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Review

Cognitive control over motor output in Tourette syndrome

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ABSTRACT

Tourette syndrome [TS] is a neurodevelopmental disorder characterised by chronic vocal and motor tics. TS has been associated with dysfunctional cognitive (inhibitory) control of behaviour, however the evidence for this, beyond the occurrence of tics, is scant. Furthermore, in recent studies of uncomplicated TS, it has been shown that adolescents with TS exhibit paradoxically enhanced cognitive control of motor output, consistent with the typical developmental profile of increasing control of tics during adolescence. Here we present arguments, together with new data, that run counter to the widely held view that prefrontal cortex (PFC) is the source of inhibitory task-control signals. Instead, we argue that PFC should be viewed as a source of facilitatory signals that bias competition in brain areas more directly involved in motor execution. Importantly, we argue that in TS, over-activation of PFC may contribute to the hyper-excitability of motor regions and the occurrence of tics; and that compensatory changes, leading to enhanced cognitive control in TS, may primarily be implemented by distributed changes in local cortical excitability.

Contents

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1. Introduction

Tourette syndrome [TS] is a developmental neurological disorder that lies at the extreme of the tic disorder spectrum and is characterised by the presence of chronic vocal and motor tics (Leckman, 2002). Tics are involuntary, repetitive, stereotyped behaviours that occur with a limited duration (Leckman, 2002). Motor tics can be simple or complex in appearance, ranging from repetitive movements to coordinated action sequences. Verbal tics can consist of repeating words or utterances (palilalia), producing inappropriate or obscene utterances (coprolalia), or the repetition of another's words (echolalia). Tics occur in bouts, typically many times in a single day, and are the most common form of movement disorder in children (with a prevalence that ranges between 1 and 29% depending upon the precise characteristics of the study population, the diagnostic criteria used, and the study design and methods employed).

Individuals with TS perceive a relatively constant demand to suppress their tics in social situations, and while the voluntary suppression of tics is possible in many cases, individuals with TS report that it can be uncomfortable and stressful to suppress tics, and that the urge to tic becomes uncontrollable after a period of suppression. Importantly, individuals with TS report that their tics are often preceded by 'premonitory sensory phenomena' (PSP) that they describe as uncomfortable cognitive or bodily sensations (e.g., tension, pressure, tickle, etc.), that precede the execution of a tic, and are experienced as a strong urge for motor discharge (Bliss, 1980; Banaschewki et al., 2003). Brain imaging evidence indicates that the source of PSPs may be associated with brain activity within the insular and cingulate motor areas of cortex (Bohlhalter et al., 2006; Jackson et al., 2011b).

While the neurological basis of TS is unclear at this time, it is generally agreed that cortical–striatal–thalamic–cortical (CSTC) circuits are likely to be dysfunctional, and a specific model of basal ganglia dysregulation in TS has been proposed as follows. Subsets of striatal neurons (matrisomes) are thought to become abnormally active in inappropriate contexts, leading to the disinhibition of thalamo-cortical projections that in turn lead to tics. Activity-dependent dopamine inappropriately reinforces such activity leading to stereotyped repetition of behaviour (Albin and Mink, 2006).

A widely held view is that the disinhibition of CSTC circuits gives rise to an impairment of executive or cognitive control of motor behaviour, characterised by a reduced behavioural inhibition (e.g., Channon et al., 2009). While this proposal is consistent with the observation that individuals with TS have difficulties suppressing their tics, there is in fact surprisingly little convincing evidence that individuals with TS are impaired on formal tests of executive function; as behavioural studies of executive function or cognitive control in TS have produced mixed findings (see below). Furthermore, recent studies of cognitive control of motor outputs in situations with high response-conflict demand have in fact shown that individuals with 'uncomplicated' TS (i.e., those without co-morbid disorders such as ADHD) exhibit paradoxically enhanced volitional control over their motor behaviour (Mueller et al., 2006; Jackson et al., 2007, 2011a,b). This finding is consistent with the proposal that the frequent need to actively suppress tics leads to a generalised enhancement in the efficacy of volitional control mechanisms in TS that extends to laboratory tasks of cognitive control of motor output.

1.1. Factors contributing to the mixed findings for cognitive control in TS

In our view the following factors likely contribute to the mixed findings reported thus far on the issue of whether individuals with TS exhibit an impairment of inhibitory or executive control of behaviour. First, previous studies have sought to address this question using a variety of behavioural tasks, for instance the Stroop task (e.g., Ozonoff and Jensen, 1999; Channon et al., 2003a,b), flanker task (e.g., Crawford et al., 2005; Channon et al., 2006), Go-NoGo task (e.g., Ozonoff et al., 1994; Serrien et al., 2005; Watkins et al., 2005), stop-signal task (e.g., Li et al., 2006), and continuous performance task (e.g., Harris et al., 1995). These tasks may differ markedly in the cognitive demands that they impose and the psychological processes or mechanisms involved in efficient task performance. In our view it is extremely unlikely that all of these tasks tap a single behavioural 'inhibition' mechanism or process that is impaired in TS.

Second, studies that do report finding an executive function impairment in individuals with TS, have often failed to exclude individuals presenting with co-morbid conditions such as ADHD (co-morbidity estimated at ~50%) or OCD (co-morbidity estimated at ~40%), that may themselves be associated with executive dysfunction (e.g., Bornstein, 1991; Georgiou et al., 1995; Farber et al., 1999; Dursun et al., 2000). By contrast, when such individuals have been excluded, and studies have been carried out on individuals with 'uncomplicated' TS, then many studies report no behavioural differences between groups (e.g., Ozonoff et al., 1998; Rice & Weyandt, 2000; Mostofsky et al., 2001; Channon et al., 2006), or report significantly enhanced performance in the TS groups (e.g., Mueller et al., 2006; Jackson et al., 2007, 2011a).

Third, studies reporting an executive impairment in individuals with TS have often been based upon sampling only adults with the disorder or mixed samples containing both adults and children (e.g., Silverstein et al., 1995; Farber et al., 1999; Channon et al., 2003a,b, 2009). Such studies may in fact be unrepresentative of the 'typical' presentation of TS for the following reason. TS typically follows a developmental timecourse that is associated with increasing control over tics (Leckman, 2002), and appears to be accompanied by compensatory, neuroplastic, alterations in brain structure and function in many individuals with TS, but not all (Plessen et al., 2004; Mueller et al., 2006; Jackson et al., 2007; Plessen et al., 2009; Jackson et al., 2011a). TS usually first presents during early childhood (~4–7 years), and the severity of tics follow a remitting pattern with increasing age. Tic severity is maximal between 11 and 14 years, but tics typically decrease by early adulthood. Importantly, approximately 70–80% of TS sufferers who present with marked tic severity at around 12 years of age have either mild tics or are free of tics by 18 years of age (Leckman et al., 2006). Importantly then, the majority of individuals with TS appear to develop a means of controlling and effectively suppressing their tics by early adulthood, but a substantial minority continue to have severe tics throughout their adult life. For this reason, studies based on adults with TS, or mixed samples of adults and children with TS, may be unrepresentative of the 'typical' TS presentation.

