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Movement control of manipulative tasks in patients with Gilles de la Tourette syndrome

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Summary

When a hand-held object is moved, grip and load force are accurately coordinated for establishing grasp stability. In the present work, the question was raised whether patients with Gilles de la Tourette syndrome (TS), who show tic-like movements, are impaired in grip–load force control when executing a manipulative task. To this end, we assessed force regulation during action patterns that required rhythmical unimanual or bimanual (iso-directional/anti-directional) movements. Results showed that the profile of grip–load force ratio was characterized by maxima and minima that were realized at upward and downward hand positions, respectively. TS patients showed increased force ratios during unimanual and bimanual movements, compared with control subjects, indicative of an inaccurate specification of the precision grip. Functional imaging data complemented the behavioural results and revealed that secondary motor areas showed no (or greatly reduced) activation in TS patients when executing the movement tasks as compared with baseline conditions. This indicates that the metabolic level in the secondary motor areas was equal during rest and task performance. At the neuronal level, this observation suggests that these cortical areas were continuously involved in movement preparation. Based on these data, we conclude that the ongoing activation of secondary motor areas may be explained by the TS patients' involuntary urges to move. Accordingly, interference will prevent an accurate planning of voluntary behaviour. Together, these findings reveal modulations in movement organization in patients with TS and exemplify degrading consequences for manual function.

Keywords: precision grip; grasping; grip–load force control; bimanual coordination; functional imaging

Abbreviations: fMRI = functional MRI; SMA = supplementary motor area; SM1 = primary sensorimotor cortex; TS = Gilles de la Tourette syndrome

Introduction

Gilles de la Tourette syndrome (TS) is a disorder characterized by irregular motor and phonic tics that typically appear in childhood. Apart from an inherited genetic vulnerability, other factors such as prenatal and perinatal stressors/insults or bacterial/viral infections may be involved in the expression of TS (Robertson, 2000). Overall, the pathophysiology of TS has been associated with dysfunction of the basal ganglia and related thalamocortical circuits (e.g. Singer, 1997; Bradshaw and Sheppard, 2000). In agreement with this hypothesis, neuroimaging data have revealed that patients with TS have reduced volumes and abnormal asymmetries of caudate, putamen and globus pallidus (Peterson *et al*., 1993; Singer *et al*., 1993; Hyde *et al*., 1995). Anomalies of the frontosubcortical circuits in TS are further underscored by cognitive deficits. In particular, patients with TS have attentional deficiencies and problems in inhibiting unsuitable responses (Georgiou *et al*., 1995*a*; Harris *et al*., 1995; Shucard *et al*., 1997) as well as abnormalities of antisaccade eye movements (Dursun *et al*., 2000).

Even though the basal ganglia-thalamocortical circuits represent an essential network for the control of motor behaviour (e.g. Hallett, 1993; Brooks, 1995; Mink, 1996; Wichmann and DeLong, 1996; Brown and Marsden, 1998), only a few studies of voluntary actions have been reported in TS patients. Whereas the spatiotemporal characteristics of aiming tasks are not impaired (Georgiou *et al*., 1997), evidence for disturbed motor control in TS comes from Sweet *et al*. (1973) who noticed abnormal motor asymmetries during rapid alternating movements. Furthermore, Georgiou *et al*. (1995*b*) examined sequential unimanual movements and

noticed that TS patients are more reliant on external cues than control subjects for executing a motor plan, suggestive of a dysfunctional internal switching mechanism. The latter observation raises the question to what extent complex actions such as bimanual behaviour, which require the combined execution of limb movements, are modified in TS. Due to the involvement of the basal ganglia and associated cortical areas in the processes of forward planning on which coordinated actions rely, it is plausible that relevant performance changes might come about in patients with TS. In this regard, a number of movement disorders such as Parkinson's disease, Huntington's disease and dystonia have been primarily related to basal ganglia pathology and are presumed to result from abnormally modulated subcortical circuitry (Hallett, 1993; Mink, 1996; Wichmann and DeLong, 1996).

In the present study, manipulative regulation of unimanual and bimanual rhythmical tasks was assessed in TS patients compared with control subjects. Previously, it has been observed that grip force (normal to the surface) anticipates load force (tangential to the surface) when manipulating an object. Both forces are part of a coupling constraint that reduces the demands on the control mechanisms because fluctuating load forces can be automatically compensated for by suitable grip force adjustments (Johansson and Westling, 1988; Flanagan and Wing, 1993, 1995; Serrien *et al*., 1999). In view of manipulative behaviour, a well-organized force regulation is important in order to avoid inappropriate grasping and probability of object loss. This implies that there is a functional prerequisite associated with response planning of a manipulative event. The present experimental paradigm allowed: (i) to determine if anticipatory grip–load force coupling during a rhythmical task is disturbed in TS; (ii) to evaluate performance differences between bimanual and unimanual actions; and (iii) to assess disparities when hand-held objects are moved bimanually according to an iso-directional versus anti-directional mode.

The organization of grasping/manipulation depends on distributed neural circuits (Jeannerod, 1996) and imaging studies have shown that a precision grip task involves activation of sensorimotor, premotor, parietal and prefrontal areas (Ehrsson *et al*., 2000) as well as cerebellum and basal ganglia (Kinoshita *et al*., 2000). In order to complement the behavioural study, bimanual motor function was examined through functional MRI (fMRI). The set-up permitted us to establish the neuronal correlates of bimanual rhythmical behaviour and potential modifications in TS patients. Taken together, these experiments are relevant to the understanding of principles for the organization of manual skills and inherent modulations that take place due to the pathology of TS.

