RESEARCH ARTICLE

Abnormal Cortical and Brain Stem Plasticity in Gilles de la Tourette Syndrome

Antonio Suppa, MD,[1] Daniele Belvisi, MD,[2] Matteo Bologna, MD,[1] Luca Marsili, MD,[2] Isabella Berardelli, MD,[2] Germana Moretti, MD,[2] Massimo Pasquini, MD,[2] Giovanni Fabbrini, MD,[1,2] and Alfredo Berardelli, MD[1,2*]

[1]*Neuromed Institute, Sapienza, University of Rome, Rome, Italy*
[2]*Department of Neurology and Psychiatry, Sapienza, University of Rome, Rome, Italy*

ABSTRACT: We investigated primary motor cortex and brain stem plasticity in patients with Gilles de la Tourette syndrome. The study group comprised 12 patients with Gilles de la Tourette syndrome and 24 healthy subjects. Patients were clinically evaluated using the Yale Global Tic Severity Scale. We tested cortical plasticity by conditioning left primary motor cortex with intermittent or continuous theta-burst stimulation in 2 separate sessions. Test stimulation consisted of 20 motor-evoked potentials recorded from right first interosseous muscle before and after theta-burst stimulation. We also tested brain stem plasticity by conditioning the right supraorbital nerve with facilitatory electric high-frequency stimulation delivered at the same time as the late response of the blink reflex or inhibitory high-frequency stimulation delivered before the late response on 2 separate sessions. Test stimulation consisted of 10 blink reflexes from the right orbicularis oculi muscle before and after high-frequency stimulation. After intermittent theta-burst stimulation, motor-evoked potential amplitudes in healthy subjects increased significantly but remained unchanged in patients. Similarly, after continuous theta-burst stimulation, motor-evoked potential amplitudes decreased significantly in healthy subjects but did not in patients. After facilitatory high-frequency stimulation, the blink reflex late response area in healthy subjects increased, whereas after inhibitory high-frequency stimulation, it decreased. Conversely, in patients, both interventions left the blink reflex late response area unchanged. The lack of the expected inhibitory and facilitatory changes in motor-evoked potential amplitudes and blink reflex late response area suggests that abnormal plasticity in the primary motor cortex and brain stem play a role in the pathophysiology of Gilles de la Tourette syndrome. © 2011 *Movement* Disorder Society

Key Words: Gilles de la Tourette syndrome; primary motor cortex; brain stem; plasticity

In Gilles de la Tourette syndrome (GTS), an early study using transcranial magnetic stimulation (TMS) over primary motor cortex (M1) found reduced short-interval intracortical inhibition (SICI). Ziemann et al[1] and others later observed reduced short-interval afferent inhibition (SAI) and a shallow input–output (I/O) curve.[2–6]

Evidence of underlying abnormalities also in brain stem excitability in GTS comes from findings obtained by investigating the blink reflex (BR). The BR is a brain stem reflex composed of early (R1) and late (R2) components mediated by different neural circuits. Studies using the paired-pulse technique found reduced inhibition of the BR-R2 recovery curve, suggesting impaired excitability of brain stem interneurons in GTS.[7]

Besides changes in M1 and brain stem excitability, GTS might arise also from mechanisms of abnormal plasticity. Among the various repetitive TMS (rTMS) techniques used in humans for testing M1 plasticity[8,9] is theta-burst stimulation (TBS). According to the

***Correspondence to:** Professor Alfredo Berardelli, Department of Neurology and Psychiatry, and Neuromed Institute, Sapienza, University of Rome, Viale dell'Università, 30, 00185 Rome, Italy; alfredo.berardelli@uniroma1.it

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TABLE 1. GTS patients' demographic and clinical features

