Motor inhibition in patients with Gilles de la Tourette syndrome: functional activation patterns as revealed by EEG coherence

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Summary

There is considerable evidence that Gilles de la Tourette syndrome (TS) is due to frontal–striatal dysfunction. Here we determine whether adaptive cortical changes occur that might ameliorate the effects of this dysfunction. Specifically we test the hypothesis that increased interactions between selected cortical areas may help compensate through strengthened inhibition of inappropriate motor responses. To this end we recorded EEG in nine unmedicated patients with TS and nine age-matched healthy subjects during a variety of behavioural tasks related to motor inhibition. Functional connectivity between cortical areas was assessed by means of EEG coherence in the alpha frequency band (8–12 Hz). Elevated coherence was found between sensorimotor areas and the prefrontal and mesial frontal cortex during the acute voluntary suppression of tics. The same frontomesial network was overactive in TS patients compared with healthy subjects even when suppression of voluntary movement rather than tics was required during a Go–NoGo task. Behavioural performance in the Go–NoGo task was not different between patients and controls, confirming that the elevated frontomesial coherence in TS was likely to be adaptive rather than functionally disruptive. It is concluded that the gain in inhibitory frontomesial cortical networks is adaptively heightened in TS, and that the same network can also be engaged in the voluntary suppression of tics.

Introduction

Gilles de la Tourette syndrome (TS) is a disorder with a strong familial component and is characterized by irregular motor tics and vocalizations that typically appear in childhood (Robertson, 2000; Leckman, 2002). Substantial evidence suggests a disorder of frontal–striatal circuits (Singer, 1997; Bradshaw and Sheppard, 2000). Volumetric abnormalities of the basal ganglia have been reported (Malison *et al*., 1995; Wolf *et al*., 1996), as well as increased dopamine binding within the caudate nucleus of the striatum (Peterson *et al*., 1993; Singer *et al*., 1993; Hyde *et al*., 1995; Malison *et al*., 1995; Wolf *et al*., 1996). Anomalies of the frontal–striatal circuits in TS are further underscored by cognitive deficits. TS patients have deficits in memory search, abstract reasoning and verbal fluency (Bornstein *et al*., 1991), processes that are believed to be regulated by frontal–striatal systems (Rauch and Savage, 1997). They also have attentional deficits and problems in inhibiting unsuitable responses and intentions (Baron-Cohen *et al*., 1994; Georgiou *et al*., 1995; Harris *et al*., 1995; Shucard *et al*., 1997; Johannes *et al*., 2001) as well as abnormalities of antisaccade eye movements (Le Vasseur *et al*., 2001).

The above studies detail the pathophysiological deficits in TS, but little is known about adaptive changes that may have an important influence on the relationship between dysfunction and its clinical expression. The importance of adaptive plasticity following peripheral injury (Cohen *et al*., 1991), stroke (Rossini *et al*., 2003) and multiple sclerosis (Cifelli and Matthews, 2002) and in degenerative disorders such

as Parkinson's disease (Devos *et al.*, 2004) is increasingly recognized. However, there is far less information regarding the role of plasticity in disorders without obvious focal or degenerative pathology, such as TS. Yet clinical observations suggest that adaptive changes can occur, as most clearly evidenced by the ability of many patients with TS to voluntarily suppress their tics. By defining the processes active in such acute suppression, we identify cortical networks involved in the dynamic suppression of tics and demonstrate that these networks are overactive even when suppression of voluntary movement rather than tics is required. Hence it is likely that the gain in these inhibitory cortical networks is persistently and adaptively heightened in TS.

Methods
Patients

Nine patients with TS (mean age 28 ± 8 years, two females) and nine control subjects (mean age 29 ± 6 years, five females) gave informed consent to participate in the study, which was approved by the Joint Medical Ethics Committee of The National Hospital for Neurology and Neurosurgery and The Institute of Neurology. Clinical characteristics of the unmedicated TS patients are listed in Table 1. TS patients were selected with limited head tics, to permit EEG recordings. Clinical assessment included the Yale Global Tic Severity Scale (Leckman *et al.*, 1989) and the Diagnostic Confidence Index, which represents a score based on an assessment of lifetime history of tics, independent of current severity and effects of treatment (Robertson *et al.*, 1999). Right-handedness was determined by the Edinburgh handedness inventory (Oldfield, 1971).

Task and procedure
Active suppression of tics in TS patients

TS patients were asked to voluntarily suppress their tics in order to characterize the cortical connections with the highest coherence during motor inhibition. This active suppression condition was contrasted with a rest condition. In the latter condition the patients were allowed to tic, but these instances were discarded such that only epochs that were not contaminated by movement were analysed. Each consisted of 2 min of recordings. The active suppression condition was recorded in one to three periods,

depending on the patient's ability to suppress their tics. Only five patients were comfortably able to continuously suppress their tics for ≤ 1 min.

Go–NoGo task

Subjects were asked to perform a visuomanual reaction time task during which a cue stimulus would carry the instruction to get ready and a subsequent target stimulus would provide the signal for the requested unilateral response. Subjects were seated in front of a desk with a custom-built button press device held in each hand, and faced a computer screen at a distance of 80 cm. A fixation cross was visible continuously in the centre of the screen. During each trial, an arrow was presented that pointed to the right or to the left, and served as a cue for a following target that consisted of a figure 0. The cue and target stimuli appeared on the right or left side of the fixation cross to enhance stimulus–response compatibility and remained visible on the screen for 500 ms; a fixed time interval of 3 s occurred between the onsets of cue and target. Both stimuli subtended a visual angle of 2° with the fixation cross. Subjects had to respond to the target signal by pressing the right-sided or left-sided button as fast as possible with the thumb of the right or left hand (as instructed by the direction of the cue arrow and the asymmetry of the target signal with respect to the central fixation cross on screen). In a number of trials (25% of the total) the target signal would display a letter S, indicating that the planned response needed to be inhibited. The interval between trials varied between 7 and 9 s. A baseline (rest) condition was also recorded.

