doi:10.1093/brain/awn223 Brain 2009: 132; 225–238 | 225

BRAIN
A JOURNAL OF NEUROLOGY

Control networks in paediatric Tourette syndrome show immature and anomalous patterns of functional connectivity

Jessica A. Church,[1] Damien A. Fair,[1] Nico U. F. Dosenbach,[2] Alexander L. Cohen,[1] Francis M. Miezin,[1,2] Steven E. Petersen[1,2,3,4] and Bradley L. Schlaggar[1,2,3,5]

1 Department of Neurology, School of Medicine, Washington University in St Louis, St Louis, MO, USA
2 Department of Radiology, School of Medicine, Washington University in St Louis, St Louis, MO, USA
3 Department of Anatomy Neurobiology, School of Medicine, Washington University in St Louis, St Louis, MO, USA
4 Department of Psychology, School of Medicine, Washington University in St Louis, St Louis, MO, USA
5 Department of Pediatrics, School of Medicine, Washington University in St Louis, St Louis, MO, USA

Correspondence to: Jessica A. Church,
Department of Neurology, Box 8111, 4525 Scott Avenue,
Washington University School of Medicine,
St Louis, MS 63110, USA
E-mail: jchurch@wustl.edu

Tourette syndrome (TS) is a developmental disorder characterized by unwanted, repetitive behaviours that manifest as stereotyped movements and vocalizations called 'tics'. Operating under the hypothesis that the brain's control systems may be impaired in TS, we measured resting-state functional connectivity MRI (rs-fcMRI) between 39 previously defined putative control regions in 33 adolescents with TS. We were particularly interested in the effect of TS on two of the brain's task control networks—a fronto-parietal network likely involved in more rapid, adaptive online control, and a cingulo-opercular network apparently important for set-maintenance. To examine the relative maturity of connections in the Tourette subjects, functional connections that changed significantly over typical development were examined. Age curves were created for each functional connection charting correlation coefficients over age for 210 healthy people aged 7–31 years, and the TS group correlation coefficients were compared to these curves. Many of these connections were significantly less 'mature' than expected in the TS group. This immaturity was true not only for functional connections that grow stronger with age, but also for those that diminish in strength with age. To explore other differences between Tourette and typically developing subjects further, we performed a second analysis in which the TS group was directly compared to an age-matched, movement-matched group of typically developing, unaffected adolescents. A number of functional connections were found to differ between the two groups. For these identified connections, a large number of connectional differences were found where the TS group value was out of range compared to typical developmental age curves. These anomalous connections were primarily found in the fronto-parietal network, thought to be important for online adaptive control. These results suggest that in adolescents with TS, immature functional connectivity is widespread, with additional, more profound deviation of connectivity in regions related to adaptive online control.

Keywords: Tourette syndrome; functional connectivity; attentional control; adolescence; cognitive development

Abbreviations: ADHD = Attention deficit-hyperactivity disorder; BOLD = blood-oxygenation-level dependent; COIs = connections of interest; CSTC = cortico-striatal-thalamo-cortical; OCD = obsessive-compulsive disorder; ROI = region of interest; rs-fcMRI = resting-state functional connectivity MRI; TS = Tourette syndrome

Received April 9, 2008. Revised August 15, 2008. Accepted August 18, 2008. Advance Access publication October 24, 2008

Introduction

Humans have proven to be a resourceful and adaptable species able to respond to changing conditions with novel behaviours utilizing a wide variety of abilities. The human brain is able to solve new problems, communicate and perform goal-directed behaviours over wide-ranging timescales (Posner and Petersen, 1990; Dosenbach *et al*., 2008). Critical to the flexible production of behaviour are the means to choose and maintain the appropriate configuration of processes related to a specific set of goals. Similarly, it is important to adapt and adjust behaviours in an ongoing fashion, including the inhibition of actions and behaviours that are prepotent, unwanted or at cross-purposes with one's goals. When any of these processes go awry, unwanted behaviours may result.

Tourette syndrome (TS) is a developmental disorder characterized by unwanted, irresistible stereotyped movements and vocalizations called 'tics'. Symptoms frequently appear around the ages of 6–7 years, and can increase in severity, often peaking in intensity in early adolescence (Leckman, 2003). The DSM-IV-R criteria for a diagnosis of Tourette syndrome requires diagnosis prior to 18 years of age, tics not due to substances or other disorders and the presence of motor tics and vocal tics for >1 year (American Psychiatric Association, 2000). Attention deficit-hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) are strongly co-morbid with TS [50% with TS also have ADHD, while 20–60% have OCD (Singer, 2005)].

As with these co-morbid disorders, TS has been hypothesized to involve the frontal cortex and its connections to subcortical regions such as the basal ganglia, through frontal cortico-striatal-thalamo-cortical (CSTC) circuits (Mink, 2001; Singer, 2005; Albin and Mink, 2006). TS has also been hypothesized to be associated with cognitive difficulties involving frontal cortex, including response inhibition and selective attention (Bornstein *et al*., 1991; Johannes *et al*., 2001; Channon *et al*., 2003). This proposition is controversial, however, because of the potential contribution of co-morbid ADHD to executive dysfunction in so many patients with TS, and since the same or similar underlying pathophysiological substrates are implicated in ADHD as well as in TS (e.g. Ozonoff *et al*., 1998; Mahone *et al*., 2002). Importantly, 'pure' TS (i.e. lacking any co-morbidity) is relatively uncommon, occurring in ~10% of TS patients (Freeman *et al*., 2000; Khalifa and von Knorring, 2006). Nonetheless, the inability to resist or inhibit unwanted movements in TS implies that regions involved in behavioural control may be affected in the disorder. We hypothesize here that TS is, in part, a consequence of atypical development of the brain's attentional control networks (Posner and Petersen, 1990).

In previous studies, we have explored the brain's control systems using resting-state functional connectivity MRI (rs-fcMRI), which measures correlations in low frequency (~<0.1 HZ) spontaneous blood-oxygenation-level dependent (BOLD) signals. rs-fcMRI has previously demonstrated that the BOLD timeseries of any given region of the brain has different degrees of correlation with other regions of the brain (Biswal *et al*., 1995; Greicius *et al*., 2003; Fox *et al*., 2005). This method has revealed the underlying structure of biologically plausible and reproducible functional networks in several domains (Fransson, 2005; Hampson *et al*., 2006; Dosenbach *et al*., 2007; Fair *et al*., 2007*a*, 2008) (also see Fox and Raichle, 2007, for review). In addition, the nature of the rs-fcMRI approach unburdens subject compliance and training demands for between group comparisons (Fair *et al*., 2007*b*). Because of these attributes, rs-fcMRI is increasingly being used to study systems organization in development (Fair *et al*., 2007*a*, 2008; Fransson *et al*., 2007) and in disease (Greicius *et al*., 2004; Greicius *et al*., 2007; Just *et al*., 2007; Castellanos *et al*., 2008); hence, rs-fcMRI is well suited to study the potential disruption of brain systems in patients with TS.

When these methods were applied to the study of brain regions that carry task control signals (i.e. task initiation signals, feedback signals and signals sustained across the entire task period) across a wide range of different tasks (Dosenbach *et al*., 2006) (Fig. 1A), these regions were found to separate into eight distinct components or networks (Dosenbach *et al*., 2007, 2008). Two of these components were particularly interesting because the regions they encompass have been repeatedly identified as being important for task control (Luna *et al*., 2001; Miller and Cohen, 2001; Corbetta and Shulman, 2002; Braver *et al*., 2003; Sakai and Passingham, 2003; Luna and Sweeney, 2004; Rueda *et al*., 2004; Rushworth *et al*., 2004; Bunge *et al*., 2005; Dosenbach *et al*., 2006; Seeley *et al*., 2007). Based on a functional activation MRI study (Dosenbach *et al*., 2006), one component, the 'cingulo-opercular' network (see Table 3 for regions), is hypothesized to maintain task sets across all the events within a task period. The other component, the 'fronto-parietal' network (see Table 3 for regions), is thought to act on a shorter timescale and is important for rapidly adaptive online control (Dosenbach *et al*., 2008) (Fig. 1B).

Recent work has described the normal developmental profile of these putative control networks using rs-fcMRI (Fair *et al*., 2007*a*). Overall, the strength of correlation coefficients 'between' these two control networks is greater in children, and declines over age, while the strength of correlation coefficients linking regions 'within' each of the networks increases over age. Direct comparisons between children and adults showed that children have a greater proportion of strongly correlated short-range functional connections (i.e. connections between regions close in space) that tend to decrease in strength over age. In contrast, long-range functional connections (i.e. connections between regions more distant in space) tend to form and to increase in strength over age [right panel of Fig. 4C; adapted from (Fair *et al*., 2007*a*)].

Three specific observations exemplifying these general observations were that (i) the dACC/msFC region, a member of the cingulo-opercular network in adults, was instead part of the fronto-parietal network in children; (ii) there were fewer connections between the frontal and parietal regions of the fronto-parietal network in children compared to adults; and (iii) the fronto-parietal and cingulo-opercular networks were linked in children via a connection between the dlPFC and aPFC that was absent in adults (Fair *et al*., 2007*a*) (Fig. 2).

In theory, TS patients could have at least three different types of task-control deficits related to aberrant functional connectivity within and between these control networks. First, the connectivity with and within cingulo-opercular network could be abnormal, affecting task-maintenance processes and resulting in unwanted breakthroughs (i.e. tics) of normally suppressed behaviours.