Fourth, if individuals with TS do follow a developmental timecourse that is accompanied by compensatory, neuroplastic, alterations in brain structure (Plessen et al., 2009; Jackson et al., 2011a) and function (Mueller et al., 2006; Jackson et al., 2007, 2011a) which are associated with increased cognitive control over

motor outputs (Serrien et al., 2005; Mueller et al., 2006; Jackson et al., 2007, 2011a), then it is likely that previous studies of executive function in TS may have sampled individuals at different points along this developmental timecourse (which may not necessarily equate perfectly with chronological age). In support of this suggestion, we have found in our own studies that there is considerable individual variability in cognitive control even within quite homogeneous TS groups (i.e., children and adolescents with uncomplicated TS), and that individual variability in tic severity is linearly associated with both individual performance levels in laboratory tasks measuring cognitive control, and with alterations in white-matter microstructure in frontal cortex and corpus callosum (Jackson et al., 2007, 2011a).

Finally, and most importantly, it is likely that the failure to obtain solid evidence in support for the proposal that there is impaired executive control/reduced behavioural inhibition in individuals with TS is because this proposal is primarily based upon an incorrect assumption over the precise role played by the prefrontal cortex (PFC) in the inhibitory control of motor outputs. Thus, a longstanding view has been that the PFC, particularly areas such as the dorsolateral prefrontal cortex (DLPFC) or inferior frontal cortex (IFC), is the source of cognitive control signals that exert inhibitory control over other brain areas to effect interference control through the active inhibition of distracting information, and the suppression of inappropriate motor responses (e.g., Nigg, 2000). More recently however, an alternative viewpoint has been proposed (e.g., Duncan, 2001; Aron, 2007; Munakata et al., 2011) where these areas of PFC, rather than being specialised for inhibitory control, are instead thought to operate as a global workspace or working memory into which can be loaded information that is currently of behavioural importance (Duncan, 2001). Within this view PFC operates largely to maintain and represent abstract task-relevant information such as task goals, rules, plans, contexts, etc. for as long as they are needed.

A key distinction between this and earlier viewpoints concerns the location of 'inhibitory' signals within cortico–cortico circuits involved in cognitive control/motor inhibition. While earlier views emphasised the role of PFC as the source of inhibitory control signals, more recent proposals have instead viewed the PFC as the source of facilitatory signals that may operate to bias response competition downstream within brain areas more directly linked to motor planning or motor execution (Sumner et al., 2007; Munakata et al., 2011).

1.2. Do individuals with TS have an impairment in inhibitory control downstream of PFC?

One hypothesis proposed my many investigators is that impairment in the operation of cortical–striatal–thalamic–cortical circuits gives rise to hyper-excitability of cortical motor areas in TS; which is brought about by dysfunctional, short-range, intra-cortical inhibitory mechanisms, as measured by transcranial magnetic stimulation (TMS) techniques (e.g., Ziemann et al., 1997; Gilbert et al., 2004, 2005; Orth et al., 2008; Orth and Rothwell, 2009; Heise et al., 2010). Thus, it has been demonstrated that the reduction in intra-cortical inhibition within motor cortex that is observed in TS is significantly correlated with measures of tic severity (i.e., reduced intra-cortical inhibition is associated with increased tic severity) [e.g., Gilbert et al., 2004; Orth et al., 2008]. Furthermore, it is highly likely that decreased intra-cortical inhibition/increased cortical excitability extends beyond motor cortex in TS to include the SMA.

The SMA has been linked previously to the volitional control of action (Nachev et al., 2008), and more recently to involuntary, non-conscious, effector-specific control of motor behaviour (Sumner et al., 2007; Boy et al., 2010). Specifically, the SMA is thought to participate in the automatic suppression of motor behaviours that might be subconsciously primed by environmental events (e.g., viewing an object might prime a hand movement toward that object). It is proposed therefore that reduced GABA-mediated short-range intra-cortical inhibition within the SMA might lead to the expression of unwanted movements (tics) in TS that are likely triggered by incoming sensory signals.

Consistent with this proposal, brain imaging studies have demonstrated: (a) that individual levels of GABA concentration in the SMA are correlated with performance on a behavioural task that is taken to index involuntary, non-conscious, control of motor responses (Boy et al., 2010); (b) that increased activity in SMA immediately precedes the occurrence of a tic (Bohlhalter et al., 2006); (c) that inhibitory (1 Hz) repetitive TMS delivered to the SMA decreases tic frequency (Mantovani et al., 2006; Kwon et al., 2011); and, (d) that the hyper-excitability within primary motor cortex observed in TS is likely due to increased functional interaction between SMA and M1 (Franzkowiak et al., 2012).

1.3. Enhanced cognitive control and compensatory adaptation in TS

It has been suggested that individuals with TS might gain control over their tics through the development of compensatory self-regulation mechanisms: most likely implemented through changes in neural pathways linking PFC with primary and secondary motor regions (Plessen et al., 2004; Serrien et al., 2005; Mueller et al., 2006; Jackson et al., 2007; Plessen et al., 2009; Jackson et al., 2011a). Recent behavioural and brain imaging studies provide supporting evidence for this view by demonstrating: (a) paradoxically enhanced cognitive control in individuals with TS, that is predicted by structural and functional brain alterations in the PFC, motor cortex, and associated white-matter tracts (Mueller et al., 2006; Jackson et al., 2007, 2011a); and, (b) that alterations in brain structure and function in TS reliably predict clinical measures of tic severity in individuals with TS (Jackson et al., 2011a).