Complementary conditions in control subjects

Two variations of the Go–NoGo task were also tested in control subjects.

Response with the contralateral hand (RevGo)

In this experiment, control subjects (*n* = 9) pressed the button held in the contralateral hand in response to a NoGo target stimulus. This paradigm represents a modified version of the Simon task, in which stimulus–response compatibility is manipulated (Simon, 1969). The RevGo trials were contrasted with the normal NoGo trials to demonstrate that activity changes in the latter condition could not be attributed to the necessity to change behaviour *per se* after the target (NoGo) signal, but rather to the nature of the instructed behavioural change. A baseline (rest) condition was also performed.

Table 1 *Clinical details of the TS patients*

	P1	P2	P3		P4	P5	P6	P7	P8	P9
Age	30	31	45		20	31	27	23	17	30
Sex	F	M	M		M	M	F	M	M	M
YGTSS—Total Motor Tic Score	10	10	8		8	12	9	9	13	20
YGTSS—Total Vocal Tic Score	7	10	5		9	9	9	8	8	20
YGTSS—Overall impairment	30	20	20		20	0	0	20	0	10
DCI	49	62	56		54	41	47	52	66	86
Comorbid symptoms	–	–	ADHD, OCD		–	–	–	–	–	ADHD

F = female, M = male. YGTSS = Yale Global Tic Severity Scale assesses the severity of motor and vocal tics and the overall impairment in self-esteem, family life, social acceptance and job functioning (Leckman *et al.*, 1989). DCI = Diagnostic Confidence Index consists of a list of 26 confidence factors with weightings that reflects a measure of determining lifetime likelihood of TS (Robertson *et al.*, 1999). ADHD = attention deficit hyperactivity disorder; OCD = obsessive-compulsive disorder.

Acoustic conditioning of the NoGo stimulus

In this experiment control subjects ($n = 4$) received an acoustic stimulus of 50 ms duration with an intensity of 100 dB transmitted through headphones at the onset of 70% of (randomly selected) NoGo target signals. This resulted in an increased number of false alarms (failed inhibition) in NoGo trials, sufficient for independent analysis. A baseline (rest) condition was also performed.

EEG recordings

Continuous EEG was recorded from Ag–AgCl surface electrodes mounted according to the 10–20 International system. Activity was recorded from left hemisphere (F3, FC3, C3, P3), right hemisphere (F4, FC4, C4, P4) and midline (Cz, FCz) electrodes. The relevant electrodes were likely to overlie the dorsolateral prefrontal (F3/4), premotor (FC3/4), sensorimotor cortex (C3/4), superior parietal (P3/4) and supplementary motor (SMA: Cz/FCz) areas (Homan *et al.*, 1987; Steinmetz *et al.*, 1989), although recorded activity was unlikely to have been solely derived from these areas. We used linked mastoid reference electrodes rather than Laplacian derivatives so as to avoid diminished discrimination at lower frequencies (Nunez, 2000), although this approach does have the disadvantage that EEG recordings were less focal. The signals were amplified (Digitimer, Hertfordshire, UK), bandpass-filtered (0.5–100 Hz), digitized by a 1401 analogue-to-digital converter (Cambridge Electronic Design, Cambridge, UK) and sampled at a rate of 200 Hz (Spike 2; Cambridge Electronic Design).

Analysis

Behavioural data

Reaction times of the button presses to the target stimuli were calculated. Times shorter than 150 ms or in excess of 1000 ms were considered outliers and excluded from data analysis. Reaction times were analysed by means of a 2 × 2 (Group × Hand) analysis of variance (ANOVA). The first factor comprised the TS patients versus control subjects and the second factor represented the right versus left hand.

EEG data

Active suppression. EEG records were visually inspected and those with prominent artefact from eye movement or scalp muscle contraction rejected. EEG coherence was used to assess functional coupling between the cortical areas in the frequency domain, and was estimated using the discrete Fourier transform and parameters derived from it. The coherence $|R_{ab}(\lambda)|^2$ was calculated by using the formula $|R_{ab}(\lambda)|^2 = |f_{ab}(\lambda)|^2/f_{aa}(\lambda)\, f_{bb}(\lambda)$. In this equation, f characterizes the spectral estimate of two EEG signals a and b for a given frequency (λ). The numerator includes the cross-spectrum for a and b (f_{ab}), whereas the denominator includes the autospectra for a (f_{aa}) and b (f_{bb}). Coherences were transformed using the inverse hyperbolic tangent. To avoid overestimated coherence scores due to volume conduction and common references (Nunez, 2000), we expressed the values of the active suppression state as a percentage of those of the resting state. In particular the percentage coherence scores were calculated as (Pa − Pr) × 100/Pr, where Pa refers to the active suppression values and Pr the rest values. The coherence data were divided into the following regional connections: six left hemisphere (F3–FC3, F3–C3, F3–P3, FC3–C3, FC3–P3, C3–P3), six right hemisphere (F4–FC4, F4–C4, F4–P4, FC4–C4, FC4–P4, C4–P4), 17 mesial (FCz–F3, FCz–FC3, FCz–C3, FCz–P3, Cz–F3, Cz–FC3, Cz–C3, Cz–P3, FCz–Cz, FCz–F4, FCz–FC4, FCz–C4, FCz–P4, Cz–F4, Cz–FC4, Cz–C4, Cz–P4) and 16 interhemispheric (F3–F4, F3–FC4, F3–C4, F3–P4, FC3–F4, FC3–FC4, FC3–C4, FC3–P4, C3–F4, C3–FC4, C3–C4, C3–P4, P3–F4, P3–FC4, P3–C4, P3–P4). To provide an absolute coherence measurement, we also estimated the task-related coherence, which expressed the values of the active suppression state minus those from the resting state. Hence, task-related coherence increments due to tic suppression are expressed as positive values and can be interpreted as indicating greater inter-regional communication. We analysed the alpha frequency band (8–12 Hz), as activity in this band may preferentially reflect the regulation of cognitive driven functions (Von Stein *et al.*, 2000; Serrien *et al.*, 2003) and captures motor inhibition as well as motor excitation (Hummel *et al.*, 2002). Qualitative assessment of EEG coherence spectra supported this approach. Figure 1 shows coherence spectra in a TS patient during active suppression and rest. It can be observed that the main peak occurs in the alpha band around 10 Hz, and is more prominent during tic suppression than rest.