					YGTSS				
Patient	Sex	Age (y)	Disease duration (y)	Therapy (mg/day)	MT (distribution)	PhT	TTS	OI	GSS
1	M	22	19	None	Face, shoulder, arm, hand	Yes	24	20	44
2	M	46	40	None	Face, shoulder, arm, hand	Yes	22	30	52
3	F	27	21	Paroxetin 20	Eyes, shoulder, leg	Yes	23	40	63
4	M	49	41	Lorazepam 4	Head, arm	Yes	16	40	56
5	M	18	10	None	Face, head, shoulder	Yes	21	10	31
6	M	22	16	Paroxetin 40	Eyes, face, shoulder, arm, hand	Yes	22	20	42
7	M	33	17	Clormetildiazepam 2	Eyes, face, head, shoulder, leg	Yes	31	30	61
8	M	18	8	Pimozide 1	Eyes, face, arm	Yes	30	30	60
9	M	28	22	Paroxetin 40	Eyes, face, arm, hand	Yes	38	30	68
10	M	39	31	Clonazepam 3	Eyes, face, head	Yes	13	30	43
11	F	31	25	None	Eyes, face, head, shoulder	Yes	28	30	58
12	F	33	24	Pimozide 2	Eyes, face, shoulder	Yes	14	10	24
Average		30	22.8				23.5	26.7	50.1
SD		9.8	10.4				7.3	9.4	13.5

YGTSS, Yale Global Tic Severity Scale; MT, motor tics; PhT, phonic tics; TTS, total tic score; OI, overall impairment; GSS, global severity score.

intermittent (iTBS) or continuous (cTBS) protocol used, TBS in healthy subjects leads to increased- or decreased-amplitude motor-evoked potentials (MEPs), reflecting long-term potentiation (LTP) or long-term depression (LTD)-like plasticity in cortical interneurons.[10] Plasticity can also be explored in the brain stem by delivering electric high-frequency stimulation (HFS) to the supraorbital nerve and measuring changes in the BR-R2 area but not in the R1 component. When HFS is timed to coincide with the BR-R2 response, it significantly increases the BR-R2 area by inducing LTP-like plasticity (LTP-HFS), whereas when HFS ends before the BR-R2 response (LTD-HFS), it inhibits the BR-R2 area by inducing LTD-like synaptic plasticity in brain stem interneurons mediating the BR-R2.[11]

Studies in animals and humans have shown that abnormal cortical, basal ganglia, and brain stem plasticity contributes to the pathophysiology of hyperkinetic movement disorders.[12–17] A study in an animal model resembling human obsessive–compulsive disorder (OCD)/GTS described disrupted plasticity at the corticostriatal transmission level.[18] No studies have investigated brain plasticity in patients with GTS. Having this information is important because LTP and LTD mechanisms in M1 play an important role in motor control and motor learning.[19–21] Hence, altered LTP- and LTD-like plasticity might account for the impaired motor skills and motor learning previously reported in GTS.[22–26]

We designed this study to investigate plasticity in the 2 central nervous system regions possibly involved in generating upper limb and cranial tics in GTS, namely, the M1 and the brain stem. To explore M1 plasticity, we measured iTBS- and cTBS-induced changes in MEP amplitudes in healthy subjects and patients with GTS. To explore brain stem plasticity, we measured LTP- and LTD-HFS-induced changes in BR-R2 area.

Patients and Materials

Subjects

We studied 12 patients with GTS (9 men and 3 women; mean age ± SD, 30 ± 9.75 years; range, 18–49 years) and 24 age-matched healthy subjects (14 men and 10 women; mean age ± SD, 30 ± 3.6 years; range, 25–40 years). Patients had a diagnosis of GTS according to DSM-IV-TR criteria. The severity of tics was rated using the Yale Global Tic Severity Scale.[27] Seven of 12 patients had a family history of GTS. Patients' clinical and demographic data are summarized in Table 1. Psychiatric evaluation using the Yale Brown Obsessive-Compulsive Scale[28,29] showed that 4 patients with GTS had OCD. None of the patients studied had a previous diagnosis of attention deficit and hyperactivity disorder (ADHD), and none fulfilled criteria for a diagnosis of "adult ADHD."[30] Four patients had never received drugs for their disease, and in the remaining 8 patients, drugs were withdrawn at least 1 week before each experimental session. The experimental procedures were conducted in accordance with regulations laid down in the Declaration of Helsinki.