How might this enhanced cognitive control in TS come about? We believe that during adolescence, altered local patterns of increased cortical excitability in motor areas (likely due to impaired, short-range, intra-cortical inhibitory mechanisms) that may give rise to tics are compensated for by functional and structural changes in long-range connectivity that operate to actively reduce cortical excitability in sensorimotor areas. We have speculated that localised suppression of cortical excitability might be achieved through an alteration in the inhibitory tone of motor areas. One means by which this could be achieved would be through modulation of local inhibitory interneurons. Consistent with this general idea, recent studies have demonstrated that in TS, comparable levels of behavioural performance to that of controls on cognitive control tasks are accompanied by significantly decreased functional activity in primary motor cortex (consistent with it being actively suppressed prior to movement [e.g., Jackson et al., 2011a]). Furthermore, converging evidence from TMS studies have demonstrated that motor cortical excitability is significantly decreased in TS adults (Heise et al., 2010) and children (Jackson et al., 2012), relative to control subjects, in the period immediately preceding the execution of a movement. It is suggested that general levels of motor hyper-excitability due to dysfunctional cortico–striatal–thalamic inputs may be actively suppressed immediately prior to planned movements by top-down inputs, likely implemented through long range connections linking PFC to motor areas (Serrien et al., 2005; Heise et al., 2010; Jackson et al., 2012).

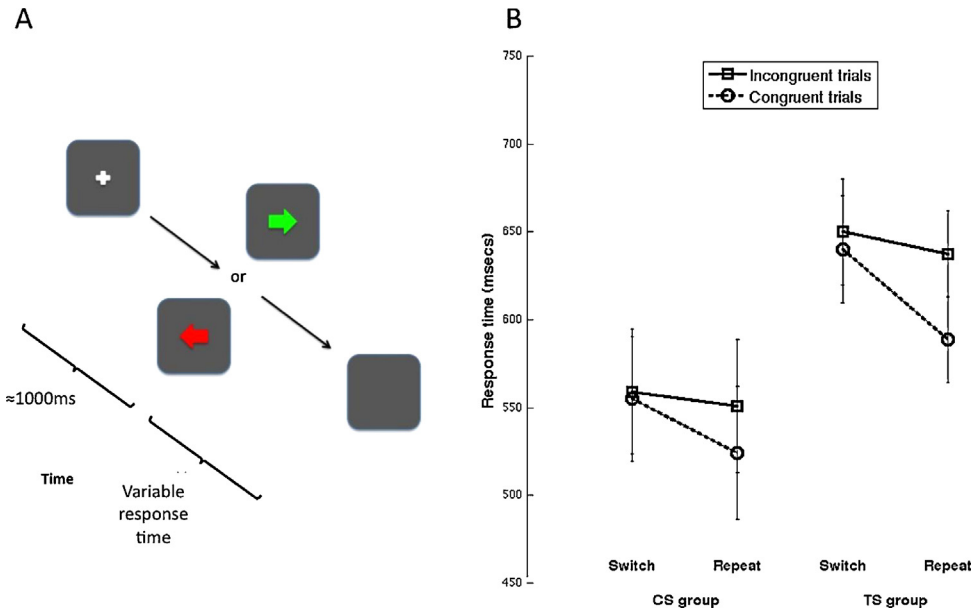

Fig. 1. (A) Graphic representation of the behavioural task-switching paradigm. After fixating a white cross participants are presented with a coloured arrow. If the arrow is green they execute a manual response with the hand indicated by the direction of the arrow. If the arrow is red they execute a manual response using the opposite hand. (B) Mean response times for the TS and CS groups for manual responses during 'task switch' and 'task repeat' trials when correctly executing incongruent (red arrow) and congruent (green arrow) responses. Error bars are standard errors.

1.4. The current study

Here we use high-field (3 T) functional magnetic resonance imaging (fMRI) to further investigate, in a group of children with 'pure' TS and a group of matched controls, how brain activation levels vary during the execution of a task previously used to investigate inhibitory control of motor output: i.e., a manual response-switching task (e.g., Jackson et al., 2011a).

More specifically, in the current studies we use fMRI to investigate how the fMRI Blood oxygenation level-dependent (BOLD) response in frontal and motor regions is related to behavioural measures of cognitive control and clinical measures of tic severity. We also use fMRI techniques to examine a hypothesis derived from the 'PFC inhibitory control' account that proposes that the PFC is the source of inhibitory control signals that operate to suppress downstream motor areas. Specifically, this account suggests that decreases in fMRI BOLD responses in motor areas (e.g., SMA and primary motor cortex) should be inversely related to increases in fMRI BOLD response in PFC areas linked to cognitive control (e.g., IFC).

2. fMRI study of manual task switching

2.1. Methods

2.1.1. Participants

Ten young patients with Tourette's syndrome (TS) participated in the study (8 male, 2 female, age 13.5 years [±1.6 years). Patients were recruited through the Tourette syndrome clinic in the Child and Adolescent Psychiatry Department at Queens Medical Centre, Nottingham. Informed consent was obtained from each participant before the start of the experiment. Participants who had a clinical diagnosis of ADHD or OCD were excluded from the sample. Current tic severity for the TS patients was assessed on the day of testing using the Yale Global Tics Severity Scale (Leckman et al., 1989). The control group comprised ten neurologically normal males (age 14.96 years [±2.1 years]). Approval for the experiment was obtained from the Nottingham Healthcare Trust and informed written consent was obtained from all subjects prior to participation. Statistical comparison confirmed that the groups did not differ significantly in terms of age ($p > 0.1$) or IQ (means: TS group = 106.5 [±17.5], CS group = 108.7 [[±12.9]; $p > 0.1$).

2.1.2. Behavioural task paradigm

Stimuli were presented using Matlab (R2006a, version 7.2) installed on a Windows-based laptop and back-projected onto a screen which the participants were able to view from within the MR scanner using a mirror mounted above the participant's head on the head coil. Participants were required to press a button on a MRI-compatible button press box with either their left or right thumbs.

A white fixation cross was presented for approximately 1000 ms before the onset of each trial (Fig. 1A). After approximately 1000 ms, an arrow was displayed in the centre of screen. If the arrow was green, the participant was instructed to press the button on the side that corresponded to the direction in which the arrow pointed (congruent trials). By contrast, if the arrow was red then the participant was instructed to press the button that was on the opposite side to the direction in which the arrow was pointing (incongruent trials). The arrow stimuli disappeared from the screen as soon as the participant responded with a button press and the screen remained blank for approximately 7000 ms before the following trial commenced. The order for both pro and anti trials in both tasks was randomised. There were 96 trials in total, split into six blocks of 16 trials with a rest break in between each.