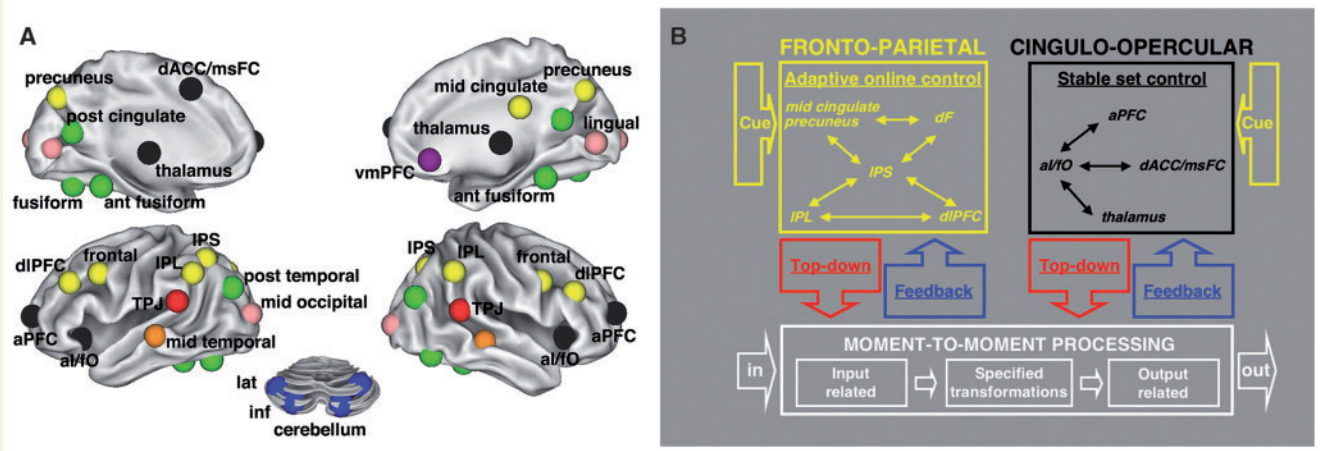

Fig. 1 Thirty-nine putative control regions and proposed dual-network model of task control (Dosenbach *et al*., 2006, 2007, 2008). (**A**) Thirty-nine putative control regions. The fronto-parietal network is shown in yellow, and the cingulo-opercular network is shown in black. (**B**) A model of two parallel control networks affecting moment-to-moment processing. The fronto-parietal network is thought to be important for adaptive online control over shorter time scales, while the cingulo-opercular network is thought to support stable set control and to be more resistant to distractions. Part A of figure is from Dosenbach *et al*., 2007; part B is from Fair *et al*., 2007*a*. Abbreviations are explained in Table 3.

Second, TS patients could have altered connectivity with and within the frontoparietal network affecting adaptive online control, such that processes that normally initiate or adjust changes in task-control are hyperactive. This impairment would manifest in the same way as the first possibility (breakthrough of unwanted behaviours). Lastly, a more widespread set of differences could affect both networks and the relations between them, again leading to unwanted behaviours.

In an attempt to differentiate between these alternatives, we conducted two types of analysis. First, to assess whether the task-control related connections were age-appropriate in TS, we identified connections of interest (COIs) that showed significant change over typical development, and examined these connections in a group of adolescents with TS. Second, we directly compared the functional connectivity among all of the 39 putative control regions in a group of adolescents aged 10–15 years with TS, and a 'matched' comparison group of adolescents without TS.

To preview the results, we found that adolescents with TS show a widespread pattern of less mature functional connectivity in connections involving both control networks. Other, more starkly anomalous connections were much more evident in the fronto-parietal network than in the cingulo-opercular network. This constellation of findings suggests that task control is generally altered in TS, with greatest impairment of more rapid, adaptive control (fronto-parietal).

Methods

Subjects

TS subjects were recruited through the Washington University School of Medicine Movement Disorder Center and the local chapter of the Tourette Syndrome Association (TSA). A total of 45 subjects diagnosed with TS and 46 unaffected subjects were recruited. The presence of diagnosed co-morbidities (primarily ADHD and/or OCD) and/or medications were not considered exclusion criteria in the TS subjects (Table 2). However, they were considered exclusion criteria for the unaffected subjects. All subjects underwent a battery of neuropsychological measures including full-scale estimated IQ (WISC-IV), Trails A and B, Stroop colour and word test (Golden *et al*., 2002), Controlled Oral Word Association (COWA-FAS), Yale Global Tic Severity Scale (YGTSS) (Leckman *et al*., 1989), Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill *et al*., 1997) and DSM-IV ADHD Symptom Rating Scale.

Because of the potential effects of head movement on rs-fcMRI data, (Cohen *et al*., 2006), differences between movement measures for the adolescents with and without TS were minimized, yielding usable resting state data from 75 subjects (33 with TS ages 10–15 years; 42 without TS ages 10–15 years; Tables 1 and 2). This 'matching' was done by calculating movement for all individuals and removing individuals with excessive movement. For the final matched groups, within-run subject motion was <1.75 mm root mean squared variance (rms-variance) for both groups and not significantly different (average rms-variance values: adolescents with TS = 0.768 mm, unaffected adolescents = 0.731 mm, $P = 0.65$).

For each subject at least 320 s (5.33 min) of resting state BOLD data were collected (TS group range = 320–640 s, median = 640 s; non-TS group range = 400–640 s, median = 640 s). For each of the 39 task-control regions of interest (ROIs) (Table 3), a resting state time series was extracted separately for each individual. For all subjects, resting periods were extracted from an interleaved experimental design that also contained task periods. Our method for extracting resting periods from blocked fMRI designs has been validated (for details, see Fair *et al*., 2007*b*).

Data acquisition and processing

fMRI data were acquired on a Siemens 1.5 Tesla MAGNETOM Vision system (Erlangen, Germany). Structural images were obtained using a sagittal magnetization-prepared rapid gradient echo (MP-RAGE)