Material and methods

Subjects

Nine patients with TS participated in the behavioural study. Assessment was staged according to the Tourette's syndrome global scale (Harcherik *et al*., 1984) and is summarized in Table 1. Eight patients (mean age 28 $\pm$ 10 years) showed no evidence of tics during their execution of the movement patterns. One patient (G.F.), who had motor tics during the voluntary movements, was not included in the group analysis but his data were subjected to a separate analysis. Eight control subjects (mean age 29 $\pm$ 10 years) with no history of neurological pathology also participated in the study. All subjects gave their informed consent and the Komission für medizinisch-ethische Fragen der Medizinischer Fakultät Universität Bern, Schweiz approved the procedures.

Three patients (G.P., R.S. and W.M.) were included in the fMRI study. One patient was not able to attend the testing, and the remaining five patients had to abort the examination because of claustrophobia. Three control subjects were also examined for comparative evaluation.

Behavioural study: experimental set-up, recording and analysis

The test object, which weighed 150 g, consisted of a U-shaped gripper frame (6 $\times$ 4 cm) with two parallel grip surfaces on top of each side (Fig. 1). The grip surfaces had a diameter of 2 cm. At the bottom and centre of the framework was a 13 cm long rod on which a mass of 400 g was added. A ball joint connected the gripper frame with the rod. The test object was instrumented with strain gauges (SPECTRIS AG, Nänikon, Switzerland). Two pairs of strain gauges (HBM, model LY 11–6/120) were used to measure grip force (normal to the surface); this represented the mean of the forces exerted by the fingertips. Load force (tangential to the surface) referred to the sum of the gravitational and inertial forces, and was measured by a strain gauge (HBM, model LY 13–6/120) attached at the top of the rod. Grip and load force were recorded at 400 Hz. Data acquisition and analyses were performed using the SC/ZOOM program (Department of Physiology, Umeå University, Sweden).

Subjects were seated in front of a table on which two test objects were positioned on either side of their body midline. Before the experiment started, pairs of flexible silver-coated PVC-electrodes were applied to the skin over the bellies of the first dorsal interosseous muscles to obtain surface EMG recordings. These were sampled at 3200 Hz, rectified and filtered (100 Hz–2.5 kHz). In the starting position, subjects held the objects with a precision grip between the tips of the index finger and thumb. They were asked to make straight-line cyclical arm movements of 12 cm in amplitude, indicated between two markers, in an upward and a downward direction. The subjects' arms were not supported at the shoulders or elbows, enabling unconstrained action patterns. The movement rate was set at 98 beats/min and paced by a metronome. There were four protocols: (i) unimanual left; (ii) unimanual right; (iii) bimanual according to an iso-directional mode, i.e. the two hand-held objects were moved concurrently in an upward and downward direction; and (iv)

Table 1 *Demographic features of the patients and details of the Tourette's syndrome global scale*

Patient	G.P.*	G.F.	G.M.	K.S.	L.M.	M.L.	Z.M.	W.M.*	R.S.*
Age/gender	24/M	44/M	25/M	27/M	23/M	26/M	51/F	32/M	16/M
Age at onset of disease (years)	6	12	11	7	6	10	11	6	5
Duration of disease till diagnosis (years)	15	15	1	20	17	2	37	15	7
Medication	None	Haloperidol	None	Haloperidol	Olanzapine	Risperidone	Bromazepam	None	None
Tourette's syndrome global scale									
Motor symptoms									
(a) Simple	4	6	12	4	16	8	6	6	16
(b) Complex	2	3	4	1	8	5	0	3	8
(1) Total motor score [(a + b)/2]	3	4.5	8	2.5	12	6.5	3	4.5	12
Phonic symptoms									
(c) Simple	1	2	4	1	16	6	8	6	16
(d) Complex	0	3	6	1	6	4	0	3	6
(2) Total phonic score [(c + d)/2]	0.5	2.5	5	1	11	5	4	4.5	11
Social functioning									
(e) Behaviour	10	15	20	10	15	20	10	15	20
(f) Motor restlessness	5	10	15	10	15	10	5	5	15
(g) School/learning problems	–	–	–	–	–	–	–	–	20
(h) Work/occupation problems	10	25	20	5	5	20	5	25	-
(3) Total social score [(e + f + g or h) × 2/3]	16.7	33.3	36.7	16.7	23.3	33.3	13.3	33.3	36.7
Global score (1 + 2 + 3)	20.2	40.3	49.7	20.2	46.3	44.8	20.3	42.3	59.7

M = male; F = female. *Patients were also involved in the fMRI experiment.

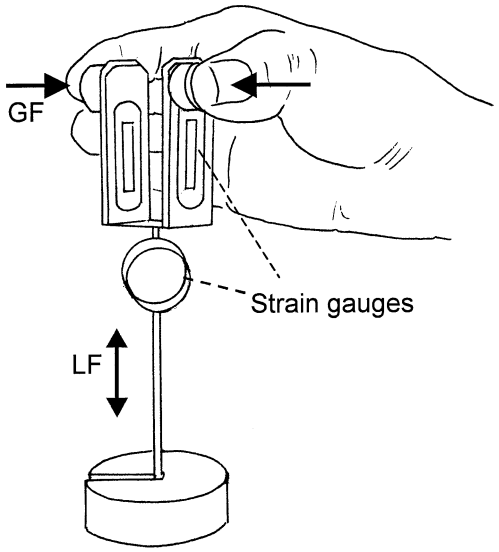

Fig. 1 Illustration of a test object held in a precision grip. Grip force (GF) and load force (LF) are oriented in a horizontal and vertical direction to the object's surface, respectively. Subjects were required to make rhythmical upward/downward movements in the different performance conditions.

bimanual according to an anti-directional mode, i.e. one hand-held object was moved in an upward direction while the other hand-held object was moved simultaneously in a downward direction. Each protocol consisted of five trials which each lasted 10 s. After each trial, there was a small break to avoid fatigue.

