

Altered modulation of intracortical excitability during movement preparation in Gilles de la Tourette syndrome

K.-F. Heise,¹ B. Steven,¹ G. Liuzzi,¹ G. Thomalla,¹ M. Jonas,¹ K. Müller-Vahl,² P. Sauseng,¹ A. Münchau,¹ C. Gerloff¹ and F. C. Hummel¹

1 Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

2 Hanover Medical School, Clinic of Psychiatry, Socialpsychiatry & Psychotherapy, Hanover, Germany

Correspondence to: Friedhelm C. Hummel, MD,
BINS Laboratory,
Department of Neurology,
University Medical Center Hamburg-Eppendorf,
20246 Hamburg,
Germany
E-mail: f.hummel@uke.uni-hamburg.de

Gilles de la Tourette syndrome is a neuropsychiatric disorder in which cortical disinhibition has been proposed as a pathophysiological mechanism involved in the generation of tics. Tics are typically reduced during task performance and concentration. How this task-dependent reduction of motor symptoms is represented in the brain is not yet understood. The aim of the current research was to study motorcortical excitability at rest and during the preparation of a simple motor task. Transcranial magnetic stimulation was used to examine corticospinal excitability, short-interval intracortical inhibition and intracortical facilitation in a group of 11 patients with Gilles de la Tourette syndrome and age-matched healthy controls. Parameters of cortical excitability were evaluated at rest and at six points in time during the preparation of a simple finger movement. Patients with Gilles de la Tourette syndrome displayed significantly reduced short-interval intracortical inhibition at rest, while no differences were apparent for unconditioned motor evoked potential or intracortical facilitation. During the premovement phase, significant differences between groups were seen for single pulse motor evoked potential amplitudes and short-interval intracortical inhibition. Short-interval intracortical inhibition was reduced in the early phase of movement preparation (similar to rest) followed by a transition towards more inhibition. Subsequently modulation of short-interval intracortical inhibition was comparable to controls, while corticospinal recruitment was reduced in later phases of movement preparation. The present data support the hypothesis of motorcortical disinhibition in Gilles de la Tourette syndrome at rest. During performance of a motor task, patients start from an abnormally disinhibited level of short-interval intracortical inhibition early during movement preparation with subsequent modulation of inhibitory activity similar to healthy controls. We hypothesize that while at rest, abnormal subcortical inputs from aberrant striato-thalamic afferents target the motor cortex, during motor performance, motor cortical excitability most likely underlies top-down control from higher motor areas and prefrontal cortex, which override these abnormal subcortical inputs to guarantee adequate behavioural performance.

Keywords: Gilles de la Tourette syndrome; intracortical inhibition; movement preparation; transcranial magnetic stimulation; motor control

Abbreviations: DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; MEP= motor evoked potential; RM-ANOVA= repeated measure analyses of variance; TMS= transcranial magnetic stimulation; SCID-1= structured clinical interview for DSM-IV Axis I disorders; SICI= short-interval intracortical inhibition

Introduction

Gilles de la Tourette syndrome is a neurodevelopmental disorder characterized by motor and phonic tics. Symptom onset is typically between 3 and 8 years of age (overview in Robertson, 2000; Leckman, 2002). Of all patients, ~10% are thought to present with a 'pure' Gilles de la Tourette syndrome without relevant comorbidities (Freeman *et al.*, 2000), in particular attention deficit hyperactivity disorder and obsessive compulsive disorder. Different subsets of the cortico-striatal-thalamo-cortical neural circuitry have been suggested as possible origins of the disturbance leading to the expression of Gilles de la Tourette syndrome (Graybiel and Canales, 2001). Direct and indirect evidence for the location of dysfunction within cortico-striatal-thalamo-cortical networks has been derived from studies of habit formation (Jog *et al.*, 1999; Orth *et al.*, 2005; Sukhodolsky *et al.*, 2007), lesion studies (Vandewalle *et al.*, 1999), application of chemical or electrical stimulation (Delfs and Kelley, 1990; Delfs *et al.*, 1990; Graybiel and Canales, 2001), structural and functional imaging studies (Biswal and Ulmer, 1999; Peterson *et al.*, 1998, 2001; Serrien *et al.*, 2002; Plessen *et al.*, 2004; Orth *et al.*, 2005; Thomalla *et al.*, 2009), and studies of saccadic eye movements (Straube *et al.*, 1997; Farber *et al.*, 1999; Dursun *et al.*, 2000).

Some lines of evidence suggest that GABA-mediated systems are involved in the dysfunctional mechanisms at the cortical as well as subcortical level. This dysfunction is thought to lead to disturbance in sensorimotor gating and motor function (Swerdlow *et al.*, 2001; Leckman *et al.*, 2006). Post-mortem analysis of basal ganglia tissue identified deviant distribution and structure of GABAergic inhibitory neurons in patients with Gilles de la Tourette syndrome, suggesting marked functional alterations (Kalanithi *et al.*, 2005). At the level of the primary motor cortex, short-interval intracortical inhibition (SICI)—associated with neural activity in GABA-mediated intracortical circuits and measured with double-pulse transcranial magnetic stimulation (TMS)—has been shown to be decreased in adults with Gilles de la Tourette syndrome at rest (Ziemann *et al.*, 1997; Gilbert *et al.*, 2004; Orth *et al.*, 2005, 2008). Furthermore, SICI has also been found to be decreased in children with Gilles de la Tourette syndrome at rest; the extent of deficient SICI was positively associated with the severity of symptoms and the concomitant attention deficit hyperactivity disorder (Gilbert *et al.*, 2004).

The ability to produce adequate behavioural responses to internal or environmental demands and to adapt behaviour continuously according to these changing conditions is an essential requirement, e.g. for functioning in everyday life and for social acceptance. Current data imply that abnormalities within the cortical aspects of the cortico-striatal-thalamo-cortical circuitry possibly lead to deficits in behavioural control, particularly those involving frontal cortical functions (Stern *et al.*, 2008). However, there are also experimental findings showing that adolescent patients with Gilles de la Tourette syndrome present with

enhanced cognitive control compared to age-matched healthy controls (Mueller *et al.*, 2006; Jackson *et al.*, 2007).