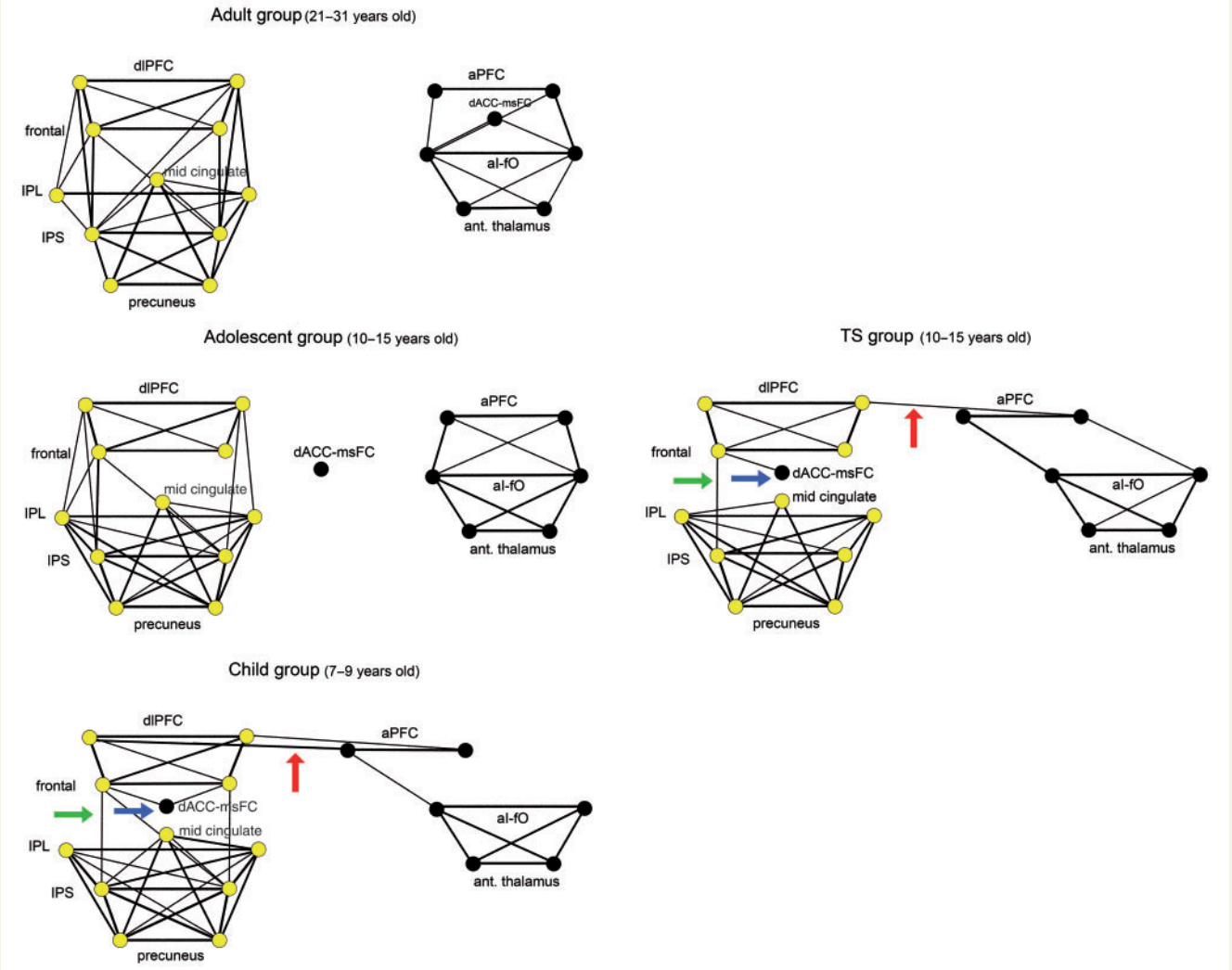

Fig. 2 The development of functional connections within and between the two control networks appears to be disrupted or delayed in adolescents with TS. Regions in the fronto-parietal network are shown in yellow, while those in the cingulo-opercular network are shown in black. Eighteen regions at a correlation threshold of $r \geqslant 0.2$ for four groups: unaffected adults, unaffected adolescents, unaffected children and the TS group (see Methods section). The regions in each of the four graphs are arranged pseudoanatomically, such that frontal regions are near the top, parietal regions are near the bottom and left hemisphere regions are on the left of each network, while right hemisphere regions are on the right. For these two networks, it has been shown that three principle connectivity differences exist between childhood and adulthood (Fair *et al*., 2007*a*). (i) There are fewer connections between the frontal and parietal regions of the frontal-parietal (yellow) network in typical children versus typical adults and adolescents (green arrow); (ii) the dACC/msFC region is integrated into the frontal-parietal network in typical children compared to typical adults and adolescents (blue arrow); and (iii) the two networks are linked via a connection between the aPFC and dlPFC in typical children versus typical adults and adolescents (red arrow). The adolescents with TS do not appear to undergo this same developmental transition as typically developing subjects. The adolescents with TS appear younger (more similar to the child group) than their age-matched peers (cf. TS group arrows with unaffected child group), suggesting a disruption or delay in the maturation of these networks. Graphs of typical adults, adolescents, and children are derived with a slightly different statistical threshold than Fair *et al*. (2007*a*).

three-dimensional T_1-weighted sequence, TR = 9.7 ms, TE = 4 ms, flip angle = 10°, voxel size = 1.25 mm × 1.0 mm × 1.0 mm resolution. Functional images were obtained using an asymmetric spin echo echo-planar sequence sensitive to BOLD contrast, TR = 2.5 s, T2 × evolution time = 50 ms, flip angle = 90°, voxel size = 3.75 mm × 3.75 mm in-plane resolution. Whole-brain coverage was obtained with 16 contiguous interleaved 8 mm axial slices acquired parallel to the plane transecting the anterior and posterior commissures (AC–PC plane). Steady state magnetization was assumed after four frames (~10 s).

Functional images were processed to reduce artifacts (Miezin *et al*., 2000). Each run of each individual was then resampled in atlas space on an isotropic 3 mm grid combining movement correction and atlas transformation in one interpolation. All subsequent operations were performed on the atlas-transformed volumetric timeseries.

Functional connectivity pre-processing

Analyses using rs-fcMRI were additionally pre-processed as previously described (Dosenbach *et al*., 2007; Fair *et al*., 2007*a*, *b*, 2008;

Table 1 Characteristics of subject groups

	Subjects with TS	Subjects without TS
N	33	42
Male/Female	25/8	24/18
Average age (range)	12.70 (9.92 to 15.83)	12.69 (10.42 to 15.75)
Average movement mm rms (range)	0.768 (0.19 to 1.56)	0.731 (0.235 to 1.51)
Average IQ (range)	105.4 (80 to 137)	108.5 (86 to 137)
Average COWA-FAS *z*-score (range)	−0.32 (−3.9 to +3.2)	−0.02 (−2.7 to +2.3)
Average stroop interference *z*-score (range)	0.15 (−0.9 to +2.2)	0.26 (−0.9 to +1.8)
Average trails B *z*-score (range)*	0.26 (−3.5 to +1.6)	0.70 (−0.9 to +2.5)
Average tic severity rating (range)*	16.3 (4 to 28)	0 (0)
Average ADHD rating (range)*	31.8 (4 to 76)	10.1 (0 to 28)
Average OCD rating (range)*	4.6 (0 to 18)	0.1 (0 to 2)
No. on medications	22	0
No. with diagnosed co-morbidities	17	0

Subjects with TS were used in both the COI and the direct comparison analyses, while the unaffected adolescent group was used in the direct comparison analysis (see text). The average Tic Severity rating was evaluated using only the motor tic and vocal tic sections of the YGTSS (maximum 50 points) and not the global assessment. Movement refers to in-scanner movement measured in millimeters (mm) of rms-variance. Significant differences ($P < 0.05$) by two-tailed *t*-test between the adolescent groups are indicated with an asterisk.

Table 2 Profile of medication use for the 22 medicated TS participants

	No. of participants
Centrally acting adrenergic agents	13
Atypical neuroleptics	7
Stimulants	7
SSRI antidepressants	6
Benzodiazepines	2
Antiseizure medications	2
Norepinephrine RI antidepressants	2
β blockers	1
Tetracyclic antidepressants	1

Thirteen TS participants were taking more than one medication.

Fox *et al*., 2007) to reduce spurious variance unlikely to reflect neuronal activity (Fox and Raichle, 2007). These steps included: (i) a temporal band-pass filter (0.009 Hz < f < 0.08 Hz); (ii) spatial smoothing (6 mm full width at half maximum); and (iii) removal of unwanted signals by regressing out signal (and its first derivative) attributable to the six parameters obtained by rigid-body head motion correction, a whole brain ROI, an overall ventricular ROI and an overall white matter ROI.

Definition of ROIs for network analysis

Thirty-nine ROIs, originally derived from cross-studies fMRI analyses (183 subjects; 10 tasks) of task control signals in adults (Dosenbach *et al*., 2006) and used in our previous publications (Dosenbach *et al*., 2007; Fair *et al*., 2007*a*), were applied to adolescents with and without TS (Table 3). These ROIs have been shown to carry several task-control-related signals including sustained, start-cue and/or error-related activity (Dosenbach *et al*., 2006). Spheres of 12 mm diameter were created around each centre of mass coordinate and BOLD timecourses were extracted for each sphere from each individual. These ROIs are shown in the left panel of Fig. 1.

Computation of group mean correlation matrices for analysis

To explore the network relationships among the 39 regions, the resting state BOLD time series were correlated region-by-region for each subject across the full length of the resting time series, creating a total of 75 39×39 square correlation matrices ($n = 33$ with TS; $n = 42$ without TS). These correlation matrices were then averaged across individuals within a group [using the Schmidt-Hunter method for meta-analyses of *r*-values (Field, 2001; Salvador *et al*., 2005; Dosenbach *et al*., 2007; Fair *et al*., 2007*a*, 2008)] to yield a single mean correlation matrix for TS and unaffected subjects, respectively. Two main analyses were performed using these matrices.

Examination of developmental COIs in Tourette syndrome data

In a previous study, a subset ($n = 55$) of the correlation coefficients from the 39×39 matrix (741 possible connections) were found to be significantly different between a group of movement-matched healthy children aged 7–9 years and adults aged 21–31 years (Fair *et al*., 2007*a*). Data on connection strength versus age for these developing functional connections were then described with LOWESS curves [a local regression smoothing procedure (Cleveland, 1981)], using 210 healthy subjects, ages 7–31 years (Fair *et al*., 2007*a*). This sort of qualitative approach can be useful for identifying data patterns that may be overlooked when using curve fitting procedures that assume a shape (Brown *et al*., 2005; Fair *et al*., 2006).

We estimated the 'maturity' of each functional connection in the TS group by comparing the mean TS group correlation coefficient to the LOWESS curve for that connection. An age estimate was done by finding the point on each connection's typical developmental LOWESS curve that most closely matched the TS group's mean correlation coefficient and obtaining the 'age' for that point. For example, if the correlation coefficient was 'normal' or 'age-appropriate', its estimated age from the LOWESS curve should be close to the actual average age of the TS group (12.7 years). If the correlation coefficient did not overlap with any value on the LOWESS curve, the functional connection was classified as anomalous or 'off-curve'. As the

Table 3 ROIs are sorted into components based on an adult rs-fcMRI analysis (Dosenbach *et al.*, 2007)

ROI	X	Y	Z	Component	
R dlPFC	43	22	34	1	Fronto-parietal
L dlPFC	−43	22	34	1	Fronto-parietal
R frontal cortex	41	3	36	1	Fronto-parietal
L frontal cortex	−41	3	36	1	Fronto-parietal
R precuneus	10	−69	39	1	Fronto-parietal
L precuneus	−9	−72	37	1	Fronto-parietal
midcingulate	0	−29	30	1	Fronto-parietal
R IPL	51	−47	42	1	Fronto-parietal
L IPL	−51	−51	36	1	Fronto-parietal
R IPS	30	−61	39	1	Fronto-parietal
L IPS	−31	−59	42	1	Fronto-parietal
R aPFC	27	50	23	2	Cingulo-opercular
L aPFC	−28	51	15	2	Cingulo-opercular
dACC/msFC	−1	10	46	2	Cingulo-opercular
R aI/fO	36	16	4	2	Cingulo-opercular
L aI/fO	−35	14	5	2	Cingulo-opercular
R ant thalamus	10	−15	8	2	Cingulo-opercular
L ant thalamus	−12	−15	7	2	Cingulo-opercular
R lat cerebellum	31	−61	−29	3	
L lat cerebellum	−32	−66	−29	3	
R inf cerebellum	18	−80	−33	3	
L inf cerebellum	−19	−78	−33	3	
R TPJ	53	−46	17	4	
L TPJ	−53	−46	17	4	
R mid occipital	27	−89	3	5	
L mid occipital	−27	−89	3	5	
R lingual	8	−82	4	5	
L lingual	−8	−82	4	5	
R fusiform	35	−65	−9	6	
L fusiform	−34	−62	−15	6	
R ant fusiform	25	−44	−12	6	
L ant fusiform	−25	−44	−12	6	
R post temporal	44	−74	26	6	
L post temporal	−40	−78	24	6	
R post cingulate	10	−56	16	6	
L post cingulate	−11	−57	13	6	
R mid temporal	51	−33	−2	7	
L mid temporal	−53	−31	−5	7	
vmPFC	1	31	−2	8	