In separate trials, the slip ratio was determined for each hand. During these trials ($n = 3$), the object was raised a few cm above the table and the subjects were asked to slowly release the thumb and index finger until the object was dropped. The slip point was set as the initial detectable downward change in load force. This measurement was used to establish the safety margin that represents the difference between the slip ratio, i.e. the minimum value determined by the friction between skin and object, and the grip–load force ratio employed by the subject (Johansson and Westling, 1984). The slip ratio was analysed in a 2 × 2 (group × hand) ANOVA (analysis of variance) with repeated measures on the last factor. The first factor indicated the TS patients versus control subjects, whereas the second factor represented the preferred versus non-preferred hand. No significant differences were observed, $P > 0.05$. The mean values were 0.92 ± 0.10 for TS patients and 0.86 ± 0.12 for control subjects.

To investigate force regulation in the unimanual and bimanual tasks, the grip–load force ratio was assessed. This variable represents a load-independent index that enables us to evaluate the scaling of both forces across the movement cycle. In this respect, the minimum and maximum values of the grip–load force ratio were determined (see Fig. 2). These scores were analysed in a 2 × 2 × 3 × 2 (group × ratio position × condition × hand) ANOVA with repeated measures on the last three factors. The first factor indicated the TS patients and control subjects, whereas the second factor represented the minimum and maximum grip–load force ratio. The third factor referred to the unimanual, bimanual iso-directional and bimanual anti-directional con-

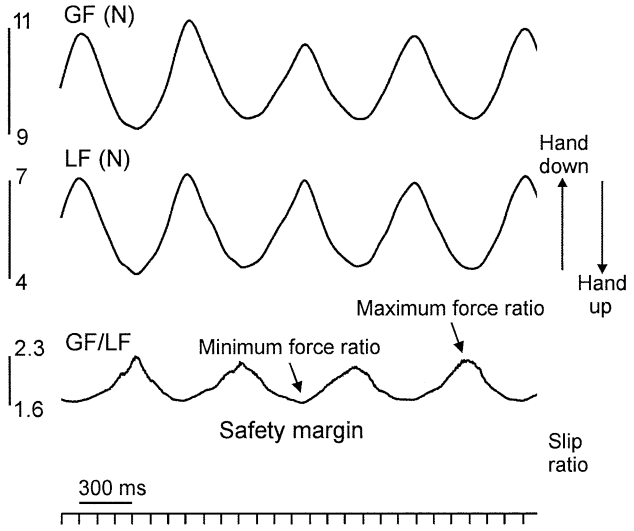

Fig. 2 Grip force (GF), load force (LF) and grip–load force ratio (GF/LF) profiles for rhythmically moving a hand-held object in the sagittal plane. The arrows indicate downward and upward motion of the hand. The safety margin represents the difference between the slip ratio, i.e. the minimum value established by the friction between skin and object, and the grip–load force ratio adopted by the subject.

ditions, whereas the fourth factor specified the preferred and non-preferred hand. An additional analysis was conducted for the load force peaks in order to ensure that comparable modulations in loads occurred for both groups during all performance conditions. The values were analysed in a $2 \times 2 \times 3 \times 2$ (group $\times$ peak position $\times$ condition $\times$ hand) ANOVA with repeated measures on the last three factors. The first factor indicated patients and controls, whereas the second factor represented the minimum and maximum load force peaks. The third factor referred to the different performance conditions and the fourth factor specified the hands.

fMRI study: experimental set-up, recording and analysis

The fMRI tests were conducted on a 1.5 T clinical whole body scanner (Magnetom Vision; Siemens, Erlangen, Germany) using the standard circular polarized head coil. In addition to the lateral head pads, a U-shaped dental plate (similar to a bite bar) was used to restrain head motion. Blood oxygenation level-dependent data was acquired using an EPI (echo planar imaging) sequence with an echo time of 82 ms, a repetition time of 6 s, a 128 $\times$ 128 matrix, 30 slices and 136 whole brain measurements, resulting in a spatial/temporal resolution of 1.56 $\times$ 1.56 $\times$ 4 mm $\times$ 6 s.

During the baseline conditions (rest), subjects grasped a 330 ml plastic bottle filled with water (350 g) between the thumb and the other fingers of each hand in an axial direction. The objects were held in a stable position and rested on the subjects' legs. During the motor tasks, the bottles were lifted vertically 10 cm and rhythmically moved ~30° in the sagittal plane (movement rate ~60 beats/min), according to an iso-directional or anti-directional mode. Even though this type of assignment deviated to some extent from that examined in the behavioural study, an equivalent regulation of the grasping synergy is expected due to the tight coupling between grip and load force during object transportation, independent of the particular grip or mode of manipulation (Flanagan and Tresilian, 1994). Two separate series with 68 whole brain measurements each were acquired. A first series consisted of consecutive runs of iso-directional, anti-directional and baseline tasks (each lasting 24 s), whereas the order of alteration was reversed in the second series (i.e. anti-directional, iso-directional, baseline) to avoid systemic errors. This design was originally created to compare iso-directional and anti-directional movements. However, due to the limited number of subjects, this issue will not be addressed in the Results section.