So far, emerging evidence results largely from TMS measurements at rest (Ziemann *et al.*, 1997; Orth *et al.*, 2005), but unlike patients with other movement disorders, deficits in controlling voluntary motor tasks have rarely been studied in patients with Gilles de la Tourette syndrome (Sweet *et al.*, 1973; Georgiou *et al.*, 1995; Serrien *et al.*, 2002). A typical clinical observation is that tics mainly occur at rest (the idling state), and are less frequent or even absent during task performance. Therefore, analysing movement-related aspects of motor cortex physiology in Gilles de la Tourette syndrome patients is a matter of particular interest. Here, we investigated how motor cortex excitability, in particular SICI, is being modulated during preparation of a voluntary movement in patients with Gilles de la Tourette syndrome.

Methods

Subjects

Modulation of cortical excitability was studied in a sample of 11 Gilles de la Tourette syndrome patients (36.82 ± 9.40 SD, range 24–55, two females), and 11 age- and sex-matched healthy persons (37.45 ± 9.21 SD, range 26–52) who volunteered as control group. Patients were recruited from two outpatient clinics specializing in Gilles de la Tourette syndrome (Department of Neurology, University Medical Center Hamburg-Eppendorf and Department of Clinical Psychiatry and Psychotherapy, Hanover Medical School). The mean symptom onset age in Gilles de la Tourette syndrome patients was 7.5 ± 0.8 years and mean disease duration 26.8 ± 2.3 years. Six patients were medication naïve; the others had stopped medical treatment weeks to years prior to participation in the study.

All patients underwent a detailed clinical neurological and psychiatric examination by a physician experienced in the assessment of Gilles de la Tourette syndrome, attention deficit hyperactivity disorder and obsessive compulsive disorder. Control subjects were only included if they did not have any history of neurological or psychiatric diseases or signs of neurological and psychiatric disturbance. For patients, lifetime clinical information was systematically collected using standardized clinical assessment and a structured interview adapted from Robertson *et al.* (1996). Gilles de la Tourette syndrome was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria (American Psychiatric Association, 2000). The lifetime history of symptoms indicative of Gilles de la Tourette syndrome was assessed using the Diagnostic Confidence Index (Robertson *et al.*, 1999). Mean Diagnostic Confidence Index score was 61.4 ± 3.4 (Diagnostic Confidence Index ranges from 0 to 100). The appropriate modules of the German version of the structured clinical interview for DSM-IV Axis I disorders (SCID-I) (Wittchen *et al.*, 1997) were used to diagnose obsessive-compulsive disorder and depression. Attention deficit hyperactivity disorder was diagnosed according to DSM-IV-TR criteria (American Psychiatric Association, 2000). Patients fulfilling DSM-IV/SCID-I criteria for obsessive compulsive disorder, attention deficit

Table 1 Clinical characteristics of patients with Gilles de la Tourette syndrome

Subject	Age	Sex	Age at onset	DCI	YGTSS	YGTSS (tic scores)	YGTSS (motor scores)	Tics—overview	Tic count/min	MRVS total	Last medication
P01	30	F	3	68	30	20	13	mMvV	Missing ^a	Missing ^a	Naïve
P02	45	M	11	64	35	25	12	mMv-	63	10	Naïve
P03	42	F	3	76	42	22	17	mMv-	63	13	>1 year
P04	38	M	11	45	22	12	9	m-v-	15	6	>1 year
P05	40	M	12	100	77	37	23	mMvV	55	14	>6 months
P06	44	M	5	67	60	30	16	mMvV	65	11	>2 years
P07	24	M	5	67	29	19	13	mMvV	41	7	Naïve
P08	28	M	6	63	49	29	18	mMv-	Missing ^a	Missing ^a	>10 years
P09	30	M	3	54	36	16	9	mMv-	17	5	Naïve
P10	29	M	6	50	44	24	12	m-v-	36	9	>1 year
P11	55	M	13	57	49	19	11	mMv-	68	15	>10 years

M = male; F = female; DCI = Diagnostic Confidence Index (0–100); YGTSS = Yale Global Tic Severity Scale (0–100), tic scores = only tic scores of the YGTSS, excluding self judgment (1–50), motor scores = only motor tic score of the YGTSS, excluding self-judgement and vocal tic scores (1–25); m = simple motor; M = complex motor; v = simple vocal; V = complex vocal tics; Tic count/min = tics per minute counted on 2 min. video; MRVS (total) = total score of the Modified Rush Videotape Rating Scale (0–20).

a One patient refused to be videotaped.

hyperactivity disorder, or other psychiatric disorders were excluded from the study. In addition, patients suffering from obsessive compulsive behaviour without fulfilling DSM-IV/SCID-I criteria were also excluded. However, it has to be mentioned that subclinical, subthreshold traits of obsessive compulsive disorder or attention deficit hyperactivity disorder cannot ultimately be excluded. Mean Yale Global Tic Severity Scale score was 43.5 ± 3.6 (range from 0 to 100). Additionally, a standardized video recording was performed and data were scored using the Modified Rush Videotape Rating Scale (Goetz *et al.*, 1999). Furthermore, the total number of tics was counted during video recording as described previously (Orth *et al.*, 2008). Absolute numbers of tics were expressed as tics per minute. Mean tic count per minute was 43.8 ± 5.2 . Clinical details of patients are provided in Table 1.

The participants of the control group were recruited from staff and via a notice posted on the campus. All participants but one were right-handed as evaluated by the Edinburgh Handedness Inventory (Oldfield, 1971). Cut-off for right-handedness was set to ≥ 70 (Oldfield, 1971). One participant of the Gilles de la Tourette syndrome group claimed to be right-handed but was interpreted as left-handed after evaluation. Full written informed consent was obtained from all subjects according to the Declaration of Helsinki. The study protocol was approved by the local ethics committee.

Experimental procedures

All subjects were seated comfortably with forearms and hands in pronation supported on a cushion about 80cm in front of a 20 inch computer monitor. Before data acquisition, the subjects were familiarized with the task and the individual's reaction time was determined without application of TMS. Following standardized procedures to establish the hotspot for first dorsal interosseus muscle and resting motor threshold (Siebner and Rothwell, 2003; Hummel *et al.*, 2009), the subjects performed the reaction time task while paired- and single-pulse TMS was applied in pseudo-randomized order at six different time points (T1–T6) during the period between the 'GO' signal and movement onset ('premovement phase', Fig. 1A). The premovement timings for TMS application were adjusted individually for each subject according to the respective reaction time (Murase *et al.*, 2004;

Duque *et al.*, 2005) and resembled equal steps between ~40 and 100% of reaction time. Each timing and stimulation condition was repeated 16 times in randomized order. At the end of the experimental session recruitment curves, conditioned and unconditioned motor evoked potential (MEP) amplitudes were evaluated at rest. The duration of the total experiment was on average 2 h per subject.