2.1.3. Behavioural task analysis

The trials were counterbalanced such that there were an equal number of congruent and incongruent manual responses and an equal number of left and right responses. The order of key press and response switch and repeat trials was pseudorandomly determined in advance by the computer, and was varied across participants. Approximately 50% of the trials (the first trial must be removed) were task repeat trials, in which the type of key press required, i.e. a congruent or incongruent was the same as on the preceding trial. The remaining trials were task switch trials in which the type of key

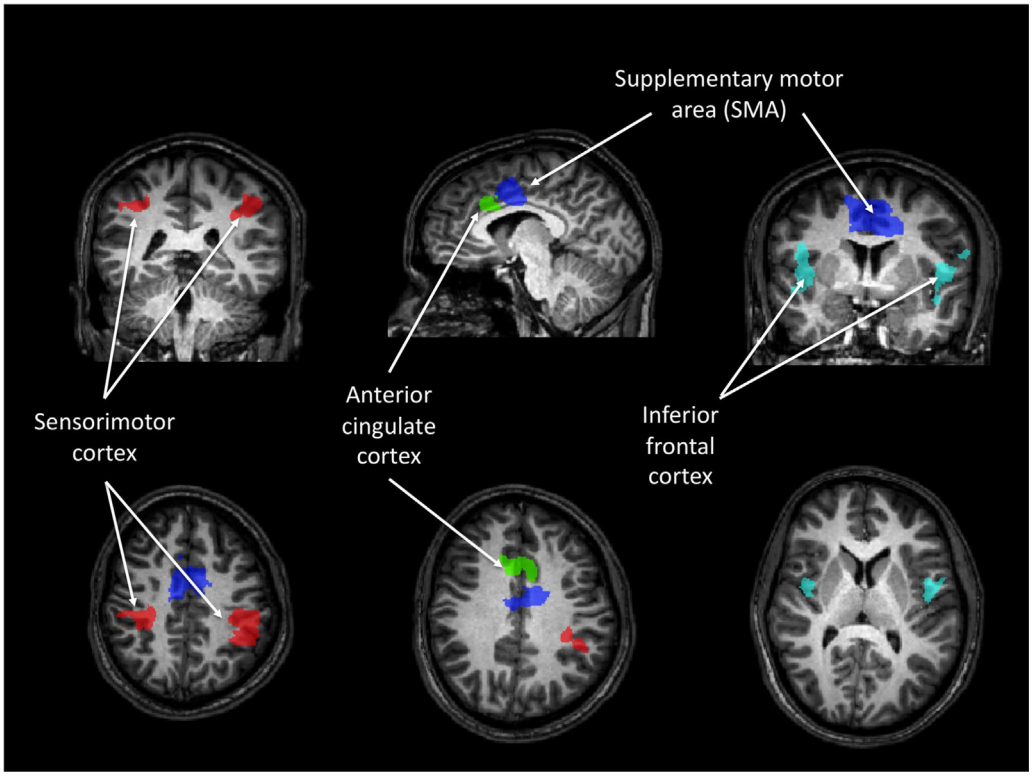

Fig. 2. Regions activated in the all task conditions > baseline contrast. fMRI BOLD activity maps were thresholded at a *t*-value corresponding to $p < 0.05$ (minimum cluster threshold of 20 voxels and FDR-corrected).

press required differed from that of the previous trial. Median RTs were calculated for each individual for each congruency and trial type condition (i.e., congruent switch, congruent repeat, incongruent switch, incongruent repeat) and then analysed within a mixed Group × Congruency × Trial type ANOVA.

2.1.4. MR Imaging parameters

All structural and functional MRI data were acquired on a 3 T Philips Achieva Scanner (Best, Netherlands) using an 8-channel SENSE head coil. High resolution T1 weighted structural images were acquired using a magnetization prepared gradient echo sequence (MPRAGE, FOV = 256 mm, 160 transverse slices) with a resolution of 1 mm isotropic. Functional images were acquired using echo-planar imaging (EPI) sensitive to BOLD contrast. T2* weighted BOLD images were acquired using the following parameters: FOV 256 mm; slice acquisition voxel size = 3 mm isotropic; 36 slices; matrix size = 96 × 96; flip angle = 80; TR = 2200 ms; and TE = 40 ms. Slices were contiguous and taken in a descending order. During experimental runs 300 volumes were acquired.

2.1.5. Image preprocessing

Analysis of fMRI data was carried out using Brain Voyager QX 1.10.2 software (Brain Innovation, Maastricht, The Netherlands). Preprocessing of the fMRI datasets consisted of the following: 3D head motion correction; slice scan timing correction to correct for the temporal differences in acquisition of different slices; spatial smoothing (Gaussian kernel of FWHM 4 mm); and linear trend and high-frequency component removal (up to and including 3 cycles in the time course).

While ten TS participants were initially recruited to this study, data from two participants had to be excluded from further analysis due to excessive head movement during the execution of the behavioural task in the MRI scanner. Subjects were excluded if translational head movements were greater than 3 mm in any direction.

Anatomical images were transformed into the Talairach coordinate system and co-registered with each individual's fMRI dataset. Regional activation maps were then obtained using a single-subject GLM (General Linear Model) for each individual. For each task, four predictors were defined; incongruent switch, incongruent repeat, congruent switch and congruent repeat.

Preliminary second level analyses involved calculating three-dimensional statistical parametric maps with separate-subject predictors for the group, using a fixed effects GLM analysis (FFX). The resulting fMRI activity maps were thresholded at a *t*-value corresponding to $p < 0.05$ (corrected for a false discovery rate in which no more than 5% of the active voxels could be false positives) and with a minimum cluster threshold of at least 20 voxels. These images were then smoothed with a 3 mm Guassian kernal. Subsequent analyses then involved the identification of functional regions-of-interest (ROIs) associated with all relevant experimental conditions (i.e., congruent switch, congruent repeat, incongruent switch, incongruent repeat trials) compared to rest.

The all-conditions vs. baseline contrast revealed four large, contiguous, regions that exceeded the statistical threshold (Fig. 2). These were located: bilaterally in the sensorimotor cortex (spanning the precentral gyrus, postcentral gyrus and associated regions of parietal cortex); bilaterally in an anterior region of medial frontal cortex corresponding to the anterior cingulate cortex; bilaterally in the inferior frontal and insular cortices; and, bilaterally in a posterior region of medial frontal cortex that corresponds with the supplementary motor area (SMA). The Talairach coordinates for centre-of-gravity and peak activations for each ROI, and the volume of each ROI, are presented in Table 1. A random-effects analysis (RFX) of contrasts within each ROI was used to test for between-group differences and Group × Condition interaction effects (see below).