Experimental Design

As an experimental approach to test plasticity at the M1 and brain stem levels, we used conditioning-test stimulation. Each experiment comprised 2 separate test sessions investigating LTP and LTD-like plasticity (Fig. 1). Two subgroups of 12 age-matched healthy subjects took part in the M1 and brain stem experiment. In both experiments testing M1 and brain stem

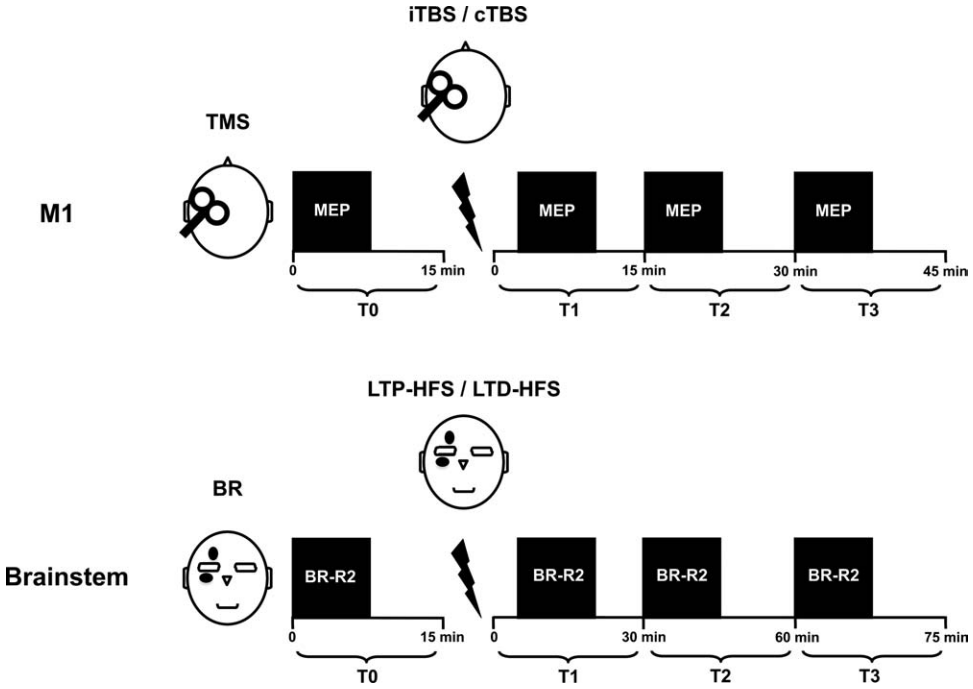

FIG. 1. Experimental protocol used for testing primary motor cortex (M1) and brain stem plasticity. Each experiment comprised 2 separate sessions investigating long-term potentiation (LTP) and long-term depression (LTD)–like plasticity. In the experiment testing M1 plasticity, we tested motor-evoked potential (MEP) amplitudes before (T0) and after intermittent and continuous theta-burst stimulation (iTBS and cTBS) at 5 (T1), 15 (T2), and 30 (T3) minutes. In the experiment testing brain stem plasticity, we tested blink reflex (BR)–R2 area before (T0) and after LTP– and LTD–high-frequency stimulation (LTP-HFS and LTD-HFS) at 5 (T1), 30 (T2) and 60 (T3) minutes.

plasticity, healthy subjects were randomly assigned to participate in the 2 sessions (LTP- and LTD-like plasticity). Patients were randomly assigned to participate in 4 different experimental sessions. At least 1 week elapsed between each experimental session.