Transcranial magnetic stimulation

Intracortical excitability at rest and during premovement phase was evaluated with single and paired-pulse TMS. We used two Magstim 200 magnetic stimulators connected via a Bistim module (Magstim Company, Whitland, Dyfed, UK) and delivered the conditioning and test stimuli through one figure of eight coil with an 80 mm wing diameter. The coil was placed over the hand motor area, contralaterally to the moving hand, with the handle in antero-medial orientation, $\sim 45^\circ$ to the interhemispheric line. Optimal scalp position to elicit consistently the largest MEPs in the first dorsal interosseus muscle with slight suprathreshold stimulator intensity was considered the motor hot spot and was marked with a skin-friendly pen. Resting motor threshold was defined as the intensity of stimulator output to produce MEP amplitudes of at least $50 \mu\text{V}$ in 5 out of 10 consecutive trials at rest (Rossini *et al.*, 1999). Subthreshold conditioning stimulus was followed by a suprathreshold test stimulus in the paired pulse paradigm. We used an interstimulus interval of 3 ms to evaluate SIC (Chen, 2004; Hallett, 2000) and an interstimulus interval of 10 ms to evaluate intracortical facilitation (Kujirai *et al.*, 1993).

Conditioning stimulus was set at 80% of resting motor threshold (Ziemann *et al.*, 1996) and the test stimulus was adjusted to elicit unconditioned MEP amplitudes of $\sim 1 \text{ mV}$ peak-to-peak. Recruitment curves with systematically increasing stimulator output in steps of 10% from 100% to 150% of resting motor threshold were evaluated at rest.

EMG activity was recorded using disposable Ag/AgCl surface electrodes placed over the first dorsal interosseus muscle in a belly-tendon montage. EMG signals were amplified (CED 1902 amplifier, sampling rate 5 kHz) then bandpass filtered (50 Hz to 1 kHz), digitized and stored offsite. Data acquisition and processing was performed using Signal software 2.13 (Cambridge Electronic Design, Cambridge, UK).

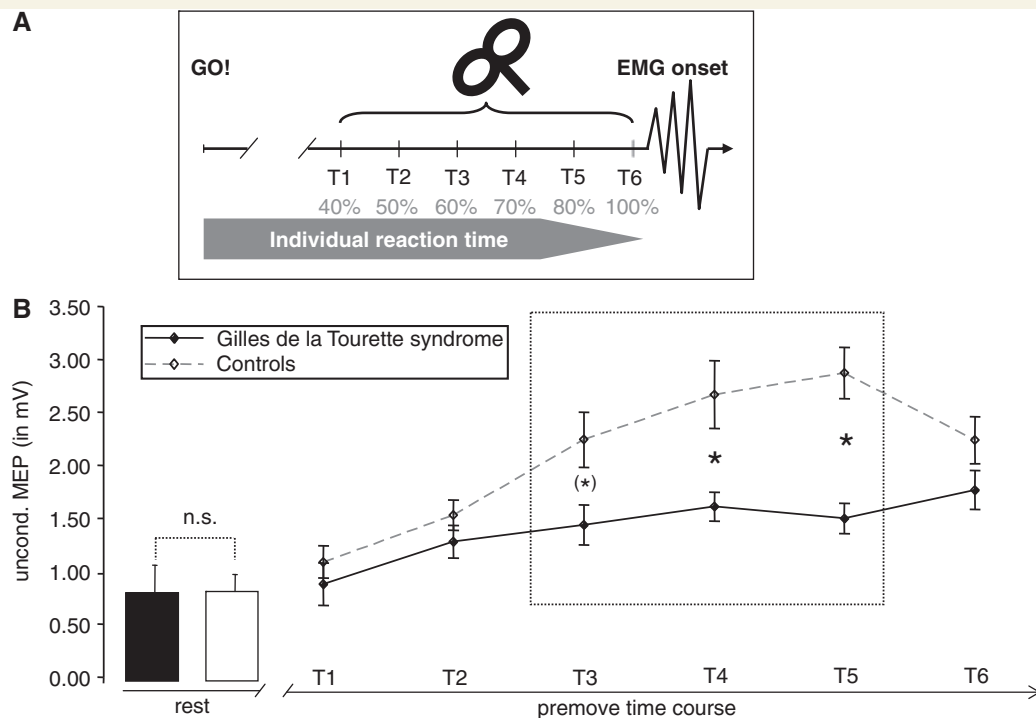


Figure 1 (A) Premovement paradigm. Based on individual reaction time, determined before the TMS experiment, unconditioned and conditioned TMS was applied at six different time points during the preparation of a simple finger movement. Time points were $T1 = 40\%$ of reaction time, $T2 = 50\%$ of reaction time, $T3 = 60\%$ of reaction time, $T4 = 70\%$ of reaction time, $T5 = 80\%$ of reaction time, $T6 = 100\%$ of reaction time. (B) Unconditioned MEP amplitude during rest and premovement phase. In the present chart the unconditioned MEP amplitudes are displayed at rest and during the time course of the premovement phase. Left panel, unconditioned MEP at rest was comparable in both groups. Right panel, unconditioned MEP during premovement phase is significantly different between groups at late time points during the premovement phase ($T3$ – $T5$). y -axis displays the unconditioned MEP amplitude in mV, x -axis displays the time course (rest, $T1$ – $T6$). * $P < 0.05$.

Motor task

In order to investigate intracortical excitability in the process of generating a voluntary movement, the subjects were asked to perform a simple reaction time task as described previously in detail (Hummel *et al.*, 2009). The 'GO' signal was visually triggered with Presentation software 0.61 (Neurobehavioral Systems, Albany, CA, USA) and presented at random intervals of 6 and 8 s. Subjects were instructed to focus on a fixation point and to perform an abduction of their right index finger as quickly as possible at the appearance of the 'GO' signal. Patients were instructed not to suppress their tics voluntarily.