Table 1
Talairach coordinates for the centre-of-gravity and peak activations for regions of significant BOLD activation identified in the All conditions > Baseline contrast. BOLD activity maps were thresholded at a *t*-value corresponding to $p < 0.05$ (minimum cluster threshold of at 20 voxels and FDR-corrected).

Region	Mean *X*	Mean *Y*	Mean *Z*	Peak *X*	Peak *Y*	Peak *Z*	Cluster size	*t*-value
Sensorimotor cortex	±36.5	−27.55	41.28	32	−26	42	11,426	6.24
Inferior frontal cortex/Insula	±43	−3.12	10.53	41	−2	18	5662	5.59
Anterior cingulate cortex	±5.5	17.7	30	5	19	30	3069	5.20
Supplementary motor area	0	0	39	−13	−2	33	12,220	6.37

3. Results

3.1. Behavioural data

3.1.1. Response time data

Median response time (RT) scores were calculated separately for each congruency condition (i.e. congruent vs. incongruent trials), for each trial type (i.e. switch vs. repeat trials), and for each participant. RT was measured as the time taken to respond after the onset of the arrow stimulus. Individual RT switch cost values (Switch RT–Repeat RT) were also computed for each condition (congruent vs. incongruent trials) and for each individual, and the predicted difference between groups were tested using planned comparisons based upon *t*-tests. The analyses confirmed that the predicted effects for this behavioural task, i.e., of task congruency and task switching, were present (see Fig. 1B). Specifically, RTs were longer for incongruent compared to congruent trials (Means: congruent trials = 573 [±116] ms, incongruent trials = 594 [±106] ms; $p = 0.03$) and also longer for task switch compared to task repeat trials (Means: switch trials = 596 [±115] ms, repeat trials = 571 [±105] ms; $p = 0.003$). However, planned comparisons between the groups revealed that the mean RT for the TS group did not differ statistically from that of the control group for any of the four congruency × trial type conditions (all $p > 0.05$).

3.1.2. RT switch cost data

Separate analyses of RT switch costs by congruency condition were also conducted. These analyses also revealed that there were no statistically significant differences in RT switch costs between the CS and TS groups (means: CS group, congruent trials = 31 [±39] ms, TS group, congruent trials = 51 [±43] ms; $p = 0.31$; CS group, incongruent trials = 8 [±41] ms; TS group, incongruent trials = 12.5 [±61] ms, $p = 0.85$).

3.1.3. Error data

Analyses were conducted to test for differences in the number of errors made. Overall the number of errors made was small across all conditions (<5%) and statistical analyses revealed that there were no differences in error rate between the CS and TS groups across any of the four congruency × trial type conditions (minimum $p > = 0.43$).

3.2. fMRI results

3.2.1.1. Region-of-interest (ROI) analyses of task effects

To assess the effects of the experimental task (incongruent vs. congruent trials) and (task switch vs. task repeat trials) within each ROI, parameter estimates for each participant were calculated for each ROI and for each condition using a random effects (RFX) GLM. Parameter estimates were entered into a 2-way mixed ANOVA with the within-subject factor of Condition (4 levels: Congruent Switch; Congruent Repeat; Incongruent Switch; Incongruent Repeat) and the between-subject factor of Group (CS vs. TS).

The results of the ANOVA revealed a similar pattern of effects within each ROI. Specifically, in each case there was a statistically significant main effect of group with the TS group exhibiting a significantly reduced BOLD response relative to the controls (Sensorimotor cortex ROI: CS group mean = 5.18 [±0.60], TS group mean = −1.41 [±0.58]; $F[1,16] = 9.03$, $p = 0.008$; SMA ROI: CS group mean = 5.94 [±0.29], TS group mean = 0.25 [±0.74]; $F[1,16] = 6.13$, $p = 0.025$; Anterior cingulate ROI: CS group mean = 5.04 [±0.81], TS group mean = −1.27 [±0.60]; $F[1,16] = 13.52$, $p = 0.002$; Inferior frontal ROI: CS group mean = 5.85 [±0.54], TS group mean = −0.15 [±0.26]; $F[1,16] = 6.49$, $p = 0.022$. By contrast, there were no significant main effects of condition (maximum $F[3,48] < 1.0$, $p > 1.0$), and no significant Group × Condition interaction effects (maximum $F[3,48] = 1.57$, $p = 0.21$) for any ROI.

3.2.1.2. Relationship between fMRI BOLD response and behavioural RT

The functional interpretation of increased (or decreased) BOLD activation must be approached with considerable caution as both increased and decreased BOLD signal can be associated with improved behavioural task performance. Furthermore, this may be particularly true of clinical populations in which brain function and structure may be subject to compensatory adaptation and plasticity. For this reason, and where practical, it is sensible to aid interpretation of changes in BOLD signal by associating them with changes in individual measures of behavioural performance.

To this end a series of correlation (Pearson) analyses were carried out which examined, for each ROI and each condition, whether the contrast parameter estimates obtained for each individual were a significant predictor of behavioural RT performance (correlations between fMRI BOLD response and RT switch costs were analysed separately and are reported below).

The analyses revealed a highly similar pattern across all four ROIs and across all task conditions. Specifically, in each case the magnitude of the fMRI BOLD response was negatively correlated with RT, suggesting that faster RTs were linearly associated with increased BOLD responses in each ROI. For illustrative purposes, and for the sake of brevity, we present data for all task conditions from the SMA ROI in Fig. 3. The analyses of SMA ROI revealed that there was a negative Pearson correlation with the BOLD response for all task conditions that ranged from −0.29 to −0.41, but did not reach conventional levels of statistical significance (all $p > 0.05$).

3.2.1.3. Relationship between fMRI BOLD response and RT switch costs

In behavioural studies of task or response switching, it is customary to assess the cognitive or executive control demands imposed by a task by measuring the magnitude of the 'switch costs', that is the difference in RT or error rate between task switch and task repeat trials. As noted above, in the current study the behavioural analyses revealed statistically significant RT differences between task switch and task repeat trials, indicating that there were significant switch costs associated with this behavioural task (see also Jackson et al., 2011a; Swainson et al., 2003).

Analyses of the relationship between overall RT switch costs and fMRI BOLD response revealed that, across all subjects and for each ROI, there was a moderate positive Pearson correlation between RT switch costs (i.e., Switch trial RT–Repeat trial RT) and the BOLD response for the Switch > Repeat contrast (ranging between 0.29 and 0.38) that failed to reach statistical significance.