Go–NoGo task. Trials that included errors, i.e. a response following a NoGo target or a failure to elicit a response after a Go target, were omitted from the analysis. Trials were segmented into periods that were aligned to the target stimulus. These periods lasted 5 s; from 1 s pre-cue until 1 s post-target and included the 3 s delay period. Event-related coherence was used to assess functional coupling between cortical areas and was estimated by means of complex demodulation (Thatcher *et al.*, 1995) using NeuroScan software (NeuroScan, El Paso, USA). Complex demodulation converts the broadband source activities to a narrowband series of complex numbers for a centre frequency of interest, plus or minus some half-bandwidth. It derives real and imaginary time series from the original time series. As such, the modulus of the resulting complex time series is the envelope of the original time series at the selected frequency, which was set in the present study at 10 Hz, with a half-bandwidth of 2 Hz and roll-off of 12 dB. The estimated coherences were transformed using the inverse hyperbolic tangent, and coherences obtained during rest were subtracted to obtain values related to the task.

The cortical connections selected for analysis, e.g. F3–C3 and FCz–C3 for the right hand and F4–C4 and FCz–C4 for the left
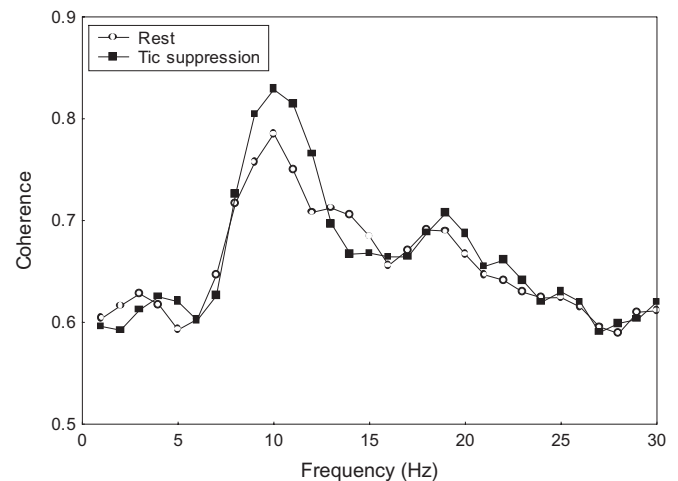

Fig. 1 Coherence spectra averaged across F3–C3, F4–C4, FCz–C3 and FCz–C4 during active suppression and rest for a TS patient. Peak coherence can be observed in the alpha band around 10 Hz, and is more pronounced during tic suppression than rest. Transformed data.

hand, were those that also showed the greatest task-related increases in coherence during active tic suppression in the TS patients. The prominence of task-related coherence changes in these connections during active tic suppression suggested that they might be important in inhibitory motor control. We therefore sought to confirm the relevance of activity in these connections to inhibitory motor control by demonstrating that the same connections showed increased coherence during NoGo trials in the Go–NoGo task in healthy subjects. The functional homology between active tic suppression and motor inhibition in NoGo trials was supported by a subsidiary analysis in which we additionally and randomly selected four connections from the active suppression condition in the TS patients. The latter included one connection for each region: left (C3–P3), right (F4–P4), mesial (FCz–Cz), interhemispheric (F3–F4). Thereafter we compared the percentage task-related coherence increases in the eight connections during tic suppression (range 10–31%) with the percentage task-related coherence change in the same eight functional links during post-target versus pre-cue intervals during NoGo trials in control subjects (range 35–82%). We hypothesized that if the functional couplings responded similarly during tic suppression and NoGo trials, then task-related coherence changes should correlate across the connections in the two tasks. The results revealed a significant correlation coefficient of 0.89 ($P < 0.01$), evidence for similar cortical behaviour across the tasks. In addition, this analysis confirmed that F3–C3, FCz–C3, F4–C4 and FCz–C4 showed the greatest increase in coherence out of the eight studied connections in the NoGo trials.

A period of 250 ms post-target stimulus was selected for analysis as this was most likely to contain processing consequent upon the imperative signal and related to the subsequent response, whether movement or inhibition. As such the relevant epoch preceded motor execution. As a reference, an equivalent time epoch of 250 ms was taken from the pre-cue interval. Thereafter, percentage scores were calculated as $(Pp - Pr) \times 100/Pr$, where Pp referred to the post-target values and Pr indicated the pre-cue values. The values were averaged across the relevant connections and analysed by means of a 2×2 (Group $\times$ Task) ANOVA. The first factor comprised the TS patients versus control subjects and the second factor represented the Go versus NoGo trials. Normality of the values was verified by the Shapiro–Wilk's W test. Additional evaluation of the percentage change of activity during NoGo versus Go trials was analysed by non-parametric t tests for TS patients and control subjects separately.

