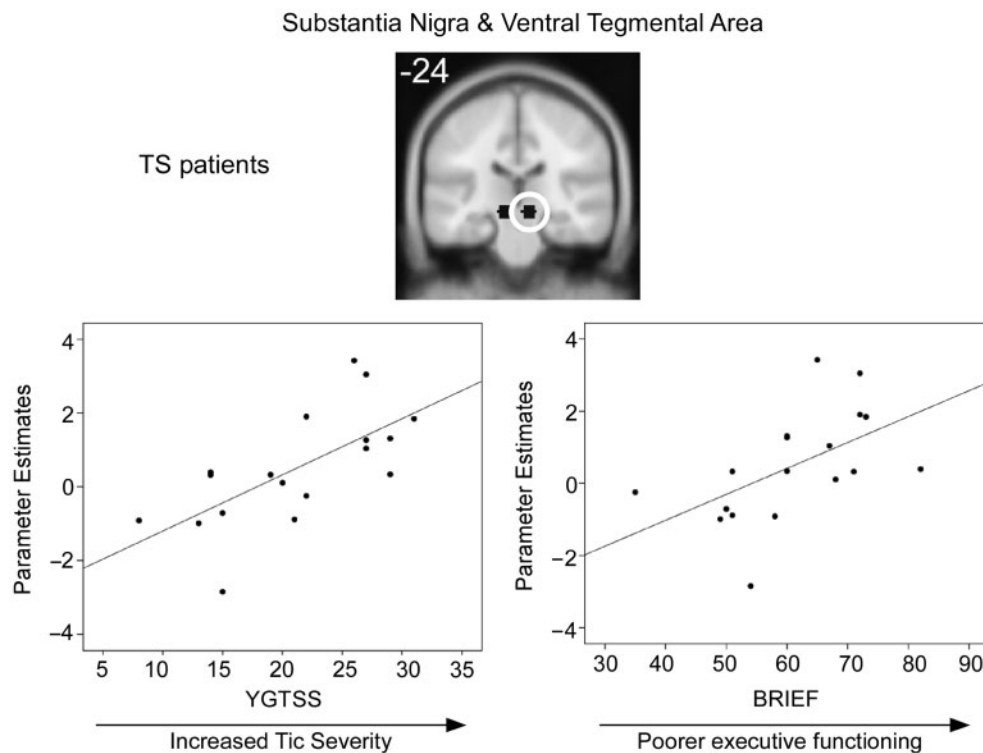


Fig. 5 Bilateral ROIs in the SN/VTA are shown (spheres with 5 mm radius centered at ± 9 , -24 , -8). Left graph: correlation plot for tic severity versus right SN/VTA parameter estimates for patients demonstrating that increased tic severity is positively correlated with activity in this region. Right graph: correlation plot for executive dysfunction (BRIEF) versus right SN/VTA parameter estimates in the patient group.

activation was not correlated with other variables; higher levels of nucleus accumbens activation was associated only with increased tic severity.

ROIs in basal ganglia and thalamus

Anatomical ROI analyses were conducted on regions of the basal ganglia (caudate nucleus, putamen and globus pallidus) and the thalamus (Fig. 6A; Table 2). Additionally, because of our predictions relating to the STN, we conducted an ROI analysis for a region in the STN area (Fig. 6B), defined anatomically based on the studies of Aron and Poldrack (2006, 2007).

For each ROI, we compared activation values between groups, separately for IncSw and ConRep trials (Fig. 6 for plots of putamen, thalamus and STN area). These plots revealed greater individual variability in the TS group than the typicals, particularly on IncSw trials. We then conducted multiple regression analyses for these regions, to identify factors that could account for the large individual differences in activation observed for IncSw trials in the patients. These analyses included YGTSS, CY-BOCS, Conners', MASC, BRIEF, estimated IQ and age as independent variables, and average parameter estimates for ConRep and IncSw as dependent variables. These analyses were uncorrected for multiple comparisons because of the number of regressors included. However, we sought to test the specific prediction that YGTSS was correlated with activation in the ROIs, specifically or most prominently on IncSw trials; the other regressors were included to ensure that our findings were not misattributed to tic severity.