Component 1 comprises the 'fronto-parietal' network, while component 2 comprises the 'cingulo-opercular' network. The other components are described further in (Dosenbach *et al.*, 2007). ROIs: dlPFC = dorsolateral prefrontal cortex; IPL = inferior parietal lobule; IPS = inferior parietal sulcus; aPFC = anterior prefrontal cortex; dACC/msFC = dorsal anterior cingulate/medial superior frontal cortex; aI/fO = anterior insula/frontal operculum; TPJ = temporal-parietal junction; vmPFC = ventro-medial prefrontal cortex. Other terms: R = right; L = left; ant = anterior; lat = lateral; mid = middle; post = posterior. Coordinates in mm are presented in Talairach space.

correlation coefficients of most of these off-curve connections were closest to the youngest correlation values for each connection, they could represent extreme immaturity in the TS group, or they could represent categorical differences in the TS group that are not well explained in a developmental context.

Direct comparisons between adolescents with Tourette syndrome and unaffected adolescents

As a second assessment of functional connectivity differences in the TS group, we performed two-sample two-tailed *t*-tests (assuming unequal variance; $P<0.05$) on all potential connections represented in the 39×39 correlation matrices (741 possible connections) between groups of adolescents with and without TS (Table 1). The developmental COIs examined above were thus a subset of these, but the direct comparison between the TS and typical adolescents could produce a new set of functional connections that showed significant differences between TS and typical adolescents.

A Fisher's Z-transformation was applied to the correlation coefficients to generate a normal distribution for the random effects analysis. Connections that had an $r<0.1$ in both groups were not analysed. Pairwise correlations with $r<0.1$, as previously reported by Cohen and Cohen (1983), even if statistically significant, may be biologically insignificant. To account for multiple comparisons, the Benjamini and Hochberg False Discovery Rate correction (Benjamini and Hochberg, 1995) was applied.

A separate permutation analysis of group membership was also conducted on each functional connection to directly compute the probability of obtaining a *t*-statistic as large as that found between the adolescents with and without TS (Nichols and Holmes, 2002). Because the initial groups included 33 adolescents with TS and 42 without TS, for this analysis we generated random groups of 33 and 42 individuals 10 000 times, from the entire set of 75 adolescents with and without TS. A *t*-test was performed between each pair of random groups generated by each permutation. The *t*-statistics resulting from those 10 000 *t*-tests formed a distribution of values from which the top and bottom 250 values represent the two-tailed $P<0.05$ levels of significance (Nichols and Holmes, 2002). The *t*-statistic obtained from performing the *t*-test between the actual TS and unaffected groups for each functional connection were compared with the permuted $P<0.05$ boundaries, and connections that were significant were noted. All functional connections that were deemed significantly different on the basis of the permutation test, that were not included in the COI analysis above, were then further analysed for developmental 'maturity' as in the COI analysis above.

As in the developmental COI analyses above, functional connections in which the TS group's average correlation coefficient value did not closely fit any value on the LOWESS curve were classified as off-curve functional connections. Off-curve functional connections resulting from the direct comparison were combined with any non-overlapping off-curve connections from the developmental COI analysis described above as 'anomalous' connections. The locations of all off-curve functional connections were examined for any pattern, as they may provide clues about the most severe functional connectivity impairments in TS.

Results

Subject characteristics

Behavioural measures are summarized in Table 1, and medication use in the TS group is summarized in Table 2. Significant group differences were found for Trails B *z*-scores ($P<0.05$), and YGTSS ($P<0.0001$), CY-BOCS ($P<0.0001$) and ADHD measures ($P<0.0001$), where the unaffected group had better Trails B *z*-scores, and lower measures on the YGTSS, CY-BOCS and ADHD rating scales. No group differences were found for several other neuropsychological measures (IQ, COWA-FAS or Stroop). The adolescent groups with and without TS were matched for age, number of males and movement, and thus showed no significant differences for those factors. No correlations were found between the results described below and the measure of tic severity (YGTSS motor and vocal assessments).

Functional connectivity of control networks are immature in adolescents with Tourette syndrome

The functional connections in the adolescent TS group appear less mature than those in the age-matched comparison group (Fig. 2) in several ways.

Qualitatively, the functional connections in the TS adolescent group appear to have a graph pattern more similar to 7- to 9-year-olds than their age matched cohort. For example, in the TS group, the dACC/msFC is incorporated into the fronto-parietal network as it is in unaffected 7- to 9-year-old children, and unlike what is seen in the group of unaffected 10- to 15-year-olds (blue arrow). In this unaffected adolescent group, the dACC/msFC is in transition from the child to the adult configuration. It has become disconnected from the fronto-parietal network, but is not yet incorporated into the cingulo-opercular network.

Second, there are fewer functional connections between the frontal and parietal regions of the fronto-parietal network in the TS group compared to the unaffected control group, which again is more similar to the child configuration (e.g. green arrow). Third, in the TS group, the cingulo-opercular network and fronto-parietal network are linked via a connection between the aPFC and dlPFC, whereas in their age-matched peers, the link between the two networks is disconnected (red arrow).

Quantitatively, we assessed this apparent 'developmental delay' in functional connectivity in the TS group more directly. For each COI that showed significant age-related change previously ($n=55$) (Fair *et al*., 2007*a*), an estimated LOWESS age was derived for the TS group based on their mean correlation coefficient for that connection (Fig. 3A). While some connections in the TS group had age-appropriate correlation strengths, a majority of the developmental COIs had estimated LOWESS ages for the TS group that were younger than expected (Fig. 3B) [$P<0.0001$ by one sample *t*-test, where off-curve functional connections (see Methods section) were excluded]. This set of applied connections was also explored in TS subgroup analyses to examine the potential role of medications on the LOWESS age estimates (see Supplementary Material).

In addition, seven functional connections were classified as off-curve, or anomalous in the TS group, because the TS group's average correlation coefficient did not intersect the LOWESS age curve at any point in our available range. In all cases, the off-curve connections had correlation values that were closest to the 'youngest' end of the LOWESS age curve. Five of these connections involved regions in the fronto-parietal adaptive control network (Dosenbach *et al*., 2006, 2007, 2008; Fair *et al*., 2007*a*). None of these off-curve connections in the TS group involved the cingulo-opercular network.

Direct comparisons between adolescents with and without TS reveal differences in the fronto-parietal network

When the groups of adolescents with and without TS were directly compared using *t*-tests, 34 functional connections were significantly different ($P<0.05$) between groups (Fig. 4A). None of these connections survived the Benjamini and Hochberg False Discovery Rate correction, and thus no individual functional connection is emphasized. In addition, a permutation test of group membership identified the same 34 connections as differing between groups. Seven of these connections overlapped with the COIs analysed above (Fair *et al*., 2007*a*).

To assess the maturity of the 34 functional connections that differed between the TS group and controls, we again derived estimated LOWESS ages for each connection. For these functional