M1 Stimulation and Recordings

Twelve patients with GTS and 12 healthy subjects (7 men and 5 women; mean age ± SD, 30 ± 4.9 years; range, 25–40 years) were studied. Subjects were asked to fully relax and to not suppress tics. Single-pulse TMS was delivered through a monophasic Magstim 200 stimulator (Magstim Co, Whitland, Dyfeld, UK) connected to a figure-of-eight coil placed over the left M1 for eliciting MEPs in the right first dorsal interosseous muscle (FDI). Resting (RMT) and active (AMT) motor thresholds were calculated.[31] Test TMS consisted of 20 single pulses delivered at the intensity able to evoke baseline unconditioned MEPs at about 1-mV peak-to-peak in amplitude. The same intensity was used for testing conditioned MEP amplitudes throughout the experiment. Conditioning TBS was delivered through a Magstim SuperRapid stimulator connected to a figure-of-eight coil placed over the left M1. In the session testing LTP-like plasticity, conditioning stimulation was delivered with iTBS in bursts of 3 pulses at 50 Hz, repeated at 5 Hz for a total of 600 pulses. In the LTD-like plasticity session, conditioning was delivered with cTBS in bursts given in a continuous train lasting 40 seconds (600 pulses in total).[10] The stimulation intensity for iTBS and cTBS was set at 80% AMT.[10]

The EMG activity from the right FDI muscle was recorded using surface electrodes (20 Hz–1 kHz; Digitimer D360, Digitimer Ltd., Hertfordshire, UK) and digitized (CED 1401 laboratory interface; Cambridge Electronic Design, Cambridge, UK). As the variable for measuring LTP and LTD-like M1 plasticity, we collected 20 MEPs before (T0) and 5 (T1), 15 (T2), and 30 (T3) minutes after TBS. MEPs were measured peak to peak and then averaged.

Brain Stem Stimulation and Recordings

Twelve patients with GTS and 12 healthy subjects (7 men and 5 women; mean age ± SD, 29 ± 1.8 years; range, 27–32 years) were studied. Subjects were asked to fully relax and not suppress tics. Conditioning and test stimulation were delivered with the cathode over the right supraorbital foramen and the anode 2 cm above. We used constant-current square-wave pulses with a pulse width of 200 μs (Digitimer DS7). We first determined the electrical threshold (Th) as the minimum intensity required to evoke a BR-R2 response with an amplitude $\geq$ 50 μV in at least 5 of 10 consecutive trials. Ten test stimuli-eliciting single BRs were collected before and after conditioning HFS. The stimulation intensity for HFS and single BR was twice the Th.[11] In sessions testing LTP-like plasticity, conditioning stimulation consisted of LTP-HFS delivered in 3 blocks, with an interblock interval of 5

TABLE 2. Transcranial magnetic stimulation (TMS) data in the experiment testing primary motor cortex (M1) plasticity in patients with Gilles de la Tourette syndrome (GTS) and in healthy subjects

	iTBS			cTBS				
	RMT (%)	AMT (%)	1 mV (%)	TBS (%)	RMT (%)	AMT (%)	1 mV (%)	TBS (%)
GTS patients	38.6 ± 8.4	46.8 ± 5.2	48.2 ± 13.9	38 ± 4.1	38.8 ± 8.3	47.3 ± 6.5	50 ± 15.1	38 ± 5.2
Healthy subjects	37 ± 6.3	42.5 ± 7.7	46 ± 8.1	33.9 ± 6.2	36.6 ± 6.9	43.4 ± 8.3	45.2 ± 7.8	34.8 ± 6.6

iTBS, intermittent theta-burst stimulation; cTBS, continuous theta-burst stimulation; RMT, resting motor threshold; AMT, active motor threshold; 1 mV, TMS intensity used for evoking motor-evoked potential (MEP) amplitudes of about 1 mV at baseline; TBS, intensity used for delivering iTBS and cTBS. RMT, AMT, 1 mV, and TBS are expressed as percentages of the maximum stimulator output (average ± SD).