These ROI analyses revealed that tic severity among patients was positively correlated with IncSw activation in bilateral putamen and thalamus (Table 2), as well as in the right STN area. This finding for the right STN ROI is consistent with the results of the regression with YGTSS reported above. Additionally, bilateral STN activation in the typical group was positively correlated with IQ (averaged across hemispheres; $R^2=0.43$, $P<0.007$). No significant correlations were observed for ConRep activation in these regions, or for the caudate or globus pallidus.

Discussion

Overall, the children with TS in our study performed the cognitive control task as well as age-matched children. However, our sample included children with a range of tic severity. Our behavioural data revealed that greater tic severity among patients was associated with disproportionate slowing of responses in both the switching and response selection manipulations, but not the rule manipulation. Unlike prior studies examining performance of patients with TS on cognitive tasks, we have shown that this cognitive deficit can be attributed to TS, rather than to the symptoms of any of the most common comorbid

conditions (ADHD, OCD or other anxiety disorders or conduct disorders). The finding that children with more severe TS have greater difficulty than their peers when forced to switch between tasks or select between competing responses underscores the point that TS is not simply a movement disorder, but a cognitive one as well.

Children with TS may compensate for underlying difficulties with cognitive control. Consistent with this idea, we observed that children with TS, particularly those with greatest tic severity, engaged lateral PFC more strongly than typically developing children. This finding is consistent that of Marsh and colleagues (2007), who reported increased activity in bilateral PFC (left BA 9/46, 10 and right BA 45, 10) with increasing tic severity across a large sample of children and adults. Several studies have provided evidence of compensatory prefrontal activity in adults with TS (Johannes et al., 2001; Hershey et al., 2004); the present study is suggestive of the early stages of a compensatory mechanism present already in childhood and in the absence of tic medication. The possibility that this enhanced PFC recruitment is part of a compensatory mechanism, rather than being a consequence of heightened dopaminergic activity in TS, is bolstered by our finding of increased activation in the STN (an inhibitory nucleus linked to the ability to suppress inappropriate responses) as a function of tic severity, as described below.

While the current data suggest that children with TS only weakly engaged compensatory mechanisms, more dramatic compensation may be observed over development or with appropriate training.

Our fMRI data revealed that tic severity scores were strongly associated with elevated activation in a number of brain regions aside from lateral PFC. Notably, these correlations were observed primarily for the most cognitively challenging trials (Incongruent Switch), strongly suggesting that they are not the result of a confound, such as increased movement artifacts in the TS group. Rather, these results indicate that children with TS, in particular those with higher tic severity, engage a number of regions more strongly than do typical children when asked to perform a cognitively challenging task. Below we discuss four sets of brain regions for which a positive correlation was observed with tic severity.

First, greater tic severity was correlated with stronger activation of the SN/VTA, consistent with the dopamine hypothesis of TS (Nomura and Segawa, 2003; Yoon et al., 2007; Fig. 7). To our knowledge, this is the first functional brain imaging study to provide evidence of elevated activation in the SN/VTA, although this finding fits well with other results, such as the PET finding of higher [18F] fluorodopa accumulation in the caudate nucleus of children with TS than typicals (Ernst et al., 1999).