In order to establish that power changes were not responsible for modulations in coherence, logarithmically transformed EEG power was assessed in the alpha band at the individual electrodes of interest (C3, F3, C4, F4, FCz) in the pre-cue and post-target intervals. EEG power was evaluated by subtracting the values at rest from those of the active state, averaged across the connections and analysed by means of a 2×2 (Group $\times$ Task) ANOVA. Normality of the values was verified by the Shapiro–Wilk's W test. EEG power was primarily estimated to ensure that changes in coherence were not due to modulations in non-linearly related frequency components (Florian *et al*., 1998).

Results

Active suppression of tics in TS patients

Figure 2A illustrates a mean-centred plot of all cortical connections in the active suppression versus rest condition in the alpha frequency band for the TS patients. Overall tic suppression showed an increased degree of coherence compared with rest (17 ± 4%), suggesting that inhibitory control processes required augmented information processing between cortical areas. The values were highest in the right hemisphere (19 ± 4%, corresponding to transformed task-related coherence scores of 0.05 ± 0.02), which might be related to its dominance for inhibitory control (Garavan *et al*., 1999; Pliszka *et al*., 2000) followed by those in
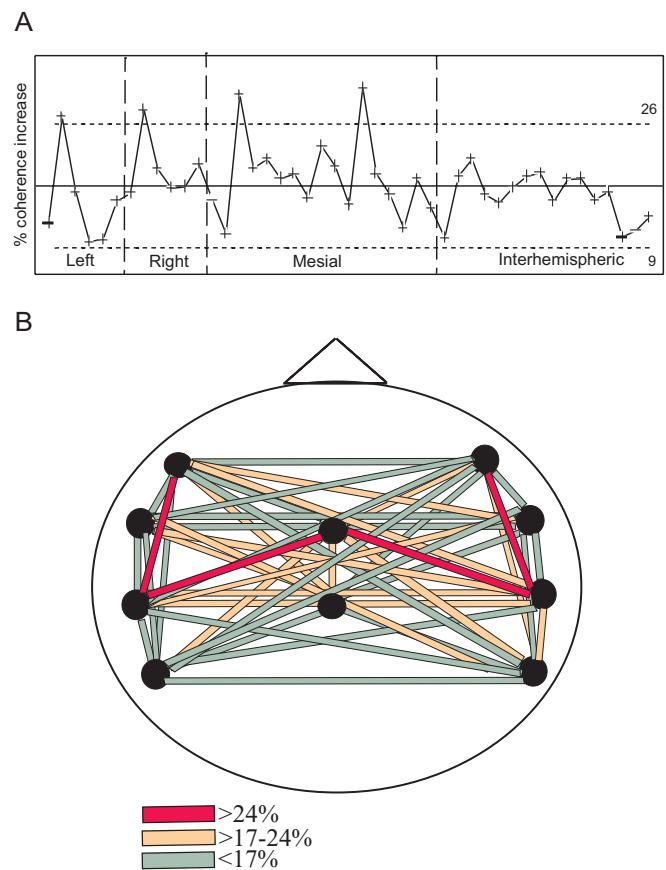

Fig. 2 (**A**) Mean-centred percentage increases in task-related coherence in the alpha frequency band in the active suppression versus rest condition for the nine TS patients. The connections are displayed in the following order: left (F3–FC3, F3–C3, F3–P3, FC3–C3, FC3–P3, C3–P3), right (F4–FC4, F4–C4, F4–P4, FC4–C4, FC4–P4, C4–P4); mesial (FCz–F3, FCz–FC3, FCz–C3, FCz–P3, Cz–F3, Cz–FC3, Cz–C3, Cz–P3, FCz–Cz, FCz–F4, FCz–FC4, FCz–C4, FCz–P4, Cz–F4, Cz–FC4, Cz–C4, Cz–P4); and interhemispheric (F3–F4, F3–FC4, F3–C4, F3–P4, FC3–F4, FC3–FC4, FC3–C4, FC3–P4, C3–F4, C3–FC4, C3–C4, C3–P4, P3–F4, P3–FC4, P3–C4, P3–P4). Overall, there was a consistent augmentation in coherence due to tic suppression across connections. The most pronounced modulations (and above the confidence limits) were those in the left hemisphere (F3–C3), right hemisphere (F4–C4) and mesial regions (FCz–C3, FCz–C4). The dotted horizontal lines denote the 95% confidence limits and the corresponding scores. (**B**) Colour-coded plot of the percentage coherence increase in all electrode combinations in the active suppression versus rest condition for the TS patients. The connections are divided into those that have an increase that is below (green) or above (orange and red) the average score of 17%. Note that the distances between electrodes are not drawn to scale.

the midline (18 ± 5%, corresponding to transformed task-related coherence scores of 0.04 ± 0.01), left hemisphere (15 ± 6% corresponding to transformed task-related coherence scores of 0.03 ± 0.01), and interhemispheric connections (14 ± 3%, corresponding to transformed task-related coherence scores of 0.02 ± 0.01). As can be observed, the functional couplings that showed the most pronounced amplifications in coherence were F3–C3 (26 ± 10%), F4–C4 (27 ± 12%), FCz–C3 (30 ± 18%) and FCz–C4 (31 ± 16%). Figure 2B shows a colour-coded plot of the coherence changes in the active suppression versus rest state and further underlines the differences between the various connections due to active tic suppression.

The voluntary suppression of tics requires increasing levels of tic inhibition and effort as time elapses and the urge to tic rises. To support the premise that activity in the above four connections was related to the suppression of tics (whether directly related to inhibition or effort) we calculated the task-related coherence averaged across the connections in intervals of 20 s during 1 min of continuous tic suppression. This was possible for the five patients able to comfortably suppress their tics for one continuous minute. The data, analysed by means of a one-way ANOVA, showed an effect of time $[F(2,8) = 5.4, P < 0.03]$. The mean scores were 0.05 ± 0.02, 0.06 ± 0.02 and 0.11 ± 0.04 for the first, middle and last intervals, respectively.