minutes. Each stimulation block consisted of 4 trains (delivered every 10 seconds) of 9 stimuli (delivered at 400 Hz) to the right supraorbital nerve. A single stimulus preceded every train by 40 ms so that the train was timed to coincide with the BR-R2 response elicited by the single stimulus. In the LTD-like plasticity sessions, conditioning stimulation consisted of the LTD-HFS protocol using experimental procedures identical to those used for LTP-HFS except that no stimulus preceded the train so that LTD-HFS ended before the BR-R2 response began.[11]

EMG activity was recorded from the right orbicularis oculi (OO) and digitized. The area of the BR-R2 component was calculated by visual inspection of single rectified EMG traces and then averaged. Ten BR-R2 responses before (T0) and 5 (T1), 30 (T2), and 60 (T3) minutes after HFS were collected as the variable measuring LTP and LTD-like brain stem plasticity. The BR-R2 area was measured and then averaged.

Statistical Analysis

Data collected after TBS and HFS were expressed as percentages of the responses obtained at baseline.

In the experiment testing the M1 area, the unpaired Student *t* test was used to compare RMT, AMT, and the intensity used for evoking MEPs and for conditioning TBS in healthy subjects and patients in all sessions. To test the effect of iTBS and cTBS on MEP amplitudes in healthy subjects and patients, we used a between-group analysis of variance (ANOVA), with "group" (healthy subjects versus GTS patients) and "time" (T0 versus T1, T2, and T3) as main factors. We also used a between-group ANOVA with "clinical features" (de novo patients versus patients withdrawn from drugs without comorbidity versus patients withdrawn from drugs with comorbidity) and "time" (T0 versus T1, T2, and T3) as main factors of analysis.

In the experiment testing the brain stem, the unpaired Student *t* test was used to compare Th and the intensity for test stimulation and for conditioning HFS in healthy subjects and patients in all sessions. A between-group ANOVA with the factors "group" (healthy subjects versus GTS patients) and "time" (T0 versus T1, T2, and T3) was used to test the effect of LTP-HFS and LTD-HFS on the BR-R2 area in LTP- and LTD-like plasticity sessions. We also used a between-group ANOVA with "clinical features" (de novo patients versus patients withdrawn from drugs without comorbidity versus patients withdrawn from drugs with comorbidity) and "time" (T0 versus T1, T2, and T3) as main factors of analysis.

We used Tukey's honestly significant difference test for all post hoc analyses.

Spearman rank correlation test was also used to assess the correlation between patients' clinical features including disease duration and tic severity evaluated with the YGTSS and TTS with TBS-induced changes in MEP amplitude or HFS-induced changes in BR-R2 area at all times. The Pearson correlation test was used to assess in patients the correlation between iTBS- and cTBS-induced changes in MEP amplitude, or LTP- and LTD-HFS-induced changes in the BR-R2 area. Finally, we also assessed possible correlation between iTBS- and cTBS-induced changes in MEP amplitude and LTP- and LTD-HFS-induced changes in the BR-R2 area.

$P < .05$ was considered statistically significant. All values are expressed as means ± SEs.

Results

None of the subjects experienced any adverse effects during or after TBS and HFS. None of the patients reported adverse effects when drugs were withdrawn.

M1 Plasticity

The unpaired *t* test showed comparable RMT and AMT values and intensity for eliciting baseline MEPs and conditioning TBS in both groups (nonsignificant *P* values for all comparisons; Table 2).