Second, tic severity was positively correlated with activation of regions involved in the direct pathway through the basal ganglia (striatum, globus pallidus interna, thalamus and motor cortex). These findings provide

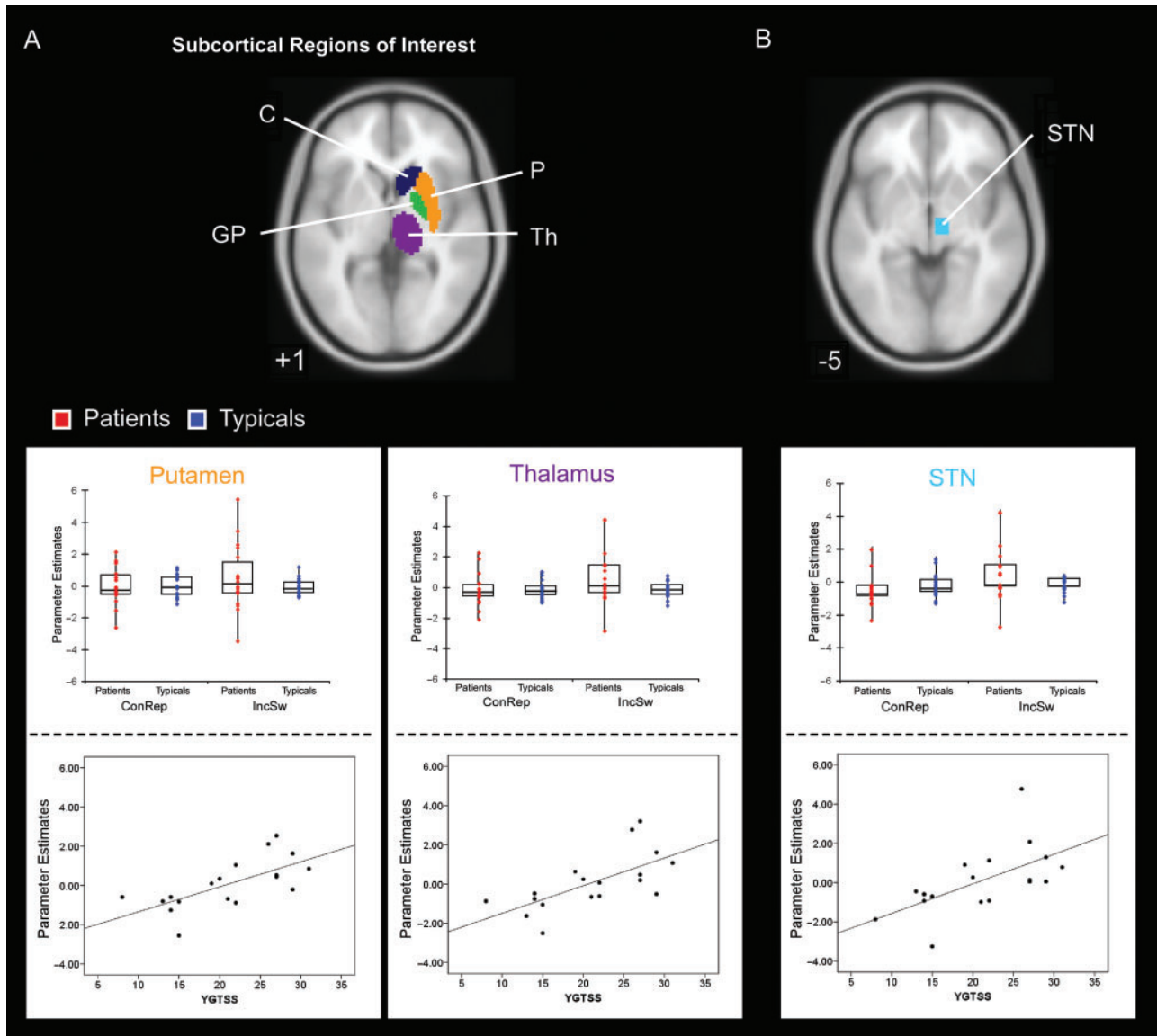


Fig. 6 (A) Subcortical ROIs in the right basal ganglia and thalamus. C = caudate; P = putamen; GP = globus pallidus; Th = thalamus. Box-and-whisker plots for right putamen and thalamus, showing min/max/first quartile/third quartile/median divided by activation for ConRep and IncSw, and by group. Plots for maximally active voxel in this ROI from IncSw-fix correlated with YGTSS (additional regressors: IncSw Accuracy and age). (B) ROI of STN, including box-and-whisker plots and correlation plot.

support for the idea that TS involves an imbalance between the direct and indirect pathways, whereby excess dopamine leads to elevated activity in the direct pathway through stimulation of D1 receptors, resulting in unchecked movements via disinhibition of the motor thalamus (Fig. 7). The disinhibition of motor pathways in TS is nicely illustrated by the observation that tic severity was positively correlated with regions in the corticospinal tract, including primary motor cortex.