Go–NoGo task in TS patients versus control subjects

We used the Go–NoGo task to further investigate the role of the candidate connections (F3–C3, F4–C4, FCz–C3 and FCz–C4) in the inhibitory regulation of movement. This paradigm involves similar planning components for Go or NoGo trials, followed by a decision to respond or withhold to the target stimulus.

Behavioural data

Reaction times in the Go trials did not reveal significant effects ($P > 0.05$) between TS patients (340 ± 71 ms) and control subjects (350 ± 54 ms). Two types of error were observed: a reaction after a NoGo target (a false alarm) and a failure to elicit a response after a Go target (a miss). Most errors were false alarms, which represent a situation that would have been a correct response if the imperative stimulus had been a Go. However, all subjects performed the task with a high level of accuracy, and the percentage error scores of false alarms was less than 8% and equivalent for TS patients and control subjects.

EEG coherence

Figure 3 shows mean-centred task-related coherence averaged across the relevant connections during Go and NoGo trials as well as the difference between the two conditions (Go – NoGo) for the control subjects. Pronounced neural activity in response to the target stimuli, which exceeds the established control limits, takes place. A smaller change in activity can also be noted after the cue. In addition, in NoGo trials the activity that is originally generated as for planned Go trials is modified at a time that probably follows stimulus discrimination of the target signal. Accordingly, the NoGo peak occurs somewhat later in time than the Go peak and is also broader and of higher magnitude. The latter can be specifically observed when considering the Go – NoGo difference. Figure 4 illustrates the mean-centred task-related coherence plots for the TS patients. As for the control subjects, peak coherence is achieved shortly after the target signal, independently of the particular condition. A more pronounced activity occurs after NoGo than Go targets. This is clear when considering the Go – NoGo difference. Figure 5 depicts the between-group difference for Go and NoGo trials. It can be noted that no prominent between-group difference arises for Go trials, whereas significantly higher activity occurs for patients compared with controls after the target for NoGo trials.

The coherence of the time epoch following the imperative signal compared with that of the reference interval showed a main effect of Task $[F(1,16) = 43.6, P < 0.01]$ and a
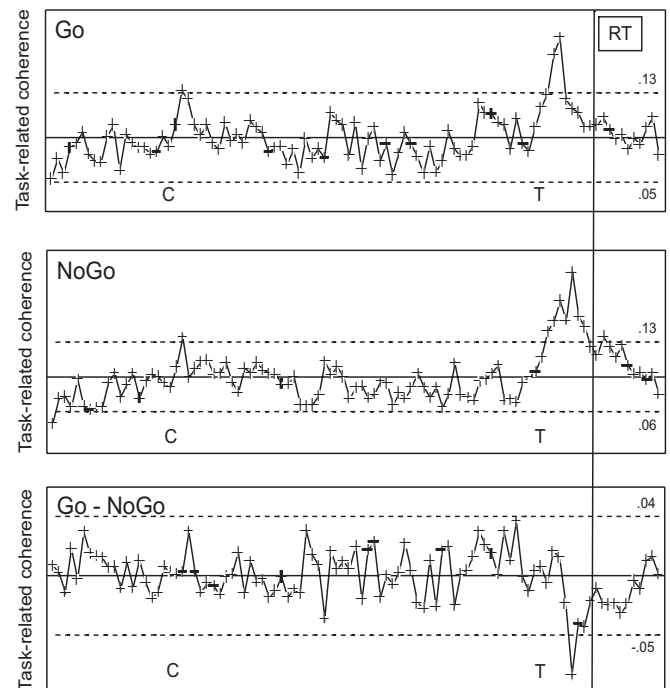

Fig. 3 Mean-centred task-related coherence plots for the nine control subjects during Go trials and NoGo trials, and the Go – NoGo difference. Transformed data averaged across F3–C3, F4–C4, FCz–C3 and FCz–C4. The time intervals show 5 s; there were pre-cue and post-target epochs of 1 s and an epoch of 3 s between cue (C) and target (T). The dotted horizontal lines denote the 99% confidence limits and the corresponding scores. The vertical line specifies the average reaction time (RT) obtained during the Go trials.
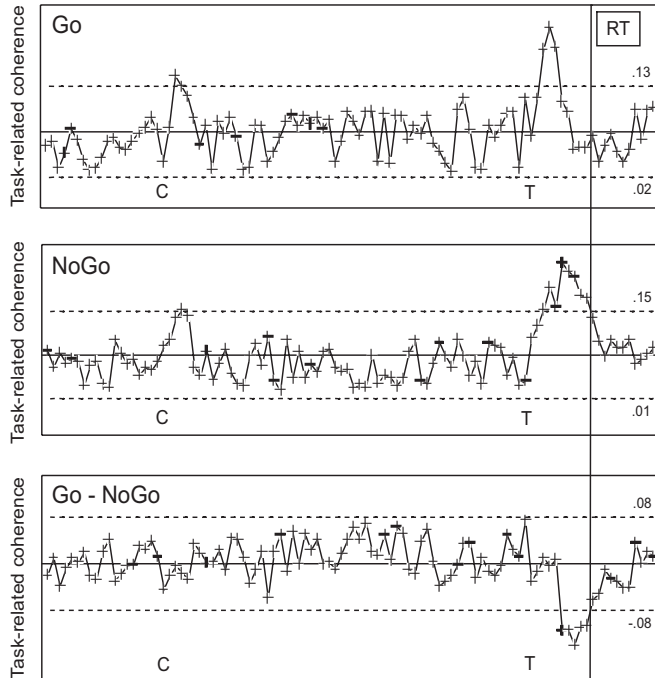
Fig. 4 Mean-centred task-related coherence plots for the nine TS patients during Go trials and NoGo trials, and the Go – NoGo difference. Averaged transformed data across cortical connections.
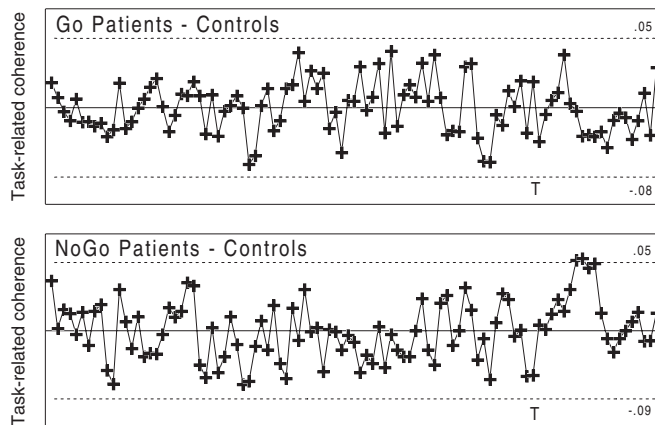