Video-based tic monitoring and tic rating

Patients with Gilles de la Tourette syndrome were monitored during the motor task experiment. The high-resolution videotape was digitally co-registered and synchronized with the 'GO' signal using an on-screen video character overlay device (VideoStamp™, Intuitive Circuits, Brinston, Troy, MI, USA). The videos were analysed for premovement trials containing tics from 6 to 8 s before the 'GO' signal (corresponding to the intertrial interval) until the onset of the index finger movement, including the different time points ($T1$ – $T6$). The tic onset was marked in relation to the 'GO' signal and all trials with tics were excluded from further analyses. One patient refused any

videotaping, therefore video data for tic rating during premovement phase were available only in 10 patients.

Data processing and statistical analysis

Trials with EMG activity before the TMS pulse were discarded after visual inspection from further analysis. Furthermore, trials with MEPs within or after the EMG burst were excluded from analyses as described previously (Hummel *et al.*, 2009). MEP amplitudes, measured peak-to-peak, were sorted according to stimulation condition (unconditioned MEP, SICI, intracortical facilitation) and premovement timing ($T1$ – $T6$). SICI and intracortical facilitation were expressed as percentages of the corresponding unconditioned MEP amplitude averaged for the particular timing ($T1$ – $T6$). Data from measurements at rest were analysed in an analogous manner. All results are given as mean \pm standard error (SEM) unless otherwise noted. Statistical analysis was performed using Statistical Package for the Social Sciences for PC version 15.0 (SPSS Inc., Chicago, USA).

The Kolmogorov–Smirnov Test was conducted to test for a normal distribution of data.

Changes in excitability during the premovement phase were evaluated for differences between the groups using separate repeated measure analyses of variance (RM-ANOVA) for unconditioned MEP, SICI and intracortical facilitation. Time ($T1$ – $T6$) was set as the within-subjects factor and Group (Gilles de la Tourette syndrome or controls) as the between-subjects factor. Mauchly's test was used to test for

assumption of sphericity, while Greenhouse–Geisser epsilon determination was used to correct in case of sphericity violation. *Post hoc* unpaired Student's *t*-test was conducted to analyse group-differences at respective time points. Unpaired Student's *t*-test (two-tailed) was used to compare resting motor threshold, 1 mV stimulus intensity and reaction time between the two groups. Paired Student's *t*-test (two-tailed) was used to compare within group differences between rest and premovement timings for unconditioned MEP, SIC1 and intracortical facilitation. Effect size for *t*-statistics was calculated using Pearson's correlation coefficient *r*.

Spearman's rho was used for the correlation between cortical excitability and standardized tic measures in the group of Gilles de la Tourette syndrome patients. *Post hoc*, we conducted an analysis of the association (i) between the amount of change in premovement SIC1 from T1 to T2 ([average SIC1 at T1]–[average SIC1 at T2]) and lowest mean unconditioned MEP of the late time points T4 and T5; and (ii) between unconditioned MEP in the late phase (averaged over T4 and T5) and reaction time using Spearman's rho correlation coefficient (two-tailed) in each group separately. For all analyses, level of statistical significance was set to $P=0.05$.

Results

Reaction time

Reaction times were not significantly different between patients with Gilles de la Tourette syndrome and healthy controls (Gilles de la Tourette syndrome patients 204.55 ± 22.57 ; controls 184.89 ± 26.55 ; $t(20)=1.87$, $P=0.08$), although there was a tendency for patients with Gilles de la Tourette syndrome to have slower reaction times, representing a medium-sized effect $r=0.39$.

Stimulus intensity

Resting motor threshold was not different between Gilles de la Tourette syndrome patients and control subjects [Gilles de la Tourette syndrome $45.27\% \pm 11.59$ SD; controls $43.45\% \pm 3.96$ SD, $t(12.30)=0.49$, $P=0.63$]. Also, the intensity necessary to elicit a MEP of 1 mV was comparable between the groups [Gilles de la Tourette syndrome 52.55 ± 13.97 SD, corresponding to 115% of resting motor threshold; controls 53.27 ± 5.85 SD, corresponding to 123% of resting motor threshold, $t(13.40)=-0.159$, $P=0.88$]. Summary of subject characteristics and basic physiological data are given in Table 2.

Table 2 Subject characteristics

	Age		Repetition time		Resting motor threshold		1 mV	
	Gilles de la Tourette syndrome	Controls	Gilles de la Tourette syndrome	Controls	Gilles de la Tourette syndrome	Controls	Gilles de la Tourette syndrome	Controls
Mean (SD)	36.82 (9.40)	37.45 (9.21)	204.55(22.57)	184.89(26.55)	45.27(11.59)	43.45(3.96)	52.55(13.97)	53.27(5.85)
Range	24–55	26–52	177–244	154–231	31–70	35–49	40–83	41–62
<i>t</i> -test	$P=0.87$		$P=0.08$		$P=0.63$		$P=0.88$	

Resting data

At rest, the average size of unconditioned MEP amplitude was comparable between both groups (Gilles de la Tourette syndrome $0.82 \text{ mV} \pm 0.23$, controls $0.83 \text{ mV} \pm 0.14$; $t(20)=-0.03$, $P=0.98$; Fig. 1B left panel). Patients with Gilles de la Tourette syndrome showed less SIC1 at rest than the control group (Gilles de la Tourette syndrome $87.9\% \pm 20.1$, controls $39.8\% \pm 6.6$; $t(12.2)=2.276$, $P=0.04$; Fig. 2 left panel), representing a large effect $r=0.55$. There was no difference between groups for intracortical facilitation (Gilles de la Tourette syndrome $179.9\% \pm 31.4$, controls $171.9\% \pm 19.9$; $t(20)=0.22$, $P=0.83$; supplemental online material Fig. 1 left panel).

Recruitment curves

Patients with Gilles de la Tourette syndrome presented with a tendency towards larger MEP amplitudes than controls, i.e. with slightly steeper recruitment curve slopes than controls subjects. RM-ANOVA with factors Group_(Patients, Controls) and Intensity_(100%–150%) revealed, as expected, a significant effect of factor Intensity [$F(1.64, 18.3)=14.954$; $P=0.00$], and a trend for the factor Group [$F(1, 11)=3.463$, $P=0.09$], and no interaction Intensity \times Group [$F(1.64, 18.3)=3.327$; $P=0.40$] (supplemental online material Fig. 2).