Third, we showed that tic severity was positively correlated with activity in the nucleus accumbens. Given the role of the nucleus accumbens in the reinforcement of behaviour, this finding suggests that tics, as habitual motor acts, are reinforced via elevated activity in the

mesoaccumbens pathway (Saka and Graybiel, 2003; Albin and Mink, 2006). It should be noted that our results provide evidence for elevated mesolimbic activity as a function of tic severity *specifically* during performance of the most cognitively challenging trials, and are therefore indicative of transient rather than sustained elevation of mesolimbic activity in TS (this same observation holds for the other regions whose activation levels were correlated with tic severity). Even though our study does not focus on tic production *per se*, our findings provide insight into the mechanism by which spontaneous motor acts may be reinforced in TS.

Finally, tic severity was positively correlated with activation of the STN, consistent with our prediction that

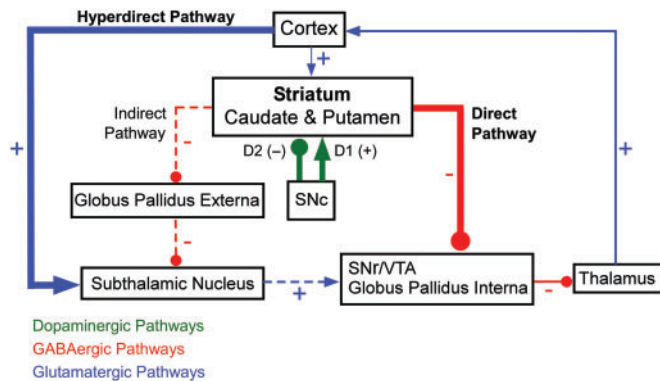


Fig. 7 Model of CSTC pathways affected in TS. Neural circuitry showing dopaminergic, GABAergic and glutamatergic pathways through the basal ganglia. The current study supports the hypothesis that patients exhibit increased activity in the direct pathway as well as increased compensatory activation of the hyperdirect pathway (both pathways bolded). The indirect pathway is shown with dotted lines. Arrows indicate excitatory connections and circles indicate inhibitory connections.

children with TS would engage the hyperdirect pathway from cortex to the STN, which would downregulate activity in the thalamus via the inhibition of the globus pallidus interna. Activation of this hyperdirect pathway would help to compensate for the disinhibition of the thalamus caused by an imbalance of activity between the direct and indirect pathways—i.e. excessive direct pathway activation (Fig. 7). It is known that dopamine stimulates D2 receptors, which leads to *inhibition* of the STN via the indirect pathway, and therefore to the facilitation of movement. Given that we observed elevated activity in dopamine-producing nuclei in TS, we might have predicted lower STN activation in patients than typicals, as a result of reduced activity in the indirect pathway. The fact that we observed *greater* STN activation in patients with more severe tics suggests that a compensatory mechanism is at work.

Conclusion

Children with TS must exert a conscious effort to suppress their involuntary thoughts and actions; the need to monitor and control themselves throughout the day can lead to poor performance in school. In future research, it will be critical to examine the relationships between TS, OCD and ADHD, all of which are frontostriatal disorders that affect cognitive control (e.g. Vaidya *et al.*, 2005; Penades *et al.*, 2006), and that can occur together or separately. Additionally, it is important to broaden the scope of research to include a larger population of children with tic disorders who do not meet criteria for a formal diagnosis of TS. It would be most helpful to be able to determine whether a child who is exhibiting tics is likely to develop TS. In this way, behavioural interventions targeting younger children could help to improve the long-term prognosis of those who are likely to experience persistent tics.