Evaluation of the fMRI data was made on a Sun workstation (Sun Microsystem, Palo Alto, Calif., USA) using purpose-written software (Nirkko *et al*., 2001). In short, *Z*-scores for the comparison of anti-directional versus baseline conditions were calculated from motion-corrected data. Clusters including *Z*-scores above 5.5 (corresponding to $P < 0.01$ with Bonferroni correction at the pixel level) and a minimal size of 15 pixels were colour-coded and overlaid onto the original EPI images. Since only three TS patients were able to participate in the examination, patients and controls were compared on the basis of the individual activation maps.

Results

Dynamic association of grip and load force during a cyclical manipulative task

Figure 2 shows profiles of grip force, load force and grip–load force ratio when rhythmically moving a hand-held object in the sagittal plane. It can be noticed that grip and load force are firmly coupled. However, the grip–load force ratio is not constant throughout the movement cycles, but follows a consistent pattern made up of maxima and minima. Maxima of grip–load force ratio take place at load force minima when the loads of weight and inertia are subtractive and happen at the higher reversal positions (hand upward). Conversely, minima of grip–load force ratio are attained at load force maxima when the loads of weight and inertia are additive, and occur at the lower reversal positions (hand downward). This denotes that regulation of the grasping synergy depends on movement direction during vertically oriented actions due to the changing involvement of the load components.

Grip–load force regulation in TS patients compared with control subjects

The analysis of the grip–load force ratio revealed a significant main effect of group [$F(1,14) = 36.9$, $P < 0.01$], ratio position

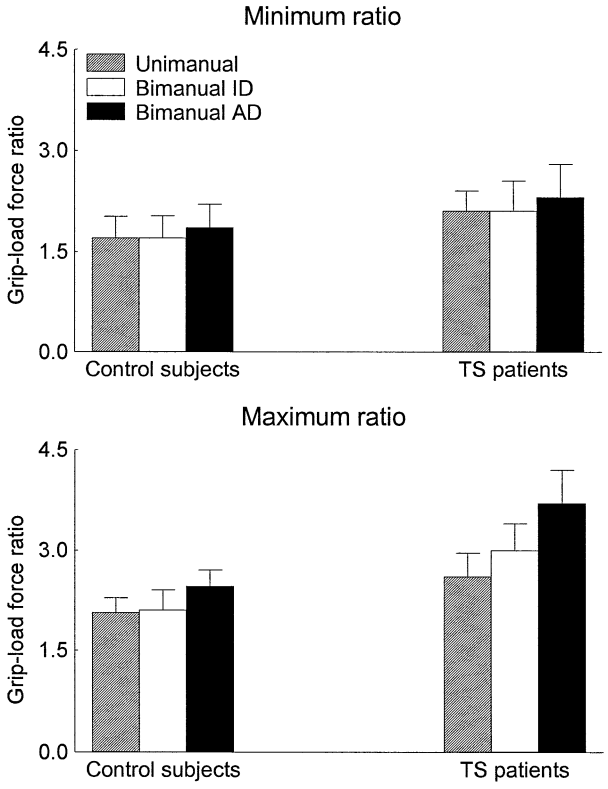

Fig. 3 Minimum and maximum grip–load force ratios for control subjects and TS patients when performing unimanual and bimanual iso-directional (ID) and anti-directional (AD) patterns. The error bars indicate the standard deviations from the means.

[$F(1,14) = 47.8$, $P < 0.01$] and condition [$F(2,28) = 11.2$, $P < 0.01$]. The interactions: group × ratio position [$F(1,14) = 5.0$, $P < 0.05$], ratio position × condition [$F(2,28) = 18.5$, $P < 0.01$] and group × ratio position × condition [$F(2,28) = 5.9$, $P < 0.01$] were also significant. Figure 3 shows that minimum force ratio was superior in TS patients compared with control subjects, but no additional differences were observed across the various performance conditions. In addition, Fig. 3 illustrates that the maximum force ratio increased for TS patients compared with control subjects. Furthermore, maximum force ratio of anti-directional movements was higher than that of iso-directional and unimanual movements for control subjects ($P < 0.01$ for both), whereas it diverged across the different manipulative tasks for TS patients ($P < 0.03$ for all).

The analysis of the load force peaks identified a significant main effect of position [$F(1,14) = 184.6$, $P < 0.01$], denoting that maximum load force (mean = 6.1 N) was higher than minimum load force (mean = 2.1 N). No other effects reached the level of significance, $P > 0.05$. The fact that no group effect was observed signifies that the generated load forces were similar in patients and controls, and implies that the observed changes in grip–load force ratios in TS were due to modifications in grip force scaling. Mean maximum and minimum values were 6.0 ± 1.1 N and 2.1 ± 0.7 N for TS patients and 6.2 ± 0.8 N and 2.2 ± 0.5 N for control subjects.