Premovement phase data

Tic rating

During the premovement experiment, the absolute numbers of trials excluded due to tic occurrence in every single Gilles de la Tourette syndrome patient were ranging from 0 to 16 trials of a total of 288 trials (8 blocks of 36 trials) per person (average 5.90 ± 5.57 SD; corresponding to 2.01% drop-out trials). The tics occurred in all patients before the 'GO'-signal (1.74% of drop-out trials) or at the moment when the 'GO'-signal appeared (0.31% of drop-out trials). Detailed analyses revealed that none of the tics started between 'GO' signal and movement onset.

Modulation of cortical excitability during premovement phase

Unconditioned MEP amplitudes

RM-ANOVA with factors Time_(T1–T6), Group_(Patients, Controls) and Time \times Group interaction for the unconditioned MEP amplitude revealed significant main effects of factors Time

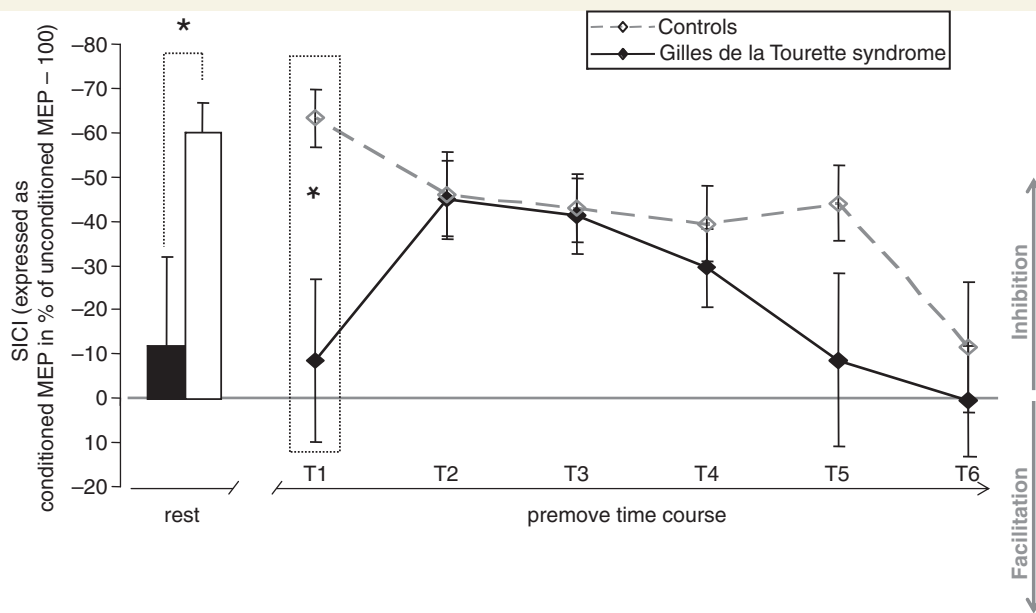


Figure 2 SICI during rest and premovement phase. In this diagram SICI is depicted as [(conditioned MEP in % of unconditioned MEP) - 100], i.e. the smaller the values (negative), the more inhibition at that respective time point. Left panel, SICI at rest is significantly different between Patients with Gilles de la Tourette syndrome and controls (CON). Right panel, premovement phase SICI modulation. It is of note that in Gilles de la Tourette syndrome SICI is significantly reduced at T1. Towards T2 inhibition is increased in Gilles de la Tourette syndrome then showing a pattern of SICI modulation comparable to healthy controls (T3–T6). y-axis displays the amount of inhibition in %, x-axis displays the time course (rest, T1–T6). * $P < 0.05$.

[$F(5, 100) = 18.88, P = 0.00$] and Group [$F(1, 20) = 5.53, P = 0.03$], and a significant Time \times Group interaction [$F(5, 100) = 4.31, P = 0.01$]. *Post hoc* analysis (*t*-test) showed significant differences between the groups for measurements at T4 [$t(12.9) = -2.90, P = 0.01$] and T5 [$t(12.0) = -2.88, P = 0.01$], and a trend at T3 [$t(20) = -2.01, P = 0.06$], with control subjects presenting a larger increase in size of unconditioned MEP amplitude than the Gilles de la Tourette syndrome patients (Fig. 1B). Unconditioned MEP amplitudes at T1 were not different from rest in Gilles de la Tourette syndrome ($[t(10) = -0.05, P = 0.96]$) and controls [$t(10) = -1.88, P = 0.09$] (Fig. 1B).

Short-interval intracortical inhibition

For SICI, RM-ANOVA revealed a significant effect of the factor Time [$F(3.0, 60.6) = 4.62, P = 0.01$], and a trend towards significance for the factor Group [$F(1, 20) = 3.27, P = 0.09$], and Time \times Group interaction [$F(3.0, 60.6) = 2.59, P = 0.06$]. We conducted a *post hoc* analysis for between-group differences. Unpaired *t*-test showed a significant difference at T1 [$t(11.5) = 2.86, P = 0.02$], where Gilles de la Tourette syndrome patients presented with less inhibition than control subjects, although subsequently SICI followed the pattern of controls (Fig. 2). This pattern of SICI modulation was present in all Gilles de la Tourette syndrome patients but not seen in any of the control subjects. SICI at T1 was not different from rest in Gilles de la Tourette syndrome [$t(10) = -0.24, P = 0.82$] and in the control group [$t(10) = 0.665, P = 0.52$] (Fig. 2).

Intracortical facilitation

For intracortical facilitation, the RM-ANOVA did not reveal significant effects for factors Time [$F(5, 100) = 1.15, P = 0.34$],

Group [$F(1, 20) = 0.88, P = 0.47$], or the Time \times Group interaction [$F(5, 100) = 1.13, P = 0.35$]. Intracortical facilitation at T1 was not significantly different from rest in Gilles de la Tourette syndrome ($[t(10) = 0.66, P = 0.52]$) or in the control group [$t(10) = 1.25, P = 0.24$]. Please see also Supplementary online material Fig. 1.