Fig. 5 Task-related mean-centred coherence plots illustrating between-group differences for Go trials and NoGo trials (*n* = 9 in each group). Averaged transformed data across cortical connections. The time intervals show 5 s; there were pre-cue and post-target epochs of 1 s and an epoch of 3 s between cue (C) and target (T). A significant between-group difference takes place after the NoGo target, with increased activity related to the inhibition of movement in TS.

Group $\times$ Task interaction [$F(1,16) = 8.6$, $P < 0.01$]. This interaction is illustrated in Figure 6 and indicated a higher degree of percentage increase of task-related coherence during the post-target versus pre-cue interval for TS patients than control subjects, which reached significance for NoGo trials
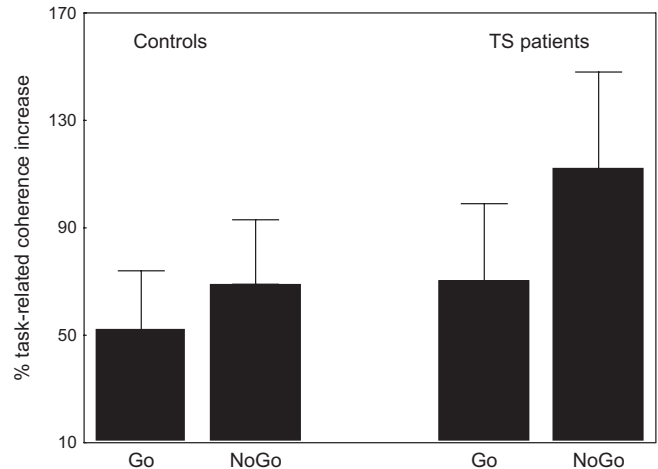

Fig. 6 TS patients have a larger task-related coherence increase in the alpha frequency band than control subjects when performing the Go–NoGo task, which was most evident for NoGo trials (*n* = 9 in each group). The error bars denote the standard deviations from the means.

($P < 0.02$) but not for Go trials. Normalized to the Go activity, the coherence increase for NoGo trials was significant for TS patients ($P < 0.01$; $42 \pm 21\%$) as well as for control subjects ($P < 0.02$; $17 \pm 12\%$). The latter suggests that NoGo trials necessitate an augmented degree of coherence across F3–C3, F4–C4, FCz–C3 and FCz–C4 compared with Go trials, with a more pronounced increase for TS patients than control subjects.

EEG power

The statistics revealed no significant effects ($P > 0.05$). EEG power increased during Go and NoGo trials compared with rest. Expressed as percentage scores, the increases in power during the post-target versus pre-cue interval, averaged across the electrodes F3, C3, F4, C4 and FCz, were $27 \pm 20\%$ for TS patients and $20 \pm 11\%$ for control subjects. Thus, coherence increments were not due to modulations in non-linearly related frequency components (Florian *et al.*, 1998).

Complementary Go–NoGo tasks in control subjects

The Go–NoGo paradigm suggested a role for F3–C3, F4–C4, FCz–C3 and FCz–C4 connectivity in motor inhibition, but did not define whether the increased inter-regional coherence with inhibition was directly related to motor inhibition *per se* or to the increased effort that might be necessary in NoGo trials. We therefore performed two further experiments. The first controlled for the effort required to change behaviour following the NoGo target by comparing EEG coherence between standard NoGo trials and trials in which the subject was asked to move with the opposite hand rather than inhibit the response altogether (RevGo). NoGo trials still involved higher coherence than RevGo trials. In the second we

increased the false alarm rate in NoGo trials by combining these with an acoustic startle phenomenon (NoGoSt). In this way we were able to show that increased coherence in F3–C3, F4–C4, FCz–C3 and FCz–C4 relative to Go trials only occurred in NoGo trials that were successfully inhibited.

Response with the contralateral hand (RevGo)

Behavioural data. The reaction times analysed by means of a paired *t* test (right versus left hand) revealed no effect of side (*P* > 0.05). However, the reaction times slowed down markedly compared with the normal Go trials, which is in line with the contention that stimulus–response incompatibility affects behavioural performance. Mean reaction time across hands was 505 ± 65 ms (versus 350 ± 54 ms for normal Go trials).

EEG coherence. The relative coherence increase from the time of presentation of the imperative signal to the time of the subsequent peak in coherence was analysed by means of a paired *t* test (RevGo versus NoGo trials) and showed a significant effect [$t_8 = 4.3$, $P < 0.01$]. The latter indicated that NoGo trials (0.11 ± 0.03) were associated with a stronger increase in functional connectivity than RevGo trials (0.07 ± 0.02). This result demonstrates that inhibition of a motor response requires a higher degree of coherence in F3–C3, F4–C4, FCz–C3 and FCz–C4 than its production, even when both targets instruct a change in performance. Likewise the mean coherence over the time epoch following the target signal compared with that of the reference interval showed a significant effect of trial type [$t_8 = 2.9$, $P < 0.02$] and was higher for NoGo (69 ± 24%) than RevGo (40 ± 15%) trials.