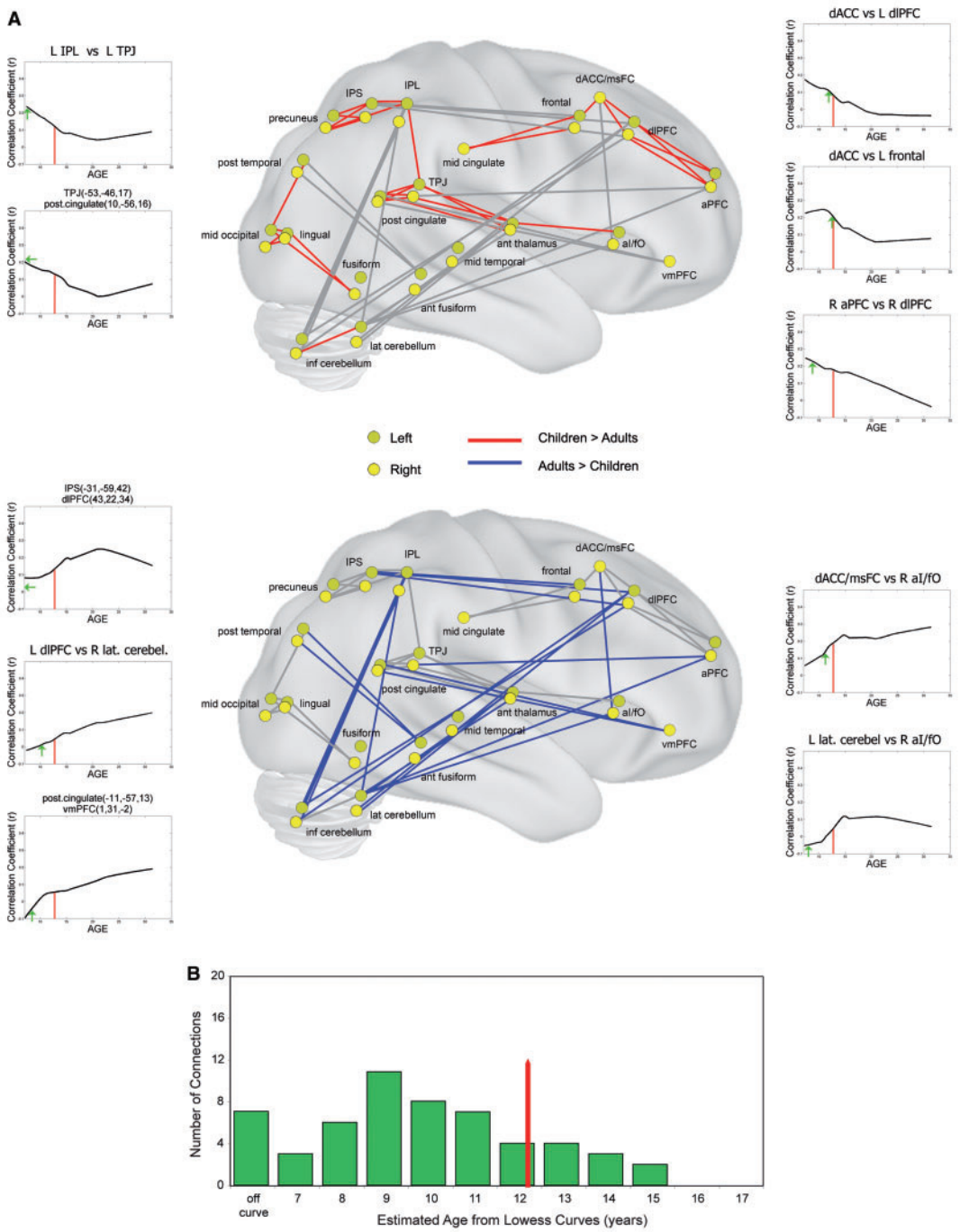

Fig. 3 Significant differences between typically developing children and adults (Fair *et al*., 2007*a*), used as COIs in this analysis. (**A**) Functional connections that are stronger in children than adults are shown on the top transparent brain (red lines); these connections decrease over age. Functional connections stronger in adults are shown on the lower transparent brain (blue lines); these connections increase over age. LOWESS curves of 210 typically developing people ages 7–31 are shown for 10 connections (figure modified from Fair *et al*., 2007*a*). For each curve, the red line indicates the expected LOWESS correlation coefficient for the TS group, given their average age (12.7 years), while the green arrow indicates the actual mean correlation coefficient for the connection in the TS group. The green arrows are often shifted to the left of their expected value, thus representing immaturity in the TS group, independent of whether the connections are growing in strength or diminishing over typical development. Two example 'off-curve' connections are highlighted with a horizontal green arrow pointing to the left in the sample LOWESS curves. (**B**) A histogram of the ages estimated for the TS group based on their actual mean correlation coefficients on the LOWESS curves (green arrows) for all 55 COIs that change significantly from childhood to adulthood. The red line indicates their actual group average age (12.7), and the green bars reveal a significant shift towards 'younger' age estimations. For seven connections, TS group average values did not fit the LOWESS curves at all; they were labelled off-curve (left most green bar of **B**). As with our qualitative observations in Fig. 2, these results suggest an overall immature network profile in adolescents with TS compared to a typically developing population. The semi-transparent brain images were made using Caret and PALS software (Van Essen *et al*., 2001; Van Essen, 2002, 2005).

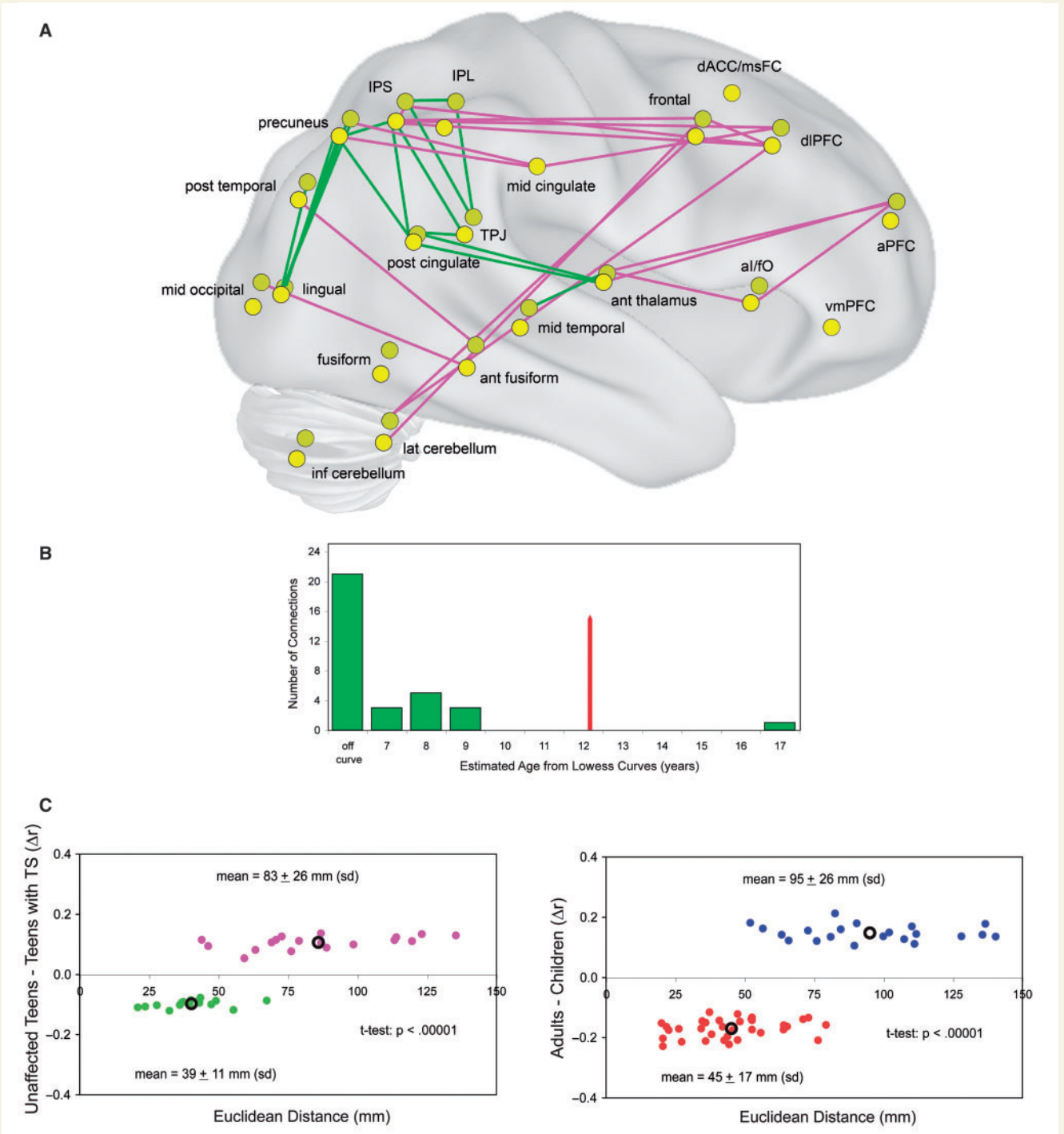

Fig. 4 Connections that are significantly different between the TS group and age-matched adolescents ($P < 0.05$ uncorrected). (**A**) Connections significantly stronger in the TS group (green) are primarily short distance connections between posterior brain regions. Connections significantly stronger in the unaffected group (pink) involve regions more distant in space. (**B**) Histogram of 'LOWESS age estimation' for the connections in A for the TS group. LOWESS curves were extracted for each connection for 210 typically developing subjects. The red line marks the TS group mean actual age. For the majority of these age curves, the TS mean group correlation coefficient did not fit the typical developmental curve at any age point ('off-curve' bin), and were most often off the curve in the same direction as the youngest typical subjects. (**C**) TS adolescents versus unaffected adolescents comparison of Euclidean distances (mm) between the 34 connections of group difference shown in **A**. Connections stronger in the unaffected group (pink dots) are significantly longer (Euclidian distance between the centres of each ROI) than connections stronger in the TS group (green dots) (Left panel). This finding is similar to a comparison of the typical adults versus children for their developmentally significant COIs, where connections stronger in adults (blue dots) are between regions significantly more distant in space and connections stronger in children are between regions close in space (red dots) (Right panel; from Fair *et al.*, 2007*a*). Black circles display the mean values for each set of connections.

connections (Fig. 4B), the majority were classified as off-curve, apparently in the young direction, for the TS group (21 out of 34), one connection was unclassifiable due to an inverted U-shaped developmental trajectory (left IPS – right IPS), and the remaining 12 functional connections intersected the LOWESS curves and had a significantly younger age distribution than would be expected for the group mean age (by one sample *t*-test, $P < 0.001$).

One of the findings of the Fair *et al*. (2007*a*) study was that local connections were relatively stronger in children, while long-range connections were stronger in adults. As can be seen from Fig. 4A, the 34 functional connection differences between TS subjects and typical subjects appear to follow a similar pattern. The TS group showed weaker correlation coefficients between frontal and parietal regions, and between cerebellar and frontal regions. Connections with greater correlation coefficients in the TS group generally involved more posterior regions, including short-distance functional connections between parietal regions in the fronto-parietal network and other neighbouring control regions.