Supplementary material

Supplementary material is available at *Brain* online.

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References

- Abelson JF, Kwan KY, O'Roak BJ, Baek DY, Stillman AA, Morgan TM, et al. Sequence variants in SLITRK1 are associated with Tourette's syndrome. *Science* 2005; 310: 317–2.
- Abidin R. The parenting stress index. Lutz, FL: Psychological Assessment Resources: Inc.; 1995.
- Achenbach TM, Rescorla, LA. Manual For the ASEBA school-age forms and profiles: an integrated system of multi-informant assessment. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2001.
- Albin RL, Mink JW. Recent advances in Tourette syndrome research. *Trends Neurosci* 2006; 29: 175–82.
- APA. Diagnostic and statistical manual of mental disorder. 4th edn., Washington, DC: American Psychiatric Association; 1994.
- Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA. Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. *J Neurosci* 2007; 27: 3743–52.
- Aron AR, Poldrack RA. Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. *J Neurosci* 2006; 26: 2424–33.
- Aron AR, Shohamy D, Clark J, Myers C, Gluck MA, Poldrack RA. Human midbrain sensitivity to cognitive feedback and uncertainty during classification learning. *J Neurophys* 2004; 92: 1144–1152.
- Baxter LR, Guze BA. eds. Neuroimaging. New York, NY: Marcel Dekker; 1992.
- Bloch MH, Leckman JF, Zhu H, Peterson BS. Caudate volumes in childhood predict symptom severity in adults with Tourette syndrome. *Neurology* 2005; 65: 1253–8.
- Bohlhalter S, Goldfine A, Matteson S, Garraux G, Hanakawa T, Kansaku K, et al. Neural correlates of tic generation in Tourette syndrome: an event-related functional MRI study. *Brain* 2006; 129: 2029–37.
- Bornstein RA, Baker GB. Neuropsychological performance and urinary phenylethylamine in Tourette's syndrome. *J Neuropsychiatry Clin Neurosci* 1991; 3: 417–21.
- Brett M, Anton JL, Valabregue R, Poline JB. Region of interest analysis using an SPM toolbox. In 8th International Conference on Functional Mapping of the Human Brain, 2002, Sendai, Japan.
- Burgund ED, Kang HC, Kelly JE, Buckner RL, Snyder AZ, Petersen SE, et al. The feasibility of a common stereotactic space for children and adults in fMRI studies of development. *NeuroImage* 2002; 17: 184–200.
- Butler T, Stern E, Silbersweig D. Functional neuroimaging of Tourette syndrome: advances and future directions. *Adv Neurol* 2006; 99: 115–29.