Acoustic conditioning of the NoGo stimulus

Behavioural data. The reaction times from the unsuccessfully inhibited responses were analysed by means of a paired *t* test (right versus left hand) and revealed no effect of side (*P* > 0.05). However, reaction times were markedly faster compared with those from the normal Go trials. The mean reaction time across hands was 184 ± 21 ms in unsuccessfully inhibited NoGo trials (versus 368 ± 36 ms for normal Go trials, *n* = 4). The percentage of false alarm trials conditioned by an acoustic stimulus was 38 ± 14.

EEG coherence. Figure 7 depicts mean-centred coherence plots for unsuccessfully and successfully inhibited NoGo trials as well as the difference between the two conditions (NoGoU – NoGoS). Marked changes in neural activity occur after the imperative signal in both types of trial. However, two differences in the coherence following the target were evident, and are highlighted where successful NoGo trials have been subtracted from unsuccessful NoGo trials. The coherence increase in unsuccessful NoGo trials was slightly earlier and less sustained than in successful NoGo trials. Hence the peak activity following the target in unsuccessfully
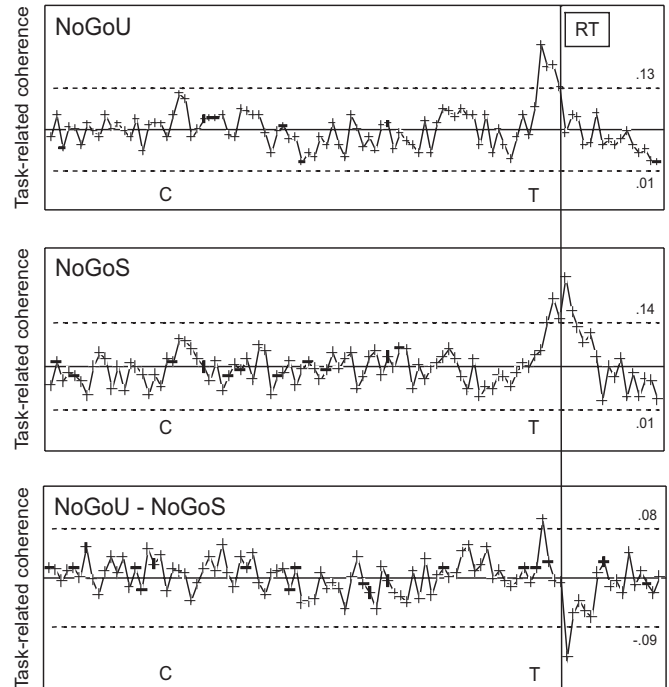

Fig. 7 Task-related mean-centred coherence plots during unsuccessfully inhibited NoGo trials (NoGoU) and successfully inhibited NoGo trials (NoGoS), and the difference between the two (NoGoU – NoGoS) for control subjects (*n* = 4). NoGo targets were conditioned by acoustic startle. Averaged transformed data across cortical connections. The time intervals show 5 s; there were pre-cue and post-target epochs of 1 s and an epoch of 3 s between cue (C) and target (T). Note that reaction time in NoGoU trials is shorter than in Go trials (Fig. 3, upper panel) and that only NoGoS trials have the extra post-target coherence seen in standard (unconditioned) NoGo trials (Fig. 3, middle panel).

inhibited NoGo trials more closely resembled the activity in Go trials in form (Fig. 3, upper panel) than in successfully inhibited trials. Of most relevance to our interpretation of the results in TS, the extra increase in network coherence seen in successfully executed NoGo trials was absent if inhibition failed (NoGoU – NoGoS).

Discussion

We have identified some key inter-regional connections involved in the acute suppression of involuntary tics that are also persistently and adaptively strengthened, as evidenced by increased frontomesial EEG coherence during suppression of voluntary movements in TS patients compared with healthy subjects. The data point to a dynamic circuit involved in normal inhibition that is overactive in TS and which can be further activated acutely in the voluntary suppression of tics.

Cortical networks involved in the inhibition of motor acts in healthy subjects

Regulation of voluntary movement requires not only the preparation and execution of actions but also the ability to

withhold these when necessary. In order to investigate this important function, we studied EEG dynamics during a Go–NoGo task and evaluated those four functional couplings that were most responsive in inhibitory regulation. Task-related coherence in the connections between sensorimotor cortex and prefrontal and midline areas increased during the Go and NoGo trials. This inhibition network was more active in TS patients than healthy subjects during the suppression of voluntary movement. Our findings are consistent with the hypothesis that the process related to the decision not to move is directed from prefrontal cortex (Sasaki and Gemba, 1986; Shibata *et al.*, 1997, 1998), possibly via modulation of the supplementary motor area, SMA (Hoshiyama *et al.*, 1996).