Change in premovement SICI from T1 to T2 showed a negative association with lowest mean unconditioned MEP amplitudes at T4 and T5 during late premovement phase in Gilles de la Tourette syndrome patients but not in control subjects: the larger the (positive) difference between premovement SICI at T1 and at T2 (increase in inhibition), the smaller the unconditioned MEPs at late time points in Gilles de la Tourette syndrome patients ($R = -0.66; P < 0.05, n = 11$). This correlation was not evident in healthy controls ($R = -0.04, P = 0.92, n = 11$).

Modulation of corticospinal excitability during late premovement phase (unconditioned MEP averaged over T4 and T5, time points which were significantly different between groups according to *post hoc* testing) was significantly correlated with reaction time in Gilles de la Tourette syndrome ($R = 0.66, P = 0.03; n = 11$) but not in controls ($R = -0.36, P = 0.27; n = 11$) (supplemental online material Fig. 3).

Correlation between tic measures and cortical excitability

Tic count during premovement phase

The total sum of premovement tics (counted during video analysis between 'GO' signal and finger movement as described above,

summed over all trials) correlated negatively with early SICI modulation expressed as difference between SICI at T1 and T2 ($R = -0.75$, $P = 0.012$, $n = 10$), i.e. the smaller the number of tics within the premovement phase, the larger the difference between SICI at T1 and SICI at T2. Hence, patients presenting the largest increase of inhibition from T1 to T2 show the least tics.

The total sum of premovement tics (as above) correlated with the average unconditioned MEP amplitude at late time points (T4 and T5) during movement preparation ($R = 0.80$, $P = 0.006$, $n = 10$), i.e. patients who had more tics during the premovement phase presented with a larger increase in excitability late during the premovement phase.

Tic measures and clinical scales evaluated at rest

When exploring the association between clinical measures for tic rating evaluated in a separate session at rest (Table 1) and intracortical excitability, those patients having higher scores in clinical tic measures (indicating greater severity) presented with smaller unconditioned MEP amplitudes during late premovement phase. For details please see Supplementary online material.

Discussion

Single- and double-pulse TMS was used to evaluate cortical excitability in a sample of 11 uncomplicated Gilles de la Tourette syndrome patients in comparison to age- and sex-matched healthy control subjects during movement preparation and at rest. The main findings were two fold. First, Gilles de la Tourette syndrome patients presented with a significant disinhibition at rest in comparison to control subjects, while there was no difference between the groups in unconditioned MEP amplitudes or intracortical facilitation at rest. Secondly, during movement preparation, two main aspects were remarkably different between patients and the control group: patients with Gilles de la Tourette syndrome showed (i) significantly decreased SICI (disinhibition) very early (T1) during movement preparation (comparable to rest) followed by a sudden increase in inhibition (towards T2), which subsequently developed into release of inhibition closer to movement onset (T3–T6), similar to the modulatory pattern seen in healthy controls; and (ii) significantly smaller unconditioned MEP amplitudes during middle and late phases (T3–T5) of movement preparation.

SICI, intracortical facilitation and corticospinal excitability at rest

The present findings of decreased SICI, i.e. disinhibition, at rest in Gilles de la Tourette syndrome patients are in accordance with previous TMS data demonstrating deficient SICI in adult Gilles de la Tourette syndrome patients at rest (Ziemann *et al.*, 1997). SICI is considered to reflect inhibition at the level of the primary motor cortex (Kujirai *et al.*, 1993; Rothwell, 1997; Hallett, 2000). There is sound evidence that it is generated by GABA_A-mediated synaptic inhibitory mechanisms at the level of local interneurons (Hanajima and Ugawa, 2008; Reis *et al.*, 2008). It has been suggested that in Gilles de la Tourette syndrome patients,

GABA-mediated circuits might either be affected by afferent signals from disturbances located subcortically (e.g. abnormalities in basal ganglia output systems, i.e. striatum), or might represent the location of primary impairment (Ziemann *et al.*, 1997; Orth *et al.*, 2008), or a conjunction of both (Stern *et al.*, 2008). The present data acquired at rest reproduce previous findings of deficiency within GABAergic intracortical inhibitory circuits in Gilles de la Tourette syndrome patients (Ziemann *et al.*, 1997; Gilbert *et al.*, 2005; Orth *et al.*, 2005).

A single, unconditioned suprathreshold TMS pulse is thought to activate cortical pyramidal neurons indirectly, via excitatory interneurons, leading to corticospinal output, measured as MEP at the respective muscle (Daskalakis and Chen, 2008; Reis *et al.*, 2008). Motor cortical output at rest was comparable in patients with Gilles de la Tourette syndrome and control subjects in the present sample. Testing motorcortical excitability at different stimulus intensities produced a non-significant tendency of steeper recruitment curves for Gilles de la Tourette syndrome patients, who also showed more variability in amplitude size. This finding differs from that of Orth and colleagues, who reported shallower recruitment curves in Gilles de la Tourette syndrome patients (Orth and Rothwell, 2009). They interpreted their results as evidence for an overall reduction of cortical excitability in Gilles de la Tourette syndrome at rest. Our findings rather point towards a more disinhibited and more excitable system as indicated by the steeper recruitment curves in Gilles de la Tourette syndrome patients at rest. The differences between the studies might be explained at least to some extent by the different samples of patients with non-medicated, less severely impaired patients without comorbidities in the present study. But conclusive data on recruitment curves in patients with and without specified comorbidities are not available to date in order to explain the different findings fully.

For intracortical facilitation, the exact neurophysiological origin is less clear. It is thought to represent a net facilitation (Reis *et al.*, 2008), which is most likely mediated by glutamatergic N-methyl-D-aspartate receptors (Ziemann *et al.*, 1998; Schwenkreis *et al.*, 1999) and represents the excitability of interneuronal circuits within M1 (Ziemann *et al.*, 1996). At rest, Gilles de la Tourette syndrome patients displayed the same pattern of intracortical facilitation as the control subjects in our experiment. This result is in accordance with previous work, which did not find differences in intracortical facilitation between Gilles de la Tourette syndrome without comorbidities and controls (Orth and Rothwell, 2009; Ziemann *et al.*, 1996). However, for Gilles de la Tourette syndrome patients with comorbid attention deficit hyperactivity disorder an increase of intracortical facilitation at rest has been suggested (Orth and Rothwell, 2009).