- Chase TN, Foster NL, Fedio P, Brooks R, Mansi L, Kessler R, et al. Gilles de la tourette syndrome: studies with the fluorine-18-labeled fluorodeoxyglucose positron emission tomographic method. *Ann Neurol* 1984; 15 (Suppl): S175.
- Comings DE, Himes JA, Comings BG. An epidemiologic study of Tourette's syndrome in a single school district. *J Clin Psychiatry* 1990; 51: 463–9.
- Como PG. Neuropsychological function in Tourette syndrome. *Adv Neurol* 2001; 85: 103–11.
- Conners KC. Conners' rating scales revised manual. Tonawanda, NY: Multi-Health Systems, Inc.; 2001.
- Curtis D, Brett P, Dearlove AM, McQuillin A, Kalsi G, Robertson MM, et al. Genome scan of Tourette syndrome in a single large pedigree shows some support for linkage to regions of chromosomes 5, 10 and 13. *Psychiatric Genetics* 2004; 14: 83–7.
- Dale AM. Optimal experimental design for event-related fMRI. *Hum Brain Mapp* 1999; 8: 109–14.
- DeVito TJ, Drost DJ, Pavlosky W, Neufeld RW, Rajakumar N, McKinlay BD, et al. Brain magnetic resonance spectroscopy in Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 2005; 44: 1301–8.
- Ernst M, Zametkin AJ, Jons PH, Matochik JA, Pascualvaca D, Cohen RM. High presynaptic dopaminergic activity in children with Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 1999; 38: 86–94.
- Fredericksen KA, Cutting LE, Kates WR, Mostofsky SH, Singer HS, Cooper KL, et al. Disproportionate increases of white matter in right frontal lobe in Tourette syndrome. *Neurology* 2002; 58: 85–9.
- Frey KA, Albin RL. Neuroimaging of Tourette syndrome. *J Child Neurol* 2006; 21: 672–7.
- Garraux G, Goldfine A, Bohlhalter S, Lerner A, Hanakawa T, Hallett M. Increased midbrain gray matter in Tourette's syndrome. *Ann Neurol* 2006; 59: 381–5.
- Gerard E, Peterson BS. Developmental processes and brain imaging studies in Tourette syndrome. *J Psychosom Res* 2003; 55: 13–22.
- Gilbert DL, Christian BT, Gelfand MJ, Shi B, Mantil J, Sallee FR. Altered mesolimbocortical and thalamic dopamine in Tourette syndrome. *Neurology* 2006; 67: 1695–7.
- Gioia GA, Isquith PK, Guy SC, Kenworthy L. The behavior rating inventory of executive function. Lutz, FL: Psychological Assessments Resources, Inc.; 2000.
- Hershey T, Black KJ, Hartlein J, Braver TS, Barch DM, Carl JL, et al. Dopaminergic modulation of response inhibition: an fMRI study. *Brain Res Cogn Brain Res* 2004; 20: 438–48.
- Johannes S, Wieringa BM, Mantey M, Nager W, Rada D, Muller-Vahl KR, et al. Altered inhibition of motor responses in Tourette Syndrome and Obsessive-Compulsive Disorder. *Acta Neurol Scand* 2001; 104: 36–43.
- Kang HC, Burgund ED, Lugar HM, Petersen SE, Schlaggar BL. Comparison of functional activation foci in children and adults using a common stereotactic space. *NeuroImage* 2003; 19: 16–28.
- Leckman JF. ed. Tourette syndrome. Washington, DC: American Psychiatric Press; 1993.
- Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry* 1998; 28: 566–73.
- Lee JS, Yoo SS, Cho SY, Ock SM, Lim MK, Panych LP. Abnormal thalamic volume in treatment-naive boys with Tourette syndrome. *Acta Psychiatr Scand* 2006; 113: 64–7.
- Ludolph AG, Juengling FD, Libal G, Ludolph AC, Fegert JM, Kassubek J. Grey-matter abnormalities in boys with Tourette syndrome: Magnetic resonance imaging study using optimised voxel-based morphometry. *Br J Psychiatry* 2006; 188: 484–5.
- March J. The multidimensional anxiety scale for children. North Tonawanda, NY: Multi-Health Systems, Inc.; 1999.
- Marsh R, Zhu H, Wang Z, Skudlarski P, Peterson BS. A Developmental fMRI Study of Self-Regulatory Control in Tourette's Syndrome. *Am J Psychiatry* 2007; 164: 955–66.