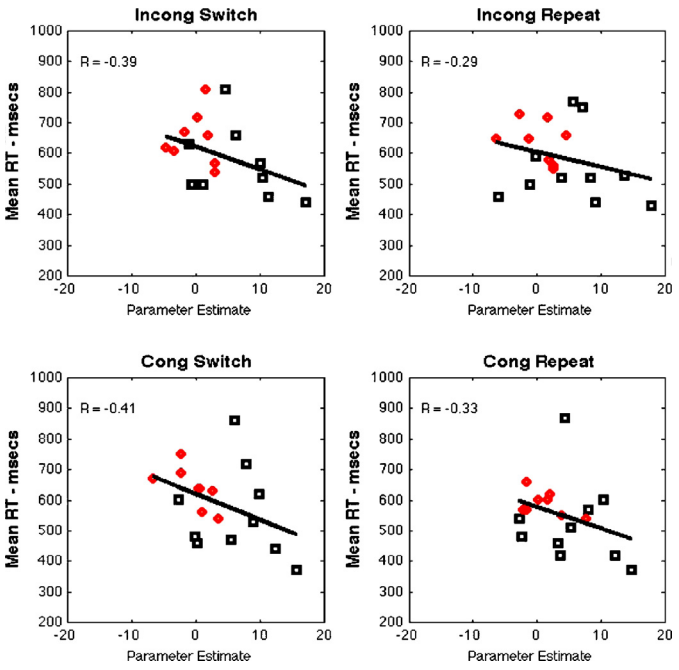

Fig. 3. Scatter plots illustrating the relationship between RT and the BOLD response for each condition of the behavioural task. Representative data are presented for the SMA region-of-interest. Pearson correlations ranged from −0.29 to −0.41 but did not reach conventional levels of statistical significance (all $p > 0.05$). The data from the TS group are represented by the red symbols and the CS group by the black symbols.

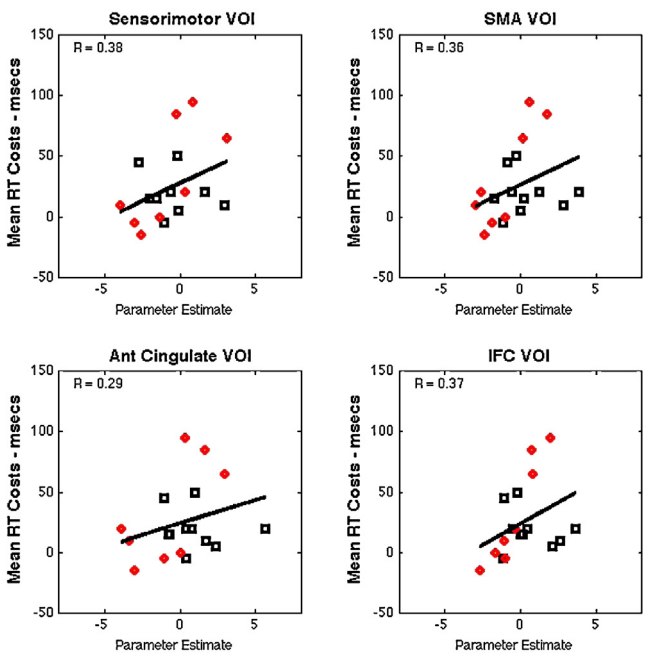

Fig. 4. Scatter plots illustrating the relationship between RT switch costs and the BOLD response within each region-of-interest. The data from the TS group are represented by the red symbols and the CS group by the black symbols. Pearson correlation coefficients for the CS group were low (−0.08 to −0.25) and did not approach conventional levels of statistical significance (see Table 2 for details). By contrast, Pearson correlation coefficients for the TS group strongly positive (ranging from 0.67 to 0.95) and statistically significant.

Importantly, however, further analyses revealed that these effects differed markedly between the TS and CS groups. Details are presented in Table 2 and data are plotted in Fig. 4. Specifically, the analyses confirmed that for the CS group, the correlation between RT switch costs and the fMRI BOLD response for the Switch > Repeat contrast was negative (ranging from −0.08 to −0.25) and statistically non-significant (all $p > = 0.49$). By contrast, the correlation for the TS group was strongly positive (ranging from 0.67 to 0.95) and statistically significant, particularly with respect to the SMA ($p < 0.007$) and IFC ($p > 0.0003$) ROIs, for which the correlation coefficients between the CS and TS groups differed significantly from one another (SMA: $Z = -2.32$, $p < 0.05$; IFC: $Z = -3.55$, $p < 0.05$) using the method proposed by Thöni (1977). In summary, these data confirm that RT switch costs in the TS group, but not the CS group, are significantly predicted by the fMRI BOLD response in frontal cortex, particularly within the medial frontal areas (SMA and anterior cingulate) and inferior frontal/insular cortex.

3.2.1.4. Correlation of BOLD response with clinical scores

To determine whether differences in fMRI BOLD response for the TS group were associated with clinical measures of tic severity (Yale global score) we carried out a series of correlation analyses, in which, for each ROI, we used the RFX parameter estimates obtained for each individual to predict that individual's Yale score. For brevity we report only the correlations between individual Yale global score and RFX parameter estimates for (i) all conditions > baseline contrast, and (ii) the incongruent switch trial contrast (i.e., the most difficult single behavioural condition). These results are presented in Table 3, and representative data are illustrated for the incongruent switch condition in Fig. 5.

Inspection of Fig. 5, and the data in Table 3, confirms that increased fMRI BOLD activation is positively associated with increased tic severity (as measured by the Yale Global Scale) in each of the four ROIs, but this relationship is strongest for the fMRI BOLD response recorded within the sensorimotor cortex. This finding is consistent with the suggestion that impairment in the operation of cortical–striatal–thalamic–cortical circuits gives rise to hyperexcitability of cortical motor areas: which may be brought about by dysfunctional, short-range, intra-cortical inhibitory mechanisms as measured by transcranial magnetic stimulation techniques. Importantly, it has been shown that the reduction in intra-cortical inhibition within motor cortex that is observed in TS is correlated

Table 2
Pearson correlation coefficients between RT switch costs (i.e., Switch trial RT–Repeat trial RT) and the fMRI BOLD response for the Switch > Repeat contrast for all participants combined and also separately for the CS and TS group. Statistically significant correlation coefficients and differences between correlations are presented in bold.