The coherence profiles showed a pronounced peak in activity shortly after the target of a Go or NoGo signal. The peak following Go targets may relate to stimulus evaluation and/or response activation. However, the post-target activity was higher during NoGo than Go trials, indicative of additional information processing during response inhibition. The extra increase in functional coupling following NoGo targets could not simply be ascribed to the change in instruction provided by the NoGo. Thus, the coherence following NoGo events also exceeded that following targets requiring a response with the contralateral hand. In addition, we were able to increase the number of false alarms following NoGo targets by combining the latter with acoustic conditioning and thereby demonstrated that the increased coherence only followed NoGo targets when movement was successfully suppressed. Whether the lack of this extra increase in coherence in unsuccessful NoGo trials was solely responsible for the lack of movement suppression is, however, unclear. Even if this extra coherence had been present in such trials, the significant shortening of the reaction time with an acoustic startle (Valls-Solé *et al.*, 1995) would have meant that many responses preceded the extra coherence in timing. In sum, our results in healthy subjects suggest that response inhibition is associated with increased coherence in a frontomesial network. Such a paradoxical increase in neural activity with incorrect or inhibited responses has also been previously noted in other situations (Gevins *et al.*, 1987; Sasaki *et al.*, 1993; Shibata *et al.*, 1997; Filipovič *et al.*, 2000; Hummel *et al.*, 2002; Yamanaka *et al.*, 2002). In this regard, it is worthwhile stressing that coherence as a measure of functional interaction does not in general discriminate between excitation and inhibition. For example, functional inter-regional coupling may be strengthened following lorazepam (Fingelkurts *et al.*, 2004), a $GABA_{ergic}$ agonist that increases the excitability of inhibitory circuits (Di Lazzaro *et al.*, 2000). Indeed, the increased coherence between sensorimotor cortex and prefrontal and mesial cortex following NoGo targets occurred under circumstances of suppressed motor cortex excitability (Hoshiyama *et al.*, 1996, 1997; Leocani *et al.*, 2000).

The importance of the prefrontal cortex in response inhibition as part of behavioural planning has been widely recognized (Miller, 2000; Fuster, 2001) and is corroborated from lesion, clinical and imaging studies (Watanabe *et al.*, 2002; Konishi *et al.*, 2003). In particular, it is suggested that the prefrontal area regulates the flow of information through multiple modules, tuning the balance between excitatory and inhibitory activity to support the organization of motor activities. So its involvement may be strongly associated with the decision to initiate or suppress a response. In this respect, Sasaki and colleagues showed that stimulation of the prefrontal loci where a NoGo potential could be recorded in monkeys performing a Go–NoGo task cancelled or delayed movement (Sasaki *et al.*, 1989). The involvement of midline regions such as SMA in motor inhibition is supported by the fact that stimulation of SMA can inhibit the initiation of movement or arrest an ongoing movement (Penfield and Welch, 1951; Chauvel *et al.*, 1996). Tight functional coupling between mesial and sensorimotor cortices is suggested by increased coherence between these areas with motor tasks (Ohara *et al.*, 2001), and reduced coupling between primary sensorimotor cortices upon repetitive transcranial magnetic stimulation of mesial motor areas (Serrien *et al.*, 2002*b*). Specifically, Ball and colleagues suggested that SMA triggers the motor act via release of inhibition of primary motor areas (Ball *et al.*, 1999). Taken together, these data suggest that prefrontal cortex and SMA are part of a dynamic system that can lead to the inhibition of motor acts, albeit with the possible involvement of attentional and monitoring requirements.

Cortical networks involved in the inhibition of motor acts in patients with TS

Even though coherence profiles were similar for TS patients and control subjects, a higher degree of functional coupling was found in the patients during the NoGo trials, despite the similar numbers of errors in the two subject groups. Accordingly, we hypothesize that this augmented activity is adaptive in nature, serving to compensate for diminished inhibitory control. The active tic suppression condition demonstrated that coherence in the same frontomesial connections was acutely elevated when voluntary suppression of tics was attempted. Coherence in this network increased over time, paralleling the increasing urge to tic during voluntary suppression. This adaptive strategy might initially compensate for deficits latent in regulatory circuits, which, however, might be comprised when performing in complex settings when behavioural performance is degraded (Serrien *et al.*, 2002*a*). Hence the adaptive ability of these networks might be exceeded in more complex behavioural situations or in more severe disease, leading to more florid tics. Adaptive changes that might preserve behavioural performance in inhibitory control disorders such as TS and attention deficit hyperactivity disorder (ADHD) have been previously noted in the frontal negativities of event-related EEG potentials (Johannes *et al.*, 2001; Smith *et al.*, 2004). The N2 component of the event-related EEG response to NoGo trials, in

particular, has been associated with inhibitory regulation as its amplitude correlates with successful performance in terms of error scores (Falkenstein *et al.*, 1999).

It is widely held that deranged basal ganglia output provides the neural substrate for the generation of tics, likely due to an inappropriate balance of signalling in the pathways involved in planning behaviour (Hallett, 1993). Imaging data have demonstrated that tics and their voluntary suppression implicate a distributed subcortico-cortical network of motor and executive systems (Peterson *et al.*, 1998; Stern *et al.*, 2000). Furthermore activity changes in basal ganglia and thalamus correlate inversely with the severity of tic symptoms (Peterson *et al.*, 1998) and might trigger abnormal activation of primary and secondary motor areas, resulting in simple and complex tics (Mink, 2003). Using TMS, it has been suggested that tics result from a subcortical disorder affecting the motor cortex and/or from impaired cortical inhibition (Ziemann *et al.*, 1997; Gilbert *et al.*, 2004). Event-related potential studies further implicate the frontal cortex in the pathophysiology of disorders that include deficiencies of motor inhibition, such as TS (Johannes *et al.*, 2001) and ADHD (Smith *et al.*, 2004).

It is therefore paradoxical that some of the very cortical areas receiving putatively deranged basal ganglia input in TS are also those that may adaptively interact to compensate for the deficits in this condition. Essentially, this implies that areas that may normally execute motor inhibition with little requirement for cortico-cortical interaction increase their cortico-cortical coupling to compensate for abnormal subcortical input. Thus a more comprehensive network is necessary to achieve the task of motor inhibition. This highlights what may be an important principle in adaptive responses to disease at the systems level, as similarly increased inter-regional connectivity has been reported following stroke (Strens *et al.*, 2004).

Acknowledgements

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