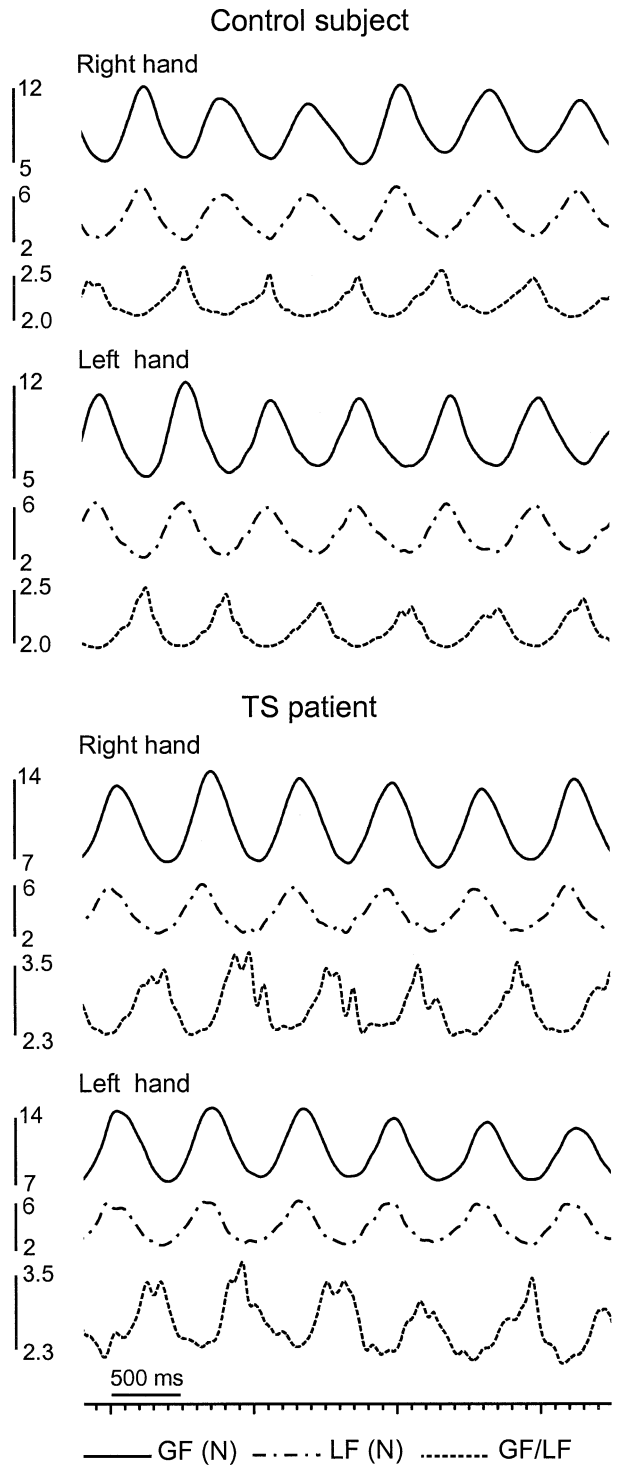

Fig. 4 Grip force (GF), load force (LF) and grip–load force ratio (GF/LF) profiles of the anti-directional mode for a representative control subject and TS patient. Single trial.

Figure 4 further demonstrates the alterations of grip–load force control that arise due to the pathology of TS. Figure 4 exemplifies grip force, load force and grip–load force ratio for a control subject and a TS patient when executing the anti-directional mode. It can be noticed that the grip–load force

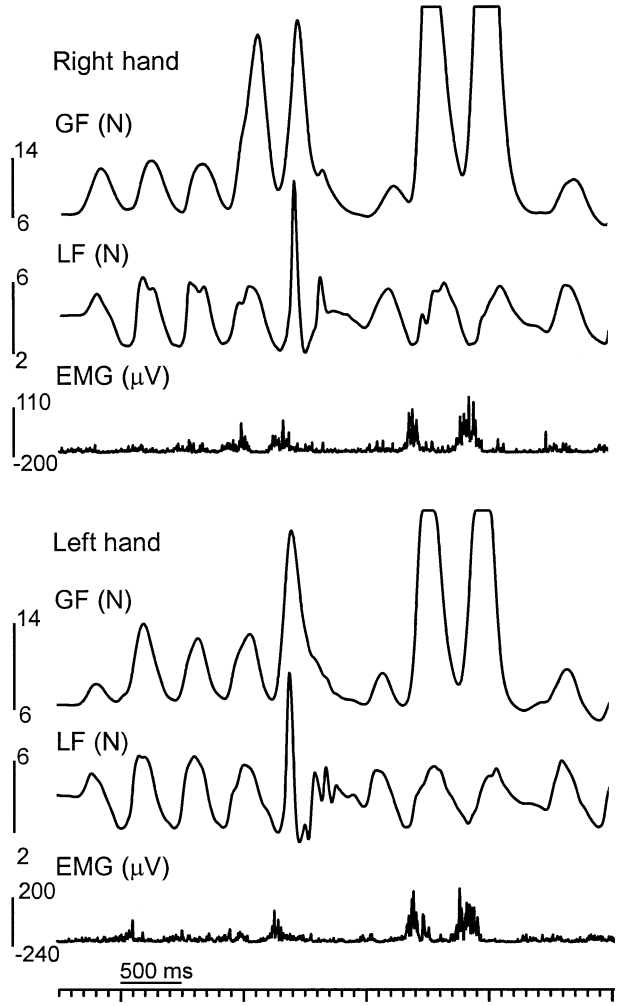

Fig. 5 Motor tics generated by Patient G.F. during the iso-directional mode. It can be observed that the patient experienced various tics that were accompanied by strong force peaks (and sometimes cut-off by the amplifier). Three different types of motor tics can be noticed: (i) a unilateral grip force tic during which an increase occurs in grip force of the right hand; (ii) a bilateral grip–load force tic during which an augmentation is generated in grip and load force of the right and left hand; and (iii) a bilateral grip force tic during which an increase is produced in grip force of the right and left hand.

ratio profile is depicted by maxima and minima which take place in a reciprocal manner. However, the values are increased for the patient compared with the control subject, in particular for the maximum force ratio. Also, the pattern of the grip–load force ratio is less smooth and is characterized by irregular features for the TS patient, illustrating the inaccurate force specifications.