To quantify these observations, the Euclidean distances between peak coordinates (mm) of functionally connected regions were calculated. The average distance between regions more strongly correlated in the TS group is significantly shorter [39 mm ± 11 mm, *t*-test ($P < 0.00001$)] than those more correlated in the unaffected adolescents (83 mm ± 26 mm), (Fig. 4C, left panel). This observation of short-range functional connections in adolescents with TS (ages 10–15 years), akin to that seen in typically developing children (ages 7–9 years), provides further evidence for a developmental delay and/or disruption of correlated spontaneous activity within and between control networks in TS. [Fig. 4C, right panel; (Fair *et al*., 2007*a*)].

Of the 25 off-curve functional connections (derived from both the developmental COIs and COIs from the direct comparison analyses) for the TS group, (i.e. the most affected connections) 21 included regions of the fronto-parietal network, while only one involved a region of the cingulo-opercular network (Fig. 5). Off-curve connections do not intersect the typical development LOWESS curves at any point. It is important to note that while

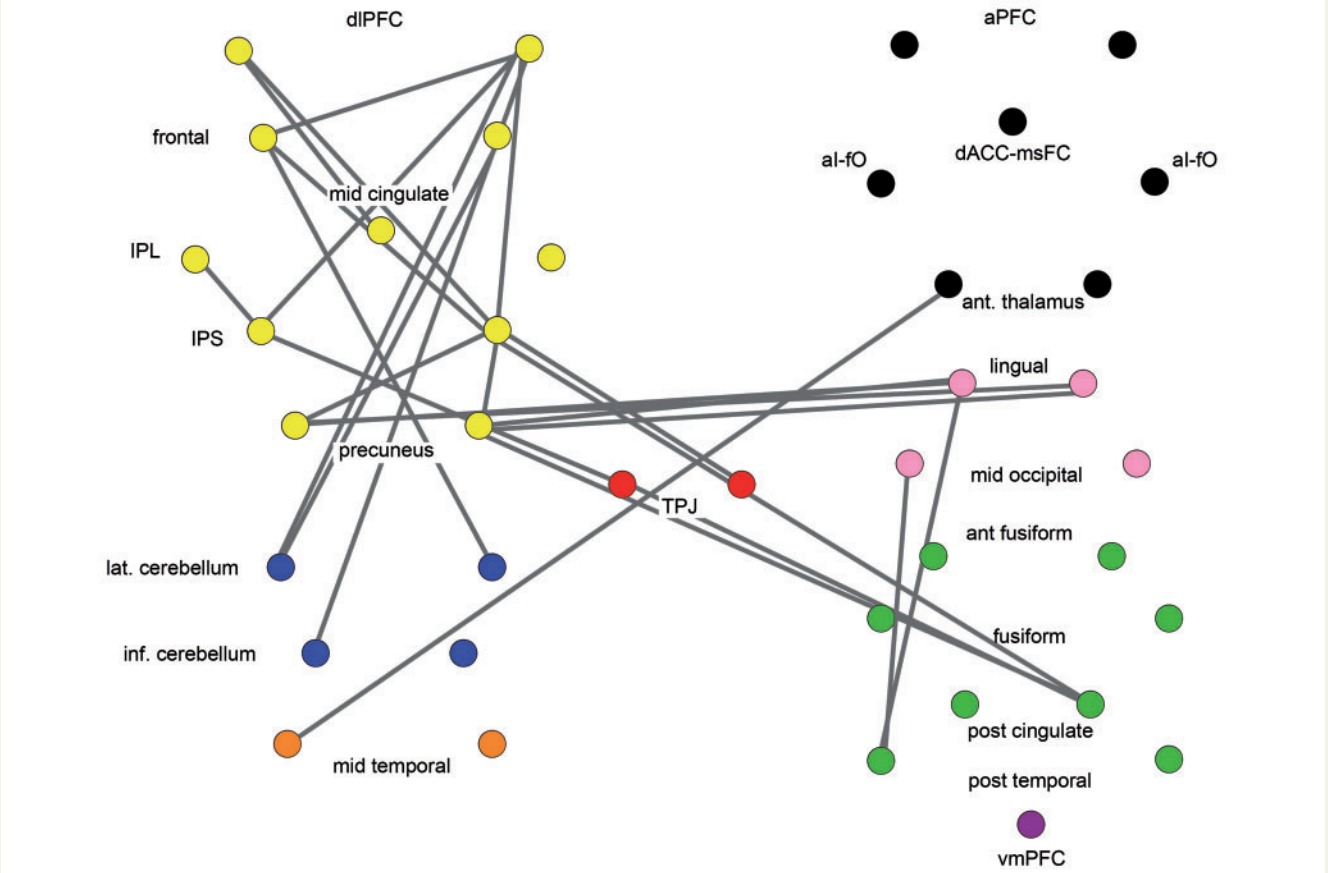

Fig. 5 TS functional connections that do not fit the typical developmental LOWESS curves (i.e. are 'off-curve') for either applied COIs derived from (Fair *et al*., 2007*a*) or from the direct comparison between adolescents with and without TS. The 39 putative control regions used in this analysis are coloured by components derived from graph analysis of healthy adult fcMRI data (Dosenbach *et al*., 2007) (see Table 3, Fig. 1 left panel for abbreviations and locations). Shown in grey are the 'off-curve' functional connections in the TS group. These off-curve functional connections are so named because they appear to deviate from the derived developmental trajectories such that the patient group does not intersect the unaffected group at any point of the LOWESS curve (see Methods section for details). Regions in the fronto-parietal, adaptive control network (yellow) are involved in 21 out of the 25 'off-curve' connections. By contrast, only one of the 25 'off-curve' connections involves the cingulo-opercular, task maintenance network (black), suggesting more severe impairment of adaptive control in TS. These may be examples of extreme functional immaturity in the TS group (functionally younger than age 7), or, instead, may be examples of anomalous connectivity in adaptive control in TS (see Discussion section).

the majority of functional connections in the TS group do intersect the LOWESS curves, some intersect in an age-appropriate manner, while others intersect at a younger functional age ('functionally immature'). The connections that are functionally immature are widespread throughout the networks. These results make the preponderance of off-curve connections involving the fronto-parietal network particularly interesting, and again suggest more impairment of the fronto-parietal network, thus predictive of impairment of adaptive control in TS.

Discussion

Using rs-fcMRI, we have shown that early and mid-adolescent subjects with TS appear to have immature functional connections compared to an age-matched unaffected group. Additionally, while functional connections in both the fronto-parietal and cingulo-opercular networks are affected, the largest off-curve differences are almost exclusively located in the fronto-parietal network, a network thought to be involved in adaptive control (Dosenbach *et al*., 2007, 2008).

Control networks appear functionally immature in TS

Previous work in typical development has characterized a set of developmentally dynamic functional connections between control-related regions from the ages of 7–31 years (Fair *et al*., 2007*a*). When we examined these functional connections in the TS group, the correlation strengths appeared younger than what we would expect based on the age of the subjects (10–15 years). For example, in a typically developing population, functional connections between closely adjacent regions are often significantly stronger in children than adults [Fig. 4B (Fair *et al*., 2007*a*)]. Our results suggest that adolescents with TS may have less effective functional communication between distant areas of cortex, and in contrast, 'over' communication between regions in close proximity, similar to younger children. As a case in point, the decreased long-range functional connectivity between control regions like the dlPFC and posterior parietal cortex, and the continued communication between short-range connections such as the dlPFC and aPFC in adolescents with TS, could help explain the inability to suppress unwanted behaviours in the disorder.

Fronto-parietal control network is especially affected in TS

Our finding that the majority of the most affected (i.e. 'off-curve') connections in TS adolescents involve regions in the fronto-parietal network has implications for our understanding of TS. As described earlier, the fronto-parietal network is thought to support online task-control that allows rapid adaptation of control settings from one event to the next (Dosenbach *et al*., 2006, 2007, 2008). We have hypothesized that a fronto-parietal network responsible for adaptive control may be more susceptible to distraction, while a cingulo-opercular network responsible for set-maintenance may be more stable and resistant to distraction. The robust abnormalities in the fronto-parietal network imply that adaptive, transient control should be more impaired in TS than the stable task set control of the cingulo-opercular network (Fig. 6).

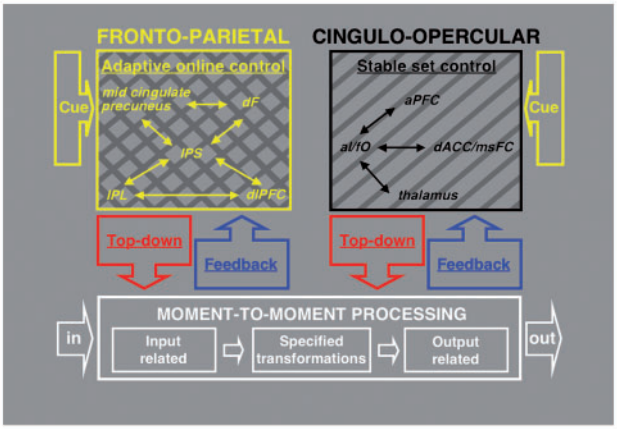

Fig. 6 Proposed task control deficit in Tourette syndrome. While both stable set control and adaptive online control networks are compromised in TS, there is more substantial impairment of the brain's adaptive online control network, as indicated by the multiple hash marks.

Perhaps the large differences seen in the set of off-curve connections in the TS group reflect more substantial immaturity beyond the age range of the normative dataset (younger than 7 years), or an effect more categorically anomalous in TS unrelated to developmental changes. One way to partially address this question would be to chart changes over age (e.g. off-curve connections in a young TS group could become on-curve in older TS participants) within a larger TS sample in future studies.