Contrast		VOI			
		Sensorimotor cortex	SMA	Anterior cingulate cortex	Inferior frontal/insular cortex
Correlation: all subjects	Pearson R	0.38	0.36	0.29	0.37
	p-value	0.12	0.15	0.24	0.13
Correlation: CS group only	Pearson R	−0.22	−0.08	−0.16	−0.25
	p-value	0.55	0.82	0.66	0.49
Correlation: TS group only	Pearson R	**0.71**	**0.86**	0.67	**0.95**
	p-value	**0.05**	**0.007**	0.07	**0.0003**
Between group *Z*-score		−1.88	**−2.32**	−1.66	**−3.55**

Table 3
Pearson correlation coefficients between fMRI BOLD response within each region-of-interest and clinical measures of tic severity (Yale global score) in the TS group.

Contrast		VOI			
		Sensorimotor cortex	SMA	Anterior cingulate cortex	Inferior frontal/insular cortex
All conditions > Baseline	Pearson R	0.61	0.10	0.34	0.36
	p-value	0.11	0.81	0.41	0.39
Incongruent Switch	Pearson R	0.62	0.28	0.53	0.34
	p-value	0.10	0.50	0.18	0.41

with increased tic severity (Ziemann et al., 1997; Gilbert et al., 2004; Orth et al., 2008).

4. Discussion

Here we used fMRI to investigate, in a group of children with uncomplicated TS, and a group of matched controls, how brain activation levels varied during the execution of a task previously used to assess cognitive control of motor output, i.e., manual response-switching (e.g., Swainson et al., 2003; Jackson et al., 2011a). We identified four bilateral regions-of-interest that were activated in all behavioural conditions. These regions were: sensorimotor cortex [M1/S1]; SMA; anterior cingulate cortex [ACC]; and, inferior frontal/insular cortex [IFC]. All regions previously linked with the planning and execution of manual responses (M1/S1 and SMA) or the cognitive control of action (ACC and IFC).

The key findings can be summarised as follows: first, the results for the behavioural task revealed no differences in task performance (neither mean error or mean RT) between the TS group and the controls. While both groups showed clear congruency and task-switching effects, the magnitude of these effects did not differ between groups. This finding is consistent with many previous studies that have assessed executive control in individuals with uncomplicated TS (Ozonoff et al., 1998; Rice & Weyandt, 2000; Mostofsky et al., 2001; Channon et al., 2006). Second, despite equivalent levels of behavioural performance across the groups, the results of the fMRI analyses demonstrated that the TS group exhibited significantly reduced BOLD responses in all regions examined. Third, the fMRI BOLD response was found to be negatively correlated with RT for all regions examined: with faster RTs being moderately linearly associated with increased fMRI BOLD responses. Fourth, and most importantly, the relationship of the fMRI BOLD response to RT switch costs (the customary measure used to assess cognitive control) was shown to differ between groups. Specifically, while the fMRI BOLD response of the CS group was uncorrelated with RT switch costs, the BOLD response in all regions was strongly positively associated with RT switch costs (range: 0.67–0.95) for the TS group, and the observed correlations for the TS group, for both the SMA and IFC regions, differed significantly from those observed for the CS group. Finally, in all regions examined, clinical measures of tic severity (Yale scores) were positively associated with the fMRI BOLD responses observed. This relationship was particularly strong in sensorimotor cortex ($R > = 0.61$). These findings are discussed below.

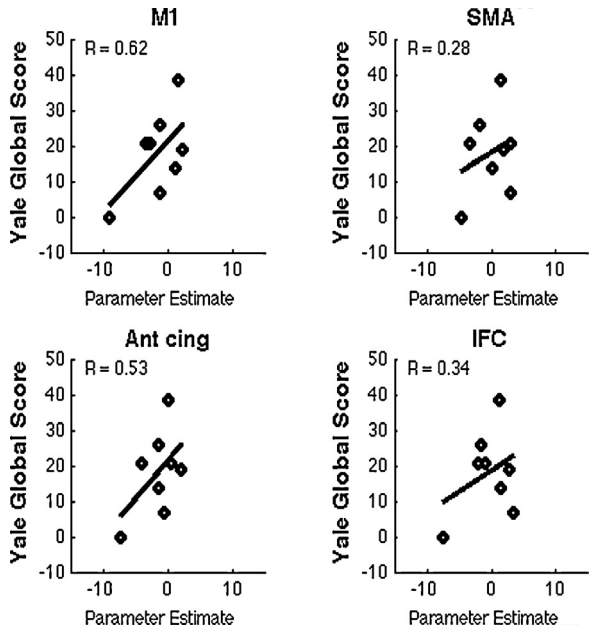

Fig. 5. Scatter plots illustrating the positive relationship between the fMRI BOLD response within each region-of-interest and clinical measures of tic severity (Yale global score) in the TS group. Pearson correlations ranged from 0.28 to 0.62 but did not reach conventional levels of statistical significance (all $p > 0.05$).

It has been suggested that individuals with TS might gain control over their tics through the development of compensatory self-regulation mechanisms: most likely implemented through changes in neural pathways linking PFC with primary and secondary motor regions (Plessen et al., 2004; Serrien et al., 2005; Mueller et al., 2006; Jackson et al., 2007; Plessen et al., 2009; Jackson et al., 2011a). Thus, altered local patterns of increased cortical excitability in motor areas that might give rise to tics may, during adolescence, be compensated for by functional and structural changes in long-range connectivity that operate to actively reduce sensorimotor cortical excitability. We have speculated that suppression of cortical excitability might be achieved through an increase in the inhibitory tone of motor areas: perhaps achieved through modulation of local inhibitory interneurons (Jackson et al., 2012). Consistent with this idea, recent TMS studies (Heise et al., 2010; Jackson et al., 2012) have demonstrated that motor cortical excitability is significantly decreased in individuals with TS adults in the period immediately preceding the execution of a movement. This proposal is also consistent with the results of the current study which found that: despite comparable levels of behavioural task performance, the TS group nevertheless showed significantly reduced levels of fMRI BOLD in all regions examined: M1/S1, SMA, ACC, and IFC. It is also consistent with our findings, that: clinical measures of tic severity (Yale scores) were positively associated with the fMRI BOLD response in all of the above regions (but particularly M1/S1); and, that for the TS group, and not the CS group, behavioural performance, as indexed by RT switch costs, was significantly correlated with the fMRI BOLD response within the SMA and IFC regions. It is noteworthy in this context that recent graph theory analyses of functional connectivity in healthy adults, based upon examination of resting-state BOLD time-series, identify these areas as two of the principle hubs within the brain sensorimotor network (Worbe et al., 2012). Importantly, hubs are thought to facilitate integration between different parts of functional networks.