Grip–load force control during motor tics

Whereas eight patients did not show motor tics during the actual task execution (although present in the pauses between trials), one patient experienced them while producing the rhythmical unimanual and bimanual assignments. Figure 5 illustrates the patient's performance during the bimanual iso-directional mode. Three different types of motor tics can be noticed: (i) a unilateral grip force tic during which a phasic increase takes place in grip force, but not in load force of the right hand; (ii) a bilateral grip–load force tic during which a phasic increase is generated in the grip and load force of the right and left hand; and (iii) a bilateral grip force tic during which a phasic increase is produced in the grip force of the right and left hand. When a motor tic involved a change in load force, it was produced in the direction of movement. All types of motor tics resulted in modified force outputs, which were variable in magnitude, but occurred at the expected timing of the rhythmical movements. In addition, EMG recordings taken at the first dorsal interosseous muscles made it possible to measure the synchronization between the bursts that triggered the motor tics in the bimanual conditions. The interlimb difference was small and the delay involved 15 ± 4 ms, with a consistent lead of the right hand. Furthermore, the mean duration of the EMG bursts was 205 ± 77 ms across conditions.

Nevertheless, compared with the other TS patients, this patient did not overscale his force ratios throughout the movement sections that were not disturbed by motor tics. For example, the mean maximum force ratios across hands before the occurrence of tics were: 2.6, 3.0 and 3.9 for unimanual, iso-directional and anti-directional movements, respectively. These findings suggest that motor tics are controlled on their incidence and do not induce an overall modulation in force control throughout the dynamically executed activity. This is in agreement with data from a single case study during a static holding task (Flanagan *et al*., 1999). The fact that force ratios were not increased on a continuous basis is probably due to the variable and/or irregular characteristics of the motor tics.

fMRI activation patterns: the comparison of anti-directional versus baseline conditions

The individual fMRI activation maps for the comparison of anti-directional versus baseline conditions are illustrated in Fig. 6. In control subjects, the comparison yielded a bilateral activation pattern: primary sensorimotor cortex (SM1, adjacent to the central sulcus, corresponding to Brodmann areas 4 and 3, 2, 1), premotor cortex (adjacent to precentral sulcus) posterior parietal cortex (adjacent to postcentral sulcus), supplementary motor area (SMA, on the mesial frontal surface), and anterior cerebellum. In TS patients, only the primary areas (bilateral SM1 and cerebellum) were significantly activated. In contrast, no (or limited) activation in the secondary areas (premotor cortex, posterior parietal cortex and SMA) was evident at the same threshold. Activation in the basal ganglia and thalamus was also reduced in patients compared with controls. The latter observation is consistent with the presumed involvement of these structures in the