The predominance of abnormalities in the frontal-parietal network (Fig. 5) predicts that adolescents with TS should have difficulty rapidly adapting task control, as well as initiating task performance. Impairments in a network involved in adaptive control, as opposed to set maintenance, could predict real-world difficulties in TS shifting between tasks, multitasking or inhibiting inappropriate responses. However, as discussed in the Introduction section, there is conflicting evidence about impairments specific to TS in inhibition or impulse regulation, though some studies do find differences (Bornstein *et al*., 1991; Johannes *et al*., 2001; Channon *et al*., 2003). Thus, the finding in TS of impaired functional connectivity in a network involved in adaptive control motivates further investigation. We are currently conducting an fMRI study that examines task control signals in TS.

Adult functional imaging studies on TS subjects that have addressed tic suppression (Peterson *et al*., 1998), production (Gates *et al*., 2004; Bohlhalter *et al*., 2006) and volitional movement (Fattapposta *et al*., 2005), have found changes in activity in putative control regions. For example, Bohlhalter *et al*. (2006) found changes in the dorsal anterior cingulate, bilateral insula/frontal operculum, and frontal and parietal regions prior to tic onset, while Peterson *et al*. (1998) found frontal and parietal regions become more active when trying to resist tic-related movements.

Prior fMRI activation studies comparing children with and without TS showed left lateral frontal regions to be activated in the TS group but not in the unaffected group during a rule-switching task (Baym *et al*., 2008) and during a Stroop task (Marsh *et al*., 2007). These lateral frontal regions are near the left dlPFC region included in the present study (Talairach coordinates: –43, 22,34), (Baym *et al*.,: –48, 23, 24) (Baym *et al*., 2008) (Marsh *et al*.,: –42, 14, 32) (Marsh *et al*., 2007). The left lateral frontal cortex activations described in children with TS are consistent with our hypothesis that the immaturity of the brain's fronto-parietal control network may play a role in the pathogenesis of TS.

Previous research using structural MRI in TS does provide some evidence for frontal and/or parietal anatomical abnormalities (e.g. Peterson *et al*., 2001; Fredericksen *et al*., 2002). Peterson *et al*. (2001) found larger dlPFC and parieto-occipital cortical volumes in TS children (5–18 years) compared to unaffected children. The regions identified by Peterson *et al*. (2001) appear to include many of the fronto-parietal regions highlighted in the present study. It is unclear whether, or how, larger frontal and parietal volumes in children with TS affect the abnormal functional connectivity seen here in those regions in adolescents with TS.

Is functional immaturity specific to TS?

Immaturity in functional connectivity measures has previously been reported in studies of other developmental disorders including autism (Courchesne and Pierce, 2005; Turner *et al*., 2006; Just *et al*., 2007) and ADHD (Tian *et al*., 2006; Kelly *et al*., 2007; Shaw *et al*., 2007; Sonuga-Barke and Castellanos, 2007). At present it remains unclear whether these immaturities are common across different developmental disorders and whether or not they involve the same or similar brain regions. Perhaps functional connectivity studies are capturing immaturities in different functional networks, or different parts of the same networks.

As ADHD is commonly co-morbid with TS, it is possible that the two disorders share a common connectivity deficit that becomes apparent in both our study, as well as studies on ADHD (Kelly *et al*., 2007; Shaw *et al*., 2007; Sonuga-Barke and Castellanos, 2007). This possibility is intriguing, and deserves further exploration. There are also potential confounds within our group due to the variety of medications used by the participants. For example, Honey *et al*. (2003) have shown increased functional connectivity with neuroleptic use. We explored the effects of stimulant and neuroleptic medications in a subgroup analysis, as well as looking at the set of TS participants who were free of all medications (see Supplementary Material). While our study is underpowered to do a full subgroup analysis of the various effects of co-morbidities and medications, our data strongly suggest that the effects we observe in the whole TS group are not contingent on specific medications. Indeed, some connections in the subgroups of those taking neuroleptics or stimulants appear to be 'off-curve' in the older direction of our unaffected sample, suggestive of possible rescue of some immaturities observed in the whole group. However, these medication issues, as well as the pathophysiological overlap between ADHD and TS, will need to be addressed with a larger group of subjects.

It has been suggested more generally that long-range functional underconnectivity could be related to deficits in the integration of information (Luna and Sweeney, 2004; Just *et al*., 2006; Fair *et al*., 2007*a*, 2008). The decrease in long-range functional connections we observed in TS adolescents relative to their age-matched peers seems consistent with this idea. In this scenario, functional underconnectivity could affect the communication and coordination of activity between the cerebellum, frontal cortex and parietal cortex. Different patterns of functional underconnectivity might explain distinctive symptoms in different developmental disorders. But these ideas leave unexplained the functional 'overconnectivity' we observed in TS (Fig. 4). It appears as if the connectional immaturity we observed is not due to general functional underconnectivity, but rather a more specific pattern of increasing and diminishing functional connections that appear to mimic the pattern observed in studies of typical development (Fair *et al*., 2007*a*).

Future challenges

It is our strong contention that a firm understanding of typical development is crucial for studying populations with developmental disorders (Johnson *et al*., 2002). Such an understanding afforded by the developmental context can help one to dissociate group differences related to a disorder, from differences related to the age of the subjects. One benefit of applying previously defined ROIs (Dosenbach *et al*., 2006) and COIs (Fair *et al*., 2007*a*) to a new data set is that these ROIs and COIS are already functionally well characterized across typical development (Fair *et al*., 2007*a*; Dosenbach *et al*., 2008). However, the focus on pre-defined ROIs and COIs also has the drawback that the region and connection set is, by definition, limited. For example, much of the extant TS literature has emphasized the putative role of the striatum in the motor and cognitive consequences of TS, through its analogy to other movement disorders. While our set of 39 pre-defined control regions, and their functional connections, covers diverse parts of the cerebrum, it does not include regions in the striatum. Future investigations should include a more comprehensive region set.

Conclusion

TS is a developmental disorder that shows significant functional connectivity differences in a set of putative task control regions when adolescents with TS are compared to age-matched, movement-matched controls. These results suggest that differences in control processing in TS may be due to immaturity, and that adaptive online control in particular is most affected.

While evidence for functional immaturity in TS and ADHD is available, the question remains open as to whether effective treatments for TS or ADHD restore age-appropriate connectivity (or fMRI activity) patterns. Particularly in TS, where symptoms often ameliorate after puberty (Leckman, 2003), it would be most interesting to see whether individuals experiencing a reduction in symptoms have control system functional connectivity patterns that better fit those of typically developed controls. Similarly, our approach could be utilized to test the efficacy of different TS treatment approaches.

For example, increasing maturity of frontal cortex has been hypothesized to be the source of successful compensatory mechanisms for reduction of tic burden in those with TS who improve over age (e.g. Leckman *et al*., 2006; Sukhodolsky *et al*., 2007). Such frontal maturity may be measurable in the functional correlation patterns of the frontal regions of the fronto-parietal and cingulo-opercular networks. But a narrow focus on frontal effects may be limiting. On the basis of the data presented here, it also may be advisable to broaden the emphasis on frontal cortex in the TS literature to include both frontal and parietal regions.

Supplementary material

Supplementary material is available at *Brain* online.

Acknowledgements

We sincerely thank the participants for their time and commitment to this project. We are grateful to Ansley Grimes and Rebecca Coalson for their help with data acquisition. We thank Steven Nelson and Alecia Vogel for their helpful discussions. Portions of this work were presented at the 37th annual meeting of the Society for Neuroscience.

Funding

The John Merck Scholars Fund; Burroughs-Wellcome Fund; Dana Foundation; Tourette Syndrome Association; National Institutes of Health K02NS053425 (to B.L.S.). Mr and Mrs Spencer T. Olin Fellowship Program at Washington University (to J.A.C.).

References

Albin RL, Mink JW. Recent advances in Tourette syndrome research. Trends Neurosci 2006; 29: 175–82.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edn., Text Revision. Washington, DC: American Psychiatric Association; 2000.

Baym CL, Corbett BA, Wright SB, Bunge SA. Neural correlates of tic severity and cognitive control in children with Tourette syndrome. Brain 2008; 131: 165–79.

Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Statist Soc B 1995; 57: 289–300.

Biswal B, Yetkin F, Haughton V, Hyde J. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995; 34: 537–41.

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, Bazylewich T, Douglass AB. Tourette syndrome and neuropsychological performance. Acta Psychiatr Scand 1991; 84: 212–6.

Braver TS, Reynolds JR, Donaldson DI. Neural mechanisms of transient and sustained cognitive control during task switching. Neuron 2003; 39: 713–26.

Brown TT, Lugar HM, Coalson RS, Miezin FM, Petersen SE, Schlaggar BL. Developmental changes in human cerebral functional organization for word generation. Cereb Cortex 2005; 15: 275–90.

Bunge SA, Wallis JD, Parker A, Brass M, Crone EA, Hoshi E, et al. Neural circuitry underlying rule use in humans and nonhuman primates. J Neurosci 2005; 25: 10347–50.

Castellanos FX, Margulies DS, Kelly AMC, Uddin LQ, Ghaffari M, Kirsch A, et al. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol. Psychiatry 2008; 63: 332–7.

Channon S, Pratt P, Robertson MM. Executive function, memory, and learning in Tourette's syndrome. Neuropsychology 2003; 17: 247–54.