Decreased corticospinal output during movement preparation

The increase in contralateral corticospinal excitability before a simple reaction time task is widely accepted to represent a gradual increase of neuronal activity within the motor cortex above the threshold for spinal neurons to discharge (Rossini *et al.*, 1988; Pascual-Leone *et al.*, 1992; Chen *et al.*, 1998). Increasing size

of unconditioned MEP amplitudes during movement preparation depends on both cortical as well as spinal mechanisms (Leocani *et al.*, 2000). Contralateral motorcortical excitability has been shown to increase progressively during preparation of a self-paced movement in young healthy volunteers from around 80–120 ms before EMG activity starts (Rossini *et al.*, 1988; Chen *et al.*, 1998; Leocani *et al.*, 2000; Nikolova *et al.*, 2006). Here, unconditioned MEP amplitudes gradually increased during movement preparation from T1 to T6 until movement occurred, i.e. EMG on-set. Our sample of Gilles de la Tourette syndrome patients, however, demonstrated significantly diminished corticospinal output compared to the control group. While both groups started off (T1 and T2, 40–50% of individual reaction time) with comparable MEP amplitudes, the difference in average amplitude size was significant for the middle and late pre-movement phase (T3–T5, i.e. 60–90% of individual reaction time). Whereas corticospinal output of the contralateral M1 was comparable for patients and controls in our study at rest, task-related modulation of cortical excitability and subsequent corticospinal output as evaluated with unconditioned TMS pulse was diminished during movement preparation in Gilles de la Tourette syndrome patients.

This pattern of decreased motorcortical excitability in Gilles de la Tourette syndrome patients was not evident in the evaluation of pre-movement intracortical facilitation. Both groups exhibited comparable curves of intracortical facilitation modulation prior to movement onset.

Initial disinhibition and subsequent increase in inhibition early during movement preparation

Intracortical inhibition in the contralateral M1 has been shown to decrease around 70–95 ms before movement onset (Reynolds and Ashby, 1999; Nikolova *et al.*, 2006). It has been suggested that this release of inhibition 'occurs alongside or later than the increase in MEP amplitudes' and therefore might have a focussing role rather than generally modulating cortical excitability (Reis *et al.*, 2008). We observed the described pattern in the control group, which presented with a continuous release of inhibition from rest levels over three quarters of their reaction time, with the largest step in release of SICI shortly before movement onset at 80%–100% of individual reaction time (T5–T6). Remarkably, Gilles de la Tourette syndrome patients demonstrated a steep increase in SICI (more inhibition) between 40 (T1) and 50% (T2) of individual reaction time, reaching a level far beyond that of rest SICI and within the range of values in the control group (Fig. 2). It is also of note that SICI at T1 in Gilles de la Tourette syndrome is comparable to the SICI levels at rest. But subsequent modulation of SICI during middle and late pre-movement phase (T3–T6, 60%–100% of individual reaction time) was similar to that of the control group. This indicates that Gilles de la Tourette syndrome patients start from an abnormally disinhibited level of SICI (comparable with the abnormally disinhibited level at rest), but enter into a pattern comparable to that of healthy controls later during the process of movement preparation.

Summarising the data from the pre-movement phase, two main aspects distinguished the patient from the control group; firstly, the inverted U-shape pattern of SICI with initial disinhibition still comparable with rest levels and subsequent increase in inhibition around 40%–50% of individual reaction time; and secondly, significantly decreased MEP amplitudes during 50%–90% of individual reaction time. Considering these two aspects, the questions whether and how they are interrelated in movement preparation remain to be answered.

A model of the interaction of pathophysiological and compensatory mechanisms

It has been hypothesized that parts of the neurophysiological alterations seen in adult Gilles de la Tourette syndrome patients are due to plastic changes in response to the given abnormalities within the nervous system in order to establish adequate online behavioural control (Stern *et al.*, 2008). It therefore appears conceivable that the phenomena seen in Gilles de la Tourette syndrome patients represent two undistinguishable mechanisms of the motor system: firstly, the activity of the aberrant, probably striato-thalamic, afferents to the cortical areas; and secondly the experience-driven reaction of the motor system in order to produce adequate motor behaviour (Peterson *et al.*, 2001, Spessot *et al.*, 2004). It might be possible that in this compensatory mechanism, the motor cortex plays a role as 'relay station', i.e. increasing inhibitory activation and thereby down-regulating neuronal excitability (Fig. 3B). During the resting state, there is no requirement for the relaxed system to generate an adequate motor response in time, thus motor cortical excitability is highly influenced by afferent input, e.g. from within the cortico-striato-thalamo-cortical loop, and consequently presenting with a state of disinhibition in Gilles de la Tourette syndrome. During coordinated activity, e.g. a simple reaction time task as in the present experiment, the system needs to generate an appropriate motor response, including the control of tics. In accordance with this hypothesis is our observation of extremely scarce tic appearance (in 2.01% of trials) all appearing before the 'GO' signal, which were counted from the video data of patients recorded during the pre-movement phase as described above. The influence of circuits integrating sensory and motor processing might also be of relevance, as proposed in the 'deficient sensorimotor gating' model (Leckman *et al.*, 2006). This model has been used to explain that the origin of tics is linked to an inability to gate sensory information effectively (Swerdlow *et al.*, 2001; Leckman *et al.*, 2006).

The initial increase in inhibition, as seen in the sample of Gilles de la Tourette syndrome patients in the present study, might be interpreted as a compensatory mechanism to down-regulate and control motorcortical excitability. It has been proposed that GABAergic interneurons within M1 work in a structuring and coordinating unit in order to regulate overall motor cortical output (Di Cristo, 2007). Starting from a state of disinhibition, net inhibition is subsequently increased in order to coordinate an adequate motor action. This might affect, at least in part, overall cortical