Between-group ANOVA showed that iTBS-induced changes in MEP amplitudes differed significantly in patients and healthy subjects, as shown by a significant interaction between factors "group" and "time" ($F_{3.66} = 7.51$; $P < .01$). In healthy subjects, post hoc analysis showed a significant effect of factor "time" ($F_{3.33} = 14.92$; $P < .01$); after conditioning iTBS, MEP amplitudes increased significantly at T1

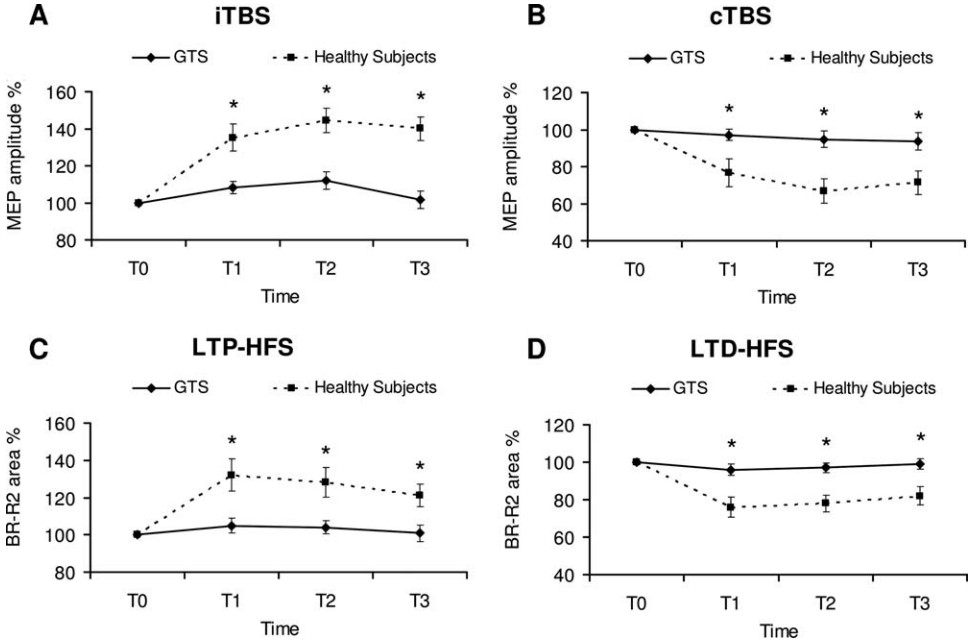

FIG. 2. Primary motor cortex (M1) and brain stem plasticity. **A:** Motor-evoked potentials (MEPs) elicited before (T0) and 5 (T1), 15 (T2), and 30 (T3) minutes after intermittent theta-burst stimulation (iTBS) in patients and in healthy subjects in the long-term potentiation (LTP)–like plasticity session. **B:** MEPs elicited before (T0) and 5 (T1), 15 (T2), and 30 (T3) minutes after continuous theta-burst stimulation (cTBS) in patients and healthy subjects in the long-term depression (LTD)–like plasticity session . **C:** Blink reflex (BR)-R2 area elicited before (T0) and after LTP–high-frequency stimulation (LTP-HFS) at 5 (T1), 30 (T2), and 60 (T3) minutes in patients and healthy subjects in the LTP-like plasticity session. **D:** BR-R2 area elicited before (T0) and after LTD–high-frequency stimulation (LTD-HFS) at 5 (T1), 30 (T2), and 60 (T3) minutes in patients and in healthy subjects in the LTD-like plasticity session. Each point corresponds to the mean response expressed as a percentage of the responses obtained at baseline; vertical bars denote SE. Note the significant difference in MEP responses before and after iTBS/cTBS and in BR-R2 area before and after LTP-HFS/LTD-HFS in healthy subjects but not in Gilles de la Tourette patients (significant values are marked by an asterisk).

($P < .01$), T2 ($P < .01$), and T3 ($P < .01$). Conversely, in patients, the factor "time" had a nonsignificant effect ($F_{3.33} = 2.01$; $P = .13$; Fig. 2A).