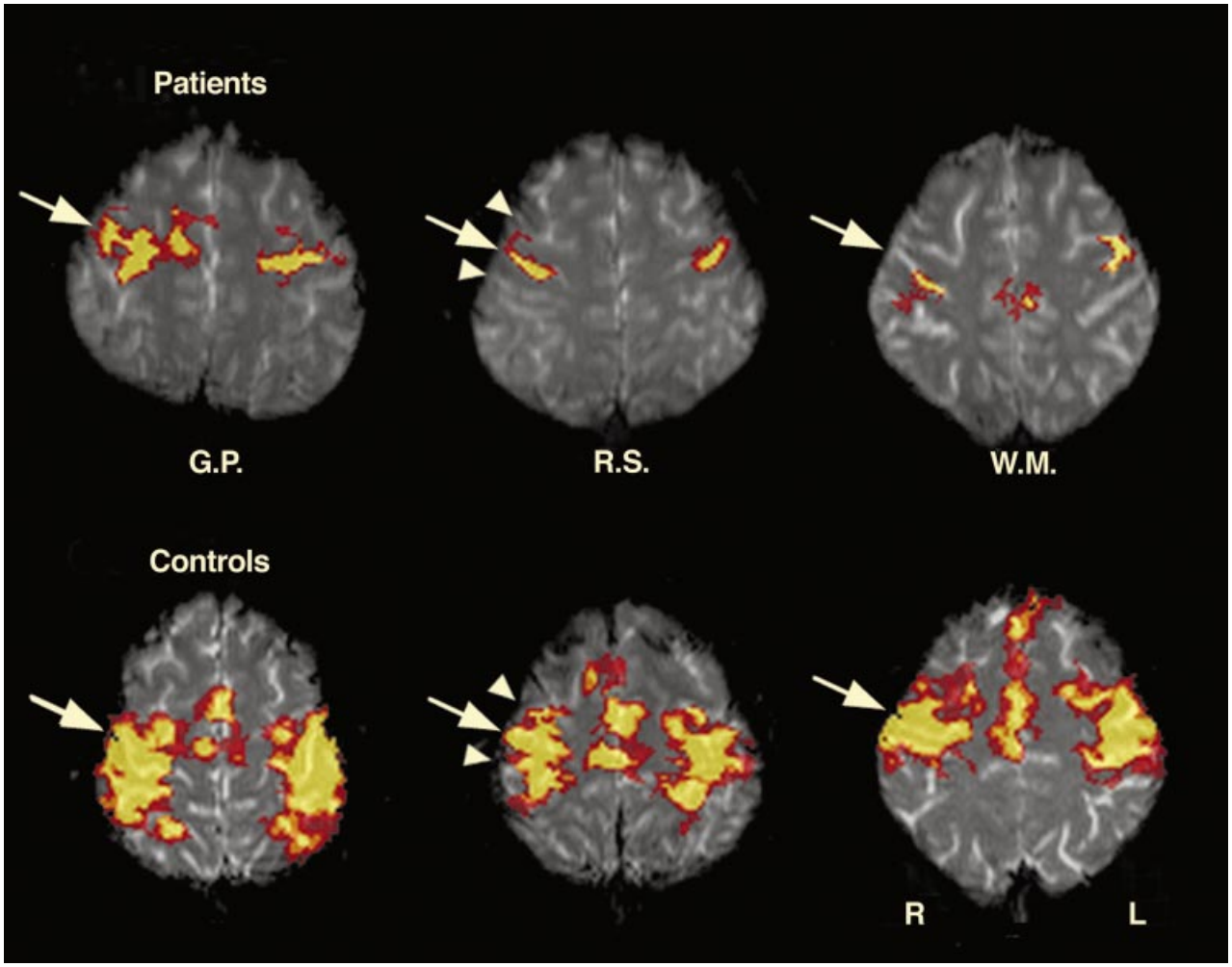

Fig. 6 Individual fMRI activation maps during anti-directional versus baseline conditions of three control subjects and three TS patients (G.P., R.S. and W.M.). Note activation of SM1 in both groups, but no (or limited) activation of secondary motor areas in the patients. The arrows denote the central sulcus (with SM1 activation alongside) and the arrowheads specify the precentral and postcentral sulcus.

disease. Similar activation maps were observed for the iso-directional mode.

Discussion

Studies focusing on transmitter systems and neuroimaging data (Singer *et al*., 1982; Haber *et al*., 1986; Peterson *et al*., 1993; Singer *et al*., 1993; Hyde *et al*., 1995; Eidelberg *et al*., 1997) have introduced the hypothesis that the basal ganglia (as part of a distributed network) are involved in the pathogenesis of TS. In particular, dysfunction exists in the frontostriatal system, which is implicated in a wide range of perceptual–motor processes and responsible for adaptive responses during goal-directed actions. In view of the present context, the integrity of the basal ganglia is important for an accurate specification of the grasping forces when manipulating a hand-held object. Evidence for the latter has been provided through performance changes in movement disorders such as Parkinson's disease, Huntington's disease and writer's cramp (Odergren *et al*., 1996; Fellows *et al*., 1998; Gordon *et al*., 2000; Serrien *et al*., 2000, 2001; Schwarz *et al*., 2001) and through a strong correlation between lesions of the basal ganglia and a poorly developed grip–load force synergy (Forssberg *et al*., 1999). In order to investigate further the consequences of basal ganglia dysfunction on manipulative control, the present work included behavioural and functional imaging experiments in which TS patients and control subjects performed manual tasks with different degrees of complexity.

Regulation of grasping forces during a rhythmical task

When a grasped hand-held object is rhythmically moved in the sagittal plane, the grip–load force ratio tracks a consistent profile of maxima and minima throughout the movement cycles. Whereas the maxima of grip–load force ratio are attained at load force minima when the hand reaches the

upward position, the minima of grip–load force ratio are realized at load force maxima when the hand arrives at the downward position. The transient increase of grip force when the hand moves upward can be viewed as a strategy to avoid slip/loss of the grasped object given that the load force is gradually decreasing and becoming small, particularly in view of changing movement direction at the upper turning point. Conversely, moving the hand downward permits a tight grip–load force association, resulting in a minimum force ratio which represents a baseline across movement cycles (Flanagan and Wing, 1995; Serrien and Wiesendanger, 2001). The present data revealed that TS patients overscaled their motor output during unimanual and bimanual conditions compared with control subjects. This resulted in increased force ratios to maintain a steady grasp and signifies that the patients had difficulty in precisely adapting their grip force in relation to the continuously fluctuating load force.

In the control subjects, maximum grip–load force ratio did not differ between unimanual and bimanual iso-directional patterns. However, an increased force ratio was noted for anti-directional compared with iso-directional movements. This finding can be associated with the divergent load components for both hands, imposing augmented processing and monitoring. TS patients had more problems in organizing bimanual compared with unimanual patterns; this effect was more pronounced for anti-directional than for iso-directional movements. The distinct increase in the maximum grip–load force ratio in the anti-directional mode suggests that rescaling occurred. This is likely to be related to the simultaneous planning of dissimilar force responses. Overall, these data denote an inaccurate specification of the precision grip due to TS pathology that affects the organization of object manipulation. An overscaling of the grasping forces in TS patients implies a reduced sensitivity of the manual system to changes in load force as well as a diminished economy of effort for performing a manipulative task.

An increased grip force has previously been noted in hyperkinetic disorders of the basal ganglia such as Huntington's disease and writer's cramp (Odergren *et al*., 1996; Gordon *et al*., 2000; Serrien *et al*., 2000, 2001; Schwarz *et al*., 2001). This finding has primarily been interpreted as a consequence of a (sensorimotor) compensatory mechanism in order to prevent the manipulated object from slipping. In the present study, the augmented grip force observed in the TS patients might be more directly related to inappropriate settings of the grasping synergy. In particular, it is hypothesized that the organization of the manipulative actions is compromised due to the patients' premonitory urges to move. Had a compensatory strategy been responsible for the modified grip force regulation, then the TS patient who showed tics during the execution of the rhythmical patterns would have adapted his behaviour throughout task performance. This was, however, not the case. Therefore, we contend that the parameterization of the grasping parameters is dysregulated in TS. However, it is worthwhile to add that, even though basal ganglia pathologies with and without structural damage are clinically considerably different and comprise dissimilar functional abnormalities, certain behavioural measurements may reveal a similar outcome due to a general subcortical dysfunction leading to a trans-thalamic impairment of cortical planning and executive areas.