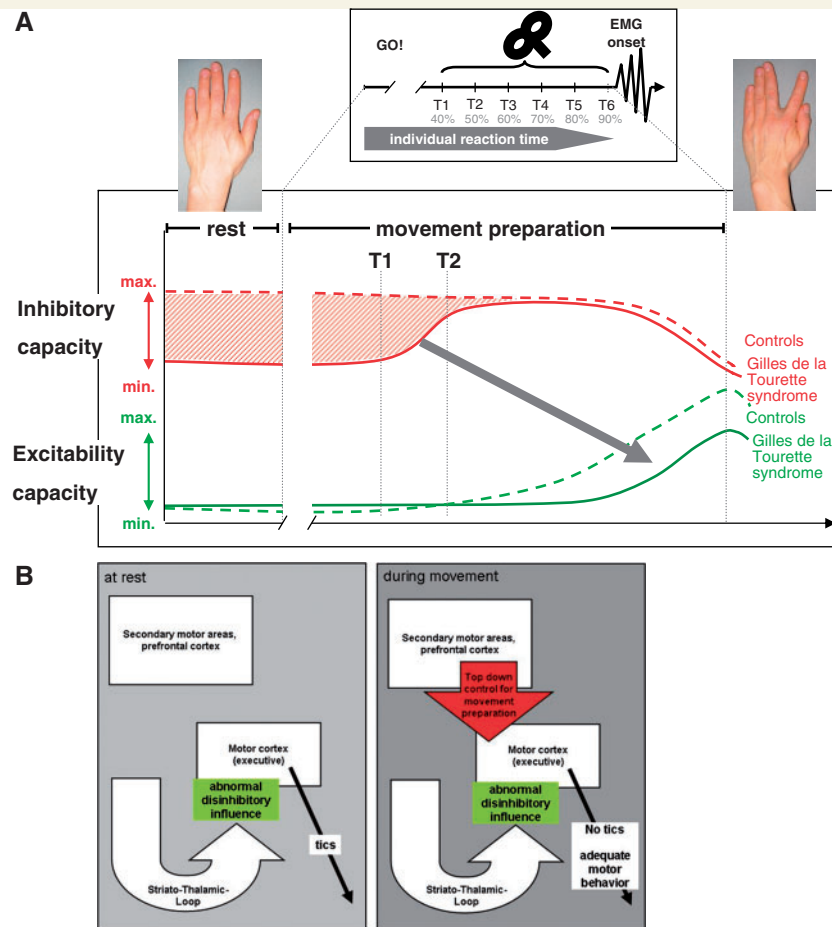


Figure 3 (A) Model of inhibitory capacity in Gilles de la Tourette syndrome showing a steep increase in inhibition early from T1 to T2 and shallower increase in excitability later during movement preparation phase. It is of note that predictions about the modulation of excitability or inhibition respectively earlier than 40% of individual reaction time cannot be made based on current data. (B) Left box: At rest, motor cortical excitability is predominantly influenced by afferent input from within the striato-thalamic loop, and consequently presenting with a state of disinhibition in Gilles de la Tourette syndrome. Right box: During motor task performance, motor cortical excitability underlies top-down control from higher motor areas and prefrontal cortex, overriding the subcortical input. The result is adequate motor performance without tics.

excitability with reduced output represented by decreased MEP amplitudes, demonstrated around 60%–90% (T3–T5) of the individual reaction time in the patient group. One argument in favour of this interpretation is that the Gilles de la Tourette syndrome patients with the most expressed change from disinhibition at T1 towards inhibition at T2 recruited least corticospinal activity, i.e. displayed smaller unconditioned MEP amplitudes later during movement preparation. Another aspect supporting the idea of a compensatory mechanism is the finding that modulation of cortical excitability during late premovement phase (T4, T5) was positively correlated with reaction time in Gilles de la Tourette syndrome patients but not in controls, indicating that patients who were effectively controlling cortical excitability with less corticospinal output (measured as smaller unconditioned MEP amplitudes), performed faster. Furthermore, patients with less increase in inhibition early (during T1) and greater unconditioned MEP amplitudes during late premovement phase (T4, T5) had

higher tic counts during movement preparation. One might interpret these findings as signs for insufficient compensation. Patients with greater tic severity as evaluated with clinical measures at rest did show most pronounced down-regulation of the corticospinal system, i.e. smaller unconditioned MEP amplitudes at late time points.

We therefore propose a model of inhibitory capacity (Fig. 3A), which describes the general possible performance of primary motor-cortical inhibitory systems in Gilles de la Tourette syndrome patients, influencing the overall output of motorcortical excitability. While inhibition during the resting state is far below the level of control subjects, and the cortical excitability is higher (tendency of steeper recruitment curves) in patients than controls while at rest, task-related modulation of cortical excitability reveals the capacity to inhibit effectively an inappropriate rise of excitability. The timing of these observations (initial increase in inhibition and secondary control of motorcortical excitability) suggests that the

GABA-mediated system reflected by SIC1 possibly subserves as the relay station controlling afferent inputs from subcortical levels (Fig. 3B).

Limitations of the study

In the present study we aimed to evaluate a homogenous group of Gilles de la Tourette syndrome without medication or co-morbidities. Therefore, the conclusions drawn from the present study primarily relate to this subgroup and it has yet to be tested whether they also apply in Gilles de la Tourette syndrome with co-morbid attention deficit hyperactivity disorder and obsessive compulsive disorder, which have been reported to be associated with more severe electrophysiological alterations in previous studies (Gilbert *et al.*, 2005; Orth and Rothwell, 2008). From an electrophysiological point of view, our findings could not be explained by differences in resting motor threshold or recruitment curves, which did not differ across groups. Furthermore, the main finding in SIC1 (disinhibition) cannot be explained as an epiphenomenon of changes in different recruitment of corticomotoneuronal connections in the premovement period, since the SIC1 difference was apparent early during movement preparation (transition from T1 to T2) and the changes in unconditioned MEP amplitudes in the middle and late phases (T3–T5). It is necessary to point out that within the present experiment the evaluation of electrophysiological measures started from 40% of individual reaction time. Therefore, the exact shape of the changes in motorcortical excitability during the very early premovement phase can only be extrapolated based on previous studies (Day *et al.*, 1989; Gilio *et al.*, 2003; Hummel *et al.*, 2009).

In conclusion, the present data are in accordance with the previous finding of deficient inhibition in Gilles de la Tourette syndrome patients at rest. Analysis of the modulation of intracortical inhibition and corticospinal excitability during movement preparation shows (i) a modulation profile of SIC1, which is inverted from rest into the beginning of the movement preparation phase, and (ii) an alleviated increase in corticospinal excitability close to movement onset in Gilles de la Tourette syndrome patients. These observations provide evidence for a model of compensatory mechanisms in intracortical circuits in order to prevent erroneous motor responses. Whether and to what extent these findings influence motor behavioural performance needs to be further addressed in prospective studies with sensorimotor tasks of different complexity.

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Supplementary material

Supplementary material is available at *Brain* online.

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