Between-group ANOVA showed that the cTBS-induced changes in MEP amplitudes differed significantly in patients and healthy subjects, as shown by a significant interaction between factors "group" and "time" ($F_{3.66} = 12.43$; $P < .01$). In healthy subjects, post hoc analysis showed a significant effect of the factor "time" ($F_{3.33} = 26.33$; $P < .01$); after cTBS,MEP amplitudes decreased significantly at T1 ($P < .01$), T2 ($P < .01$), and T3 ($P < .01$). Conversely, in patients the factor "time" had a nonsignificant effect ($F_{3.33} = 2.01$; $P = .13$; Fig. 2B).

Between-group ANOVA also showed that the factor "clinical features" had a nonsignificant effect in the LTP-like ($F_{2.9} = 0.68$; $P = .53$) and LTD-like ($F_{2.9} = .3$; $P = .75$) plasticity sessions. After iTBS and cTBS, MEPs remained unchanged at all times in de novo patients and also in those who were withdrawn, with and without psychiatric comorbidity.

Brain Stem Plasticity

The unpaired *t* test showed that although there was a trend toward increased Th intensity for baseline BR-R2 and conditioning HFS, these values were comparable in both groups (nonsignificant *P* values for all comparisons; Table 3).

Between-group ANOVA showed that LTP-induced changes in the BR-R2 area differed significantly in patients and healthy subjects, as shown by a significant interaction between factors "group" and "time" ($F_{3.66} = 6.76$; $P < .01$). In healthy subjects, post hoc analysis showed a significant effect of the factor "time" ($F_{3.33} = 6.74$; $P < .01$); after conditioning LTP-HFS, the BR-R2 area increased significantly at T1 ($P < .01$), T2 ($P = .03$), and T3 ($P = .03$). Conversely, in patients, the factor "time" had a nonsignificant effect ($F_{3.33} = 1.3$; $P = .29$; Fig. 2C).

Between-group ANOVA showed that LTD-HFS-induced changes in the BR-R2 area differed

TABLE 3. Electrical stimulation data in experiments testing brain stem plasticity in patients with Gilles de la Tourette syndrome (GTS) and in healthy subjects

	LTP-HFS		LTD-HFS	
	Th (mA)	Intensity (mA)	Th (mA)	Intensity (mA)
GTS patients	5.7 ± 1.6	11.3 ± 3.3	5.6 ± 1.7	11.3 ± 3.3
Healthy subjects	4.8 ± 0.9	9.7 ± 1.8	4.6 ± 1.1	9.3 ± 2.2

LTP-HFS, high-frequency stimulation delivered for inducing long-term potentiation (LTP)-like plasticity; LTD-HFS, high-frequency stimulation delivered for inducing long-term depression (LTD)-like plasticity; Th, electrical threshold for evoking blink reflex (BR)-R2 component; intensity, intensity used for evoking BR-R2 and for delivering LTP and LTD-HFS. Th and intensity are expressed in mA (average ± SD).

significantly in patients and healthy subjects, as shown by a significant interaction between factors "group" and "time" ($F_{3.66} = 5.31$; $P < .01$). In healthy subjects, post hoc analysis showed a significant effect of the factor "time" ($F_{3.33} = 5.9$; $P < .01$); after LTD-HFS, the BR-R2 area decreased significantly at T1 ($P < .01$), T2 ($P < .01$), and T3 ($P < .01$). Conversely, in patients the factor "time" had a nonsignificant effect ($F_{3.33} = 0.46$; $P = .71$; Fig. 2D).

Between-group ANOVA also showed that the factor "clinical features" had a nonsignificant effect in the LTP-like ($F_{2.9} = 1.07$; $P = .98$) and in the LTD-like ($F_{2.9} = 0.37$; $P = .69$) plasticity sessions. After LTP-HFS and LTD-HFS, the BR-R2 area remained unchanged in de novo patients and also in those in whom drugs were withdrawn, with and without psychiatric comorbidity.