fMRI activation patterns

A deficient inhibitory control or abnormally high levels of neuronal drive in the circuits connecting the basal ganglia and associated cortical areas are likely to be involved in tic disorders (Greenberg *et al*., 2000; Mink, 2001). Accordingly, unwanted behaviour needs to be suppressed or it will be released inappropriately. The results of the fMRI experiment revealed that secondary motor areas showed no (or greatly reduced) activation in the TS patients during execution of the rhythmical tasks compared with baseline conditions. This suggests that these cortical regions were already active during rest, which pre-empted a significant difference when compared with movement. As secondary areas are implicated in higher-order control (Passingham, 1993), an increased activation during baseline conditions in TS patients is likely to be due to their premonitory urges. This ensures an outcome similar to a continuous preparation of motor acts. The latter fits in with the observation that secondary motor areas are activated during the urge to scratch (Hsieh *et al*., 1994). In addition, electrical stimulation of the SMA can elicit the desire to perform a movement or the expectation that an action is going to occur in the absence of overt motor activity (Fried *et al*., 1991).

This viewpoint is also in line with previous work showing that preparation for action is closely linked with motor imagery provided that similar regions are activated (Decety *et al*., 1994; Stephan *et al*., 1995). Thus, motor preparation, imagery and premonitory urges may all be an expression of a common phenomenon in terms of an activation map involving secondary areas. It also suggests that the dynamic patterning of these events underlies neuronal processes that are part of a spectrum for action planning, whether or not under volitional control. Based on these data, we suggest that the organization of voluntary movement is hampered in TS due to a simultaneous occupation of the same cortical areas due to involuntary urges. Accordingly, interference will prevent an accurate planning of movement parameters and synergies, as evidenced in our behavioural data. Alternatively, it is possible that the secondary motor areas experienced an increased inhibitory drive due to the suppression of tics. However, this inhibitory process, which is coupled with impulse control, possibly contributed to the increased metabolic response during baseline conditions and therefore reduced activation when compared with motor tasks.

In contrast with the secondary areas, normal activation of the SM1 and cerebellum was noted in the TS patients. This finding is consistent with the point of view that these regions are directly linked with task execution, given that the

generated rhythmical patterns involved more motor accomplishment than the tics. It also implies that the patients exploited the settings of the motor assignments to integrate their premonitory sensations. This indicates that any motor behaviour, whether tics or voluntary actions, may relieve the inner tension these patients experience. Also, we noticed that the TS patients had reduced tic-like movements in the scanner during execution of the rhythmical tasks compared with rest. This supports the notion that distraction and concentration tend to decrease tics (Tolosa and Jankovic, 1993).

The present fMRI results are in contrast with the findings of Biswal *et al*. (1998), who showed increased activation in the SM1 and SMA in patients with TS when performing bimanual finger tapping movements compared with control subjects. The reasons for this contradiction might be related to technical discrepancies besides a difference in the tasks. First, Biswal *et al*. (1998) employed low-resolution acquisition and only one slice to measure differences in the area (not volume) of activation. Secondly, they appeared to have used dissimilar methods of evaluation for patients and controls, as evidenced in their Figure 1 (i.e. smooth interpolation for which thresholding reduces activation areas in controls versus raw square pixels in patients). In view of our results, it is noteworthy to emphasize that we obtained similar activation in the SM1 in both groups—an outcome that provides a direct evaluation regarding the comparable quality of experimental data in patients and controls.

Motor tics in TS

Tics ranging from simple to complex patterns are a defining clinical characteristic of TS (Jankovic, 1997). Using transcranial magnetic stimulation, Ziemann *et al*. (1997) concluded that tics in TS result from a subcortical disorder affecting the motor cortex and/or from an impaired inhibition at the level of the motor cortex. Similarly, imaging data have demonstrated that tics implicate a network of motor, paralimbic, premotor and executive frontosubcortical systems (Stern *et al*., 2000), whereas voluntary tic suppression involves significant changes in the activity of basal ganglia, thalamus and associated cortical areas (Peterson *et al*., 1998).

Even though the absence of a pre-movement potential has suggested that motor tics are not generated through typical pathways (Obeso *et al*., 1981; but see Karp *et al*., 1996), evidence exists that voluntary aspects are involved. For example, patients with TS are able to suppress their tics for brief periods and are sometimes able to trigger them voluntarily to relieve involuntary urges. In our behavioural experiment, we recorded data from one patient who had motor tics during the actual performance of the rhythmical tasks. These tics appeared to be incorporated in the voluntary movements, which is in agreement with the interpretation of our fMRI results. Furthermore, the patient's bilaterally induced motor tics in the bimanual conditions included a time lag that corresponded to a fast callosal pathway, indicating that the established interlimb coupling mechanisms were exploited.

In conclusion, there has been little experimental work for unveiling changes of movement organization due to TS. In this respect, the aim of the present behavioural study was to quantify the grasping forces that are employed during manipulative tasks using the precision grip. Results indicated that TS patients showed a modified grip–load force regulation when moving hand-held objects compared with control subjects. fMRI data complemented the behavioural observations and depicted secondary motor areas with minimal metabolic responses during movement tasks compared with baseline conditions in TS patients. Based on these findings, it is suggested that these cortical areas were continuously involved in movement preparation due to premonitory urges. Accordingly, interference will result in inaccurate response specifications of manipulative actions. Together, these findings disclose modulations in movement planning in patients with TS and illustrate a degrading effect on manual function.

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