4.1. Role of altered cortico–cortico connections in TS

It is suggested that impairment in the operation of cortical–striatal–thalamic–cortical (CSTC) circuits gives rise to hyper-excitability of cortical sensorimotor areas in TS and

contributes to the occurrence of tics (Albin and Mink, 2006). Consistent with this proposal studies have found: decreased number, and altered distribution, of inhibitory (GABA-ergic) interneurons within the striatum for individuals with TS (Kalanithi et al., 2005); structural alteration in the volume of striatal (for review see Plessen et al., 2009) and thalamic nuclei (Miller et al., 2011); and, altered patterns of functional connectivity within CSTC networks, the magnitude of which are significantly correlated with tic severity (Worbe et al., 2012).

Other studies have reported changed patterns of structural and functional cortico–cortico connectivity in individuals with TS, which include alterations in the microstructure of cortical white-matter tracts (e.g., Plessen et al., 2004; Neuner et al., 2010; Jackson et al., 2011a) and alterations in functional or effective connectivity between frontal and motor areas (e.g., Serrien et al., 2005; Church et al., 2009), or between premotor and primary motor regions (Franzkowiak et al., 2012).

A fundamental issue is how best to interpret altered patterns of cortico–cortico connectivity: particularly those involving connections linking the PFC and premotor regions with primary sensorimotor cortex. One approach might be to take the widely held view that such connections implement task-control networks within the brain (e.g., Nigg, 2000; Church et al., 2009) that may be impaired in TS and give rise to the occurrence of tics (e.g., Channon et al., 2009; Church et al., 2009). Within this view, deviation from the typical, age-appropriate, developmental pattern might be viewed as evidence of functional immaturity of developing brain networks (e.g., Church et al., 2009; Worbe et al., 2012).

A second approach might be to accept the view that these connections implement task-control networks, but interpret observed deviations from the typical, age-appropriate, developmental patterns instead as evidence for compensatory, neuroplastic, structural and functional alterations that lead to enhanced top-down control of motor outputs (Plessen et al., 2004; Mueller et al., 2006; Jackson et al., 2007; Plessen et al., 2009; Orth and Rothwell, 2009; Heise et al., 2010; Jackson et al., 2011a, 2012). A key assumption of this approach might be that compensatory changes are accompanied by strengthened coupling of PFC and motor regions (Serrien et al., 2005).

Alternatively, a third approach might take the view, for the reasons outlined above, that the PFC is not the source of inhibitory control signals, but is instead a source of facilitatory signals that operate to bias response competition within areas more directly linked to motor planning or motor execution (Sumner et al., 2007; Munakata et al., 2011). Within this view hyper-activity in PFC or pre-motor brain areas might contribute, in individuals with TS, to the over-activation of sensorimotor cortex, and the occurrence of tics (Bohlhalter et al., 2006; Mantovani et al., 2006; Kwon et al., 2011; Franzkowiak et al., 2012). Moreover, compensatory structural or functional changes in brain networks might operate instead to reduce input to sensorimotor cortex from upstream brain areas such as PFC. Support for this proposition comes from the finding that: structural changes in cortical white-matter pathways, such as decreased corpus callosum area (e.g., Plessen et al., 2004) or decreased fractional anisotropy in PFC white-matter (Jackson et al., 2011a) may nevertheless be positively correlated with measures of tic severity; and that increases in number and strength of functional connections within CSTC networks in individuals with TS are also positively correlated with tic severity (Worbe et al., 2012).

The results of the current study are generally consistent with the latter account. First, we find that the TS group exhibited significantly reduced levels of fMRI BOLD in all frontal regions examined: SMA, ACC, and IFC, even though behavioural task performance was equivalent across groups. Second, we found that in these same frontal areas fMRI BOLD response was inversely related to RT, such that faster RTs were associated with increased BOLD. Taken together these two findings are difficult to reconcile with the 'Frontal Inhibitory Control Signal' account that proposes that PFC generates inhibitory control signals that are used to suppress hyper-excitability in motor areas, as this account would predict that the reduced activations observed in sensorimotor cortex would be inversely related to increased frontal activation.

Importantly, we also found that the fMRI BOLD response in frontal (IFC) and premotor (SMA) areas for the TS group, but not for the CS group, was highly positively correlated with behavioural measures of cognitive control (RT switch costs), such that increased switch costs were associated with increased fMRI BOLD. Again this runs counter to the general idea that increased PFC activation leads to increased inhibition of motor responses, and is more consistent with recent reports that regions such as SMA may bias suppression mechanisms elsewhere rather than to be the direct source of suppression (Boy et al., 2010).

Finally, and perhaps most importantly, we find that in all areas examined (but particularly within sensorimotor cortex), clinical measures of tic severity were positively associated with the fMRI BOLD response. We note that this result confirms a previous fMRI study of task switching in TS that also found a positive correlation between fMRI BOLD and tic severity (Baym et al., 2008). This result is also difficult to reconcile with the idea that frontal regions are the source of inhibitory control signals, but it is quite consistent with the notion that frontal regions may operate to bias response selection in sensorimotor cortex, and that increased activity within frontal regions could contribute to hyper-activity within motor cortex. In this context it is again of interest to note that in individuals with TS: increased number and strength of functional connections between regions within CSTC networks is positively correlated with tic severity (Worbe et al., 2012); that rTMS suppression of cortical excitability in the SMA leads to reduced tic severity (Mantovani et al., 2006; Kwon et al., 2011); and, that whereas white-matter measurements are often reduced in TS (i.e., reduced corpus callosum area and reduced FA values), such reductions are nevertheless positively correlated with reductions in tic severity (Plessen et al., 2004; Neuner et al., 2010; Jackson et al., 2011a).

In summary, in the current paper we have presented arguments, together with new data that run counter to the widely held view that frontal cortex is the source of inhibitory task-control signals that operate to suppress competing responses in motor areas and thus aid motor selection. In contrast, we present arguments and new evidence that the PFC may be better viewed in general as the source of facilitatory signals that act to bias competition in brain areas more directly involved in motor execution. Importantly, we argue that in TS over activation of frontal cortex may contribute to the hyper-excitability of sensorimotor cortex and the occurrence of tics, and that compensatory changes leading to enhanced cognitive control in TS may be largely implemented by distributed local changes in cortical excitability.

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