- Mink JW. Basal ganglia dysfunction in Tourette's syndrome: a new hypothesis. *Pediatr Neurol* 2001; 25: 190–8.
- Mink JW, Walkup J, Frey KA, Como P, Cath D, DeLong MR, et al. Patient selection and assessment recommendations for deep brain stimulation in Tourette syndrome. *Mov Disord* 2006; 21: 1831–8.
- Mueller SC, Jackson GM, Dhalla R, Datsopoulos S, Hollis CP. Enhanced cognitive control in young people with Tourette's syndrome. *Curr Biol* 2006; 16: 570–3.
- Nomura Y, Segawa M. Neurology of Tourette's syndrome (TS) TS as a developmental dopamine disorder: a hypothesis. *Brain Dev* 2003; 25 (Suppl 1): S37–42.
- Ozonoff S, Strayer DL, McMahon WM, Filloux F. Inhibitory deficits in Tourette syndrome: a function of comorbidity and symptom severity. *J Child Psychol Psychiatry* 1998; 39: 1109–18.
- Pauls DL. An update on the genetics of Gilles de la Tourette syndrome. *J Psychosom Res* 2003; 55: 7–12.
- Pauls DL, Leckman JF. The inheritance of Gilles de la Tourette's syndrome and associated behaviors. Evidence for autosomal dominant transmission. *N Engl J Med* 1986; 315: 993–7.
- Penades R, Catalan R, Rubia K, Andres S, Salamero M, Gasto C. Impaired response inhibition in obsessive compulsive disorder. *Eur Psychiatry* 2007; 22: 404–10.
- Peterson BS, Pine DS, Cohen P, Brook JS. Prospective, longitudinal study of tic, obsessive-compulsive, and attention-deficit/hyperactivity disorders in an epidemiological sample. *J Am Acad Child Adolesc Psychiatry* 2001; 40: 685–95.
- Peterson BS, Thomas P, Kane MJ, Scahill L, Zhang H, Bronen R, et al. Basal Ganglia volumes in patients with Gilles de la Tourette syndrome. *Arch Gen Psychiatry* 2003; 60: 415–24.
- Pringsheim T, Davenport WJ, Lang A. Tics. *Curr Opin Neurol* 2003; 16: 523–7.
- Rutter M, Bailey A, Berument SK, Lord C, Pickles A. Social communication questionnaire. Los Angeles, CA: Western Psychological Services; 2003.
- Saka E, Graybiel AM. Pathophysiology of Tourette's syndrome: striatal pathways revisited. *Brain Dev* 2003; 25 (Suppl 1): S15–9.
- Scahill L, Riddle MA, McSwiggan-Hardin M, Ort SI, King RA, Goodman WK, et al. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. *J Am Acad Child Adolesc Psychiatry* 1997; 36: 844–52.
- Serrien DJ, Orth M, Evans AH, Lees AJ, Brown P. Motor inhibition in patients with Gilles de la Tourette syndrome: functional activation patterns as revealed by EEG coherence. *Brain* 2005; 128: 116–25.
- Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *J Am Acad Child Adolesc Psychiatry* 2000; 39: 28–38.
- Stern E, Silbersweig DA, Chee KY, Holmes A, Robertson MM, Trimble M, et al. A functional neuroanatomy of tics in Tourette syndrome. *Arch Gen Psychiatry* 2000; 57: 741–8.
- Thesen S, Heid O, Mueller E, Schad LR. Prospective acquisition correction for head motion with image-based tracking for real-time fMRI. *Magn Reson Med* 2000; 44: 457–65.
- Vaidya CJ, Bunge SA, Dudukovic NM, Zalecki CA, Elliott GR, Gabrieli JD. Altered neural substrates of cognitive control in childhood ADHD: evidence from functional magnetic resonance imaging. *Am J Psychiatry* 2005; 162: 1605–13.
- Verte S, Geurts HM, Roeyers H, Oosterlaan J, Sergeant JA. Executive functioning in children with autism and Tourette syndrome. *Dev Psychopathol* 2005; 17: 415–45.
- Watkins LH, Sahakian BJ, Robertson MM, Veale DM, Rogers RD, Pickard KM, et al. Executive function in Tourette's syndrome and obsessive-compulsive disorder. *Psychol Med* 2005; 35: 571–82.
- Wechsler D. Wechsler Abbreviated Scale of Intelligence. San Antonio, TX: Psychological Corporation; 1999.
- Yoon DY, Gause CD, Leckman JF, Singer HS. Frontal dopaminergic abnormality in Tourette syndrome: a postmortem analysis. *J Neurol Sci* 2007; 255: 50–6.