Cleveland WS. LOWESS: a program for smoothing scatterplots by robust locally weighted regression. Am Stat 1981; 35: 54.

Cohen J, Cohen P. Applied multiple regression/correlation analysis for the behavioral sciences. Hillsdale, New Jersey: Lawrence Erlbaum Associates; 1983.

Cohen AL, Fair DA, Miezin FM, Dosenbach NUF, Wenger KK, Fox MD, et al. The effect of movement in functional connectivity in children and adults. Soc Neurosci 2006; Program No. 665.20. Neuroscience Meeting Planner Online.

Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002; 3: 201–15.

Courchesne E, Pierce K. Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. Curr Opin Neurobiol 2005; 15: 225–30.

Dosenbach NU, Fair DA, Cohen AL, Schlaggar BL, Petersen SE. A dual-networks architecture of top-down control. TICS 2008; 12: 99–105.

Dosenbach NU, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RAT, et al. Distinct brain networks for adaptive and stable task control in humans. Proc Natl Acad Sci USA 2007; 104: 11073–8.

Dosenbach NU, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, et al. A core system for the implementation of task sets. Neuron 2006; 50: 799–812.

Fair DA, Brown TT, Petersen SE, Schlaggar BL. A comparison of ANOVA and correlation methods for investigating cognitive development with fMRI. Dev Neuropsychol 2006; 30: 531–46.

Fair DA, Cohen AL, Dosenbach NU, Church JA, Miezin FM, Barch DM, et al. The maturing architecture of the brain's default network. PNAS 2008; 105: 4028–32.

Fair DA, Dosenbach NUF, Church JA, Cohen AL, Brahmbhatt S, Miezin FM, et al. Development of distinct control networks through segregation and integration. Proc Natl Acad Sci USA 2007a; 104: 13507–12.

Fair DA, Schlaggar BL, Cohen AL, Miezin FM, Dosenbach NU, Wenger KK, et al. A method for using blocked and event-related fMRI data to study ''resting state'' functional connectivity. Neuroimage 2007b; 35: 396–405.

Fattapposta F, Restuccia R, Colonnese C, Labruna L, Garreffa G, Bianco F. Gilles de la Tourette syndrome and voluntary movement: a functional MRI study. Psychiatry Res 2005; 138: 269–72.

Field AP. Meta-analysis of correlation coefficients: a Monte Carlo comparison of fixed- and random-effects methods. Psychol Methods 2001; 6: 161–80.

Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007; 8: 700–11.

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA 2005; 102: 9673–8.

Fox MD, Snyder AZ, Vincent JL, Raichle ME. Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. Neuron 2007; 56: 171–84.

Fransson P. Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum Brain Mapp 2005; 26: 15–29.

Fransson P, Skiold B, Horsch S, Nordell A, Blennow M, Lagercrantz H, et al. Resting-state networks in the infant brain. Proc Natl Acad Sci USA 2007; 104: 15531–6.

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.

Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P. An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. Dev Med Child Neurol 2000; 42: 436–47.

Gates L, Clarke JR, Stokes A, Somorjai R, Jarmasz M, Vandorpe R, et al. Neuroanatomy of coprolalia in Tourette syndrome using functional magnetic resonance imaging. Prog Neuropsychopharmacol Biol Psychiatry 2004; 28: 397–400.

Golden C, Freshwater S, Golden Z. Stroop color and word test: children's version. Wood Dale, IL: Stoelting Co.; 2002.

Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, et al. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry 2007; 62: 429–37.

Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA 2003; 100: 253–8.

Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci USA 2004; 101: 4637–42.

Hampson M, Tokoglu F, Sun Z, Schafer RJ, Skudlarski P, Gore JC, et al. Connectivity-behavior analysis reveals that functional connectivity between left BA39 and Broca's area varies with reading ability. Neuroimage 2006; 31: 513–9.

Honey GD, Suckling J, Zelaya F, Long C, Routledge C, Jackson S, et al. Dopaminergic drug effects on physiological connectivity in a human cortico-striato-thalamic system. Brain 2003; 126: 1767–81.

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.

Johnson MH, Halit H, Grice SJ, Karmiloff-Smith A. Neuroimaging of typical and atypical development: a perspective from multiple levels of analysis. Dev Psychopathol 2002; 14: 521–36.

Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ. Functional and anatomical cortical underconnectivity in autism: evidence from an FMRI study of an executive function task and corpus callosum morphometry. Cereb Cortex 2007; 17: 951–61.

Kelly AM, Margulies DS, Castellanos FX. Recent advances in structural and functional brain imaging studies of attention-deficit/hyperactivity disorder. Curr Psychiatry Rep 2007; 9: 401–7.

Khalifa N, von Knorring AL. Psychopathology in a Swedish population of school children with tic disorders. J Am Acad Child Adolesc Psychiatry 2006; 45: 1346–53.

Leckman JF. Phenomenology of tics and natural history of tic disorders. Brain Dev 2003; 25 (Suppl 1): S24–8.

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 1989; 28: 566–73.

Leckman JF, Vaccarino FM, Kalanithi PS, Rothenberger A. Annotation: Tourette syndrome: a relentless drumbeat–driven by misguided brain oscillations. J Child Psychol Psychiatry 2006; 47: 537–50.

Luna B, Sweeney JA. The emergence of collaborative brain function: FMRI studies of the development of response inhibition. Ann NY Acad Sci 2004; 1021: 296–309.

Luna B, Thulborn KR, Munoz DP, Merriam EP, Garver KE, Minshew NJ, et al. Maturation of widely distributed brain function subserves cognitive development. Neuroimage 2001; 13: 786–93.

Mahone EM, Cirino PT, Cutting LE, Cerrone PM, Hagelthorn KM, Hiemenz JR, et al. Validity of the behavior rating inventory of executive function in children with ADHD and/or Tourette syndrome. Arch Clin Neuropsychol 2002; 17: 643–62.

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.

Miezin FM, Maccotta L, Ollinger JM, Petersen SE, Buckner RL. Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. NeuroImage 2000; 11: 735–59.

Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001; 24: 167–202.

Mink JW. Neurobiology of basal ganglia circuits in Tourette syndrome: faulty inhibition of unwanted motor patterns? In: Cohen DJ, Jankovic J, Goetz CG, editors. Advances in neurology: Tourette syndrome, Vol. 85. Philadelphia, PA: Lippincott Williams & Wilkins; 2001. p. 113–22.

Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 2002; 15: 1–25.

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.

Peterson BS, Skudlarski P, Anderson AW, Zhang H, Gatenby JC, Lacadie CM, et al. A functional magnetic resonance imaging study of tic suppression in Tourette syndrome. Arch Gen Psychiatry 1998; 55: 326–33.

Peterson BS, Staib L, Scahill L, Zhang H, Anderson C, Leckman JF, et al. Regional brain and ventricular volumes in Tourette syndrome. Arch Gen Psychiatry 2001; 58: 427–40.

Posner MI, Petersen SE. The attention system of the human brain. Annu Rev Neurosci 1990; 13: 25–42.

Rueda MR, Fan J, McCandliss BD, Halparin JD, Gruber DB, Lercari LP, et al. Development of attentional networks in childhood. Neuropsychologia 2004; 42: 1029–40.

Rushworth MF, Walton ME, Kennerley SW, Bannerman DM. Action sets and decisions in the medial frontal cortex. Trends Cogn Sci 2004; 8: 410–7.

Sakai K, Passingham RE. Prefrontal interactions reflect future task operations. Nat Neurosci 2003; 6: 75–81.

Salvador R, Suckling J, Schwarzbauer C, Bullmore E. Undirected graphs of frequency-dependent functional connectivity in whole brain networks. Philos Trans R Soc Lond B Biol Sci 2005; 360: 937–46.

Scahill L, Riddle MA, McSwiggin-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.

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007; 27: 2349–56.

Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci USA 2007; 104: 19649–54.

Singer HS. Tourette's syndrome: from behaviour to biology. Lancet Neurol 2005; 4: 149–59.

Sonuga-Barke EJ, Castellanos FX. Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. Neurosci Biobehav Rev 2007; 31: 977–86.

Sukhodolsky DG, Leckman JF, Rothenberger A, Scahill L. The role of abnormal neural oscillations in the pathophysiology of co-occurring Tourette syndrome and attention-deficit/hyperactivity disorder. Eur Child Adolesc Psychiatry 2007; 16 (Suppl 1): 51–9.

Tian L, Jiang T, Wang Y, Zang Y, He Y, Liang M, et al. Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neurosci Lett 2006; 400: 39–43.

Turner KC, Frost L, Linsenbardt D, McIlroy JR, Muller RA. Atypically diffuse functional connectivity between caudate nuclei and cerebral cortex in autism. Behav Brain Funct 2006; 2: 34.

Van Essen DC. Windows on the brain: the emerging role of atlases and databases in neuroscience. Curr Opin Neurobiol 2002; 12: 574–9. See also: http://pulvinar.wustl.edu:8081/sums/search.do?filename=ATLAS&filetype=tar.gz.

Van Essen DC. A Population-Average, Landmark- and Surface-based (PALS) Atlas of human cerebral cortex. Neuroimage 2005; 28: 635–62.

Van Essen DC, Dickson J, Harwell J, Hanlon D, Anderson CH, Drury HA. An integrated software suite for surface-based analyses of cerebral cortex. J Am Med Inform Assoc 2001; 41: 1359–78. See also: http://brainmap.wustl.edu/caret.