Correlation Between Neurophysiological Measures and Patients' Clinical Features

The Spearman rank correlation test found no correlation of clinical features with TBS-induced changes in MEP amplitudes or with HFS-induced changes in the BR-R2 area. Finally, the Pearson correlation test detected no correlation between the iTBS- and cTBS-induced changes in MEP amplitudes or the LTP-HFS- and LTD-HFS-induced changes in the BR-R2 area. Finally, no correlation was found between iTBS- and cTBS-induced changes in MEP amplitudes and LTP-HFS- and LTD-HFS-induced changes in the BR-R2 area.

Discussion

In this study, we report 2 novel findings in GTS. In the experiment testing M1 plasticity, none of the patients had the expected iTBS- and cTBS-induced changes in MEP amplitudes. Again, in the experiment testing brain stem plasticity, none of the patients had the expected LTP-HFS- and LTD-HFS-induced changes in the BR-R2 area. We therefore provide new evidence showing abnormal plasticity in M1 and the brain stem, the 2 central nervous system regions possibly involved in generating upper limb and cranial tics in GTS.

Given the similar baseline RMT, AMT, and MEP amplitudes and the similar absolute TBS intensity in both groups, we practically excluded differences that might have altered the response to TBS. Given that the response to a plasticity-inducing protocol depends on the history of neural activity in M1,[8,9,32–34] the lack of TBS-induced changes in MEP amplitude might depend on involuntary target muscle activation due to patients' tics. None of the patients' recordings showed involuntary EMG activity during TBS.[32] Nor did we detect TBS-induced changes in MEP amplitude in patients who had tics in other body regions but not in the target hand muscle. Possible homeostatic interference between the different experimental sessions[9,35,36] was also excluded because in all subjects at least 1 week elapsed between the different sessions. Finally, given that we also found these neurophysiological abnormalities in patients who had never taken drugs, the altered M1 responses to TBS seem unlikely to depend on a long-lasting history of drug intake or on incomplete drug withdrawal. We therefore conclude that patients with GTS lack the normal TBS-induced changes in MEP amplitudes,[10] probably because GTS alters LTP-like and LTD-like plasticity in M1 intracortical neurons.

In this study, we confirmed that when we delivered LTP-HFS, the BR-R2 response in healthy individuals, as expected, significantly increased, whereas after LTD-HFS, the BR-R2 area significantly decreased.[11] Conversely, in GTS, both protocols left the BR-R2 area unchanged. Given the similar threshold and intensity for eliciting baseline BR-R2 and conditioning HFS in both groups, we can exclude differences that might have prevented the BR-R2 area changes. In addition, we delivered HFS at an intensity similar to that previously used by Mao and Evinger,[11] and in neither patients with GTS nor healthy subjects did HFS elicit late EMG responses due to C-fiber activation,[11] thus excluding possible pain-related changes in the HFS-induced aftereffects. We also exclude the possibility that LTP-HFS failed to facilitate BR-R2 and LTD-HFS failed to inhibit BR-R2 secondary to involuntary OO muscle activity because of cranial tics. EMG interference seems unlikely because a previous study in healthy subjects showed that voluntary OO muscle activation during LTP-HFS has no effect on the expected LTP-HFS-induced BR-R2 area facilitation.[37] Second, LTP-HFS also elicited abnormal BR-R2 responses in patients who had tics involving body regions remote from the face. Because the HFS-induced aftereffects on the BR-R2 area reflect LTP- and LTD-like plasticity,[11] our findings support the hypothesis that in GTS the lack of response to LTP- and LTD-HFS depends on abnormal plasticity within brain stem interneurons mediating the BR-R2 and not the BR-R1.[11,38]

Unlike previous studies investigating cortical excitability in GTS,[6,39] the lack of M1 and brainstem plasticity makes it hardly surprising that we found no significant correlation between clinical and neurophysiological data. Finally, because we also detected similar abnormalities in patients without psychiatric disturbances, we believe that abnormal M1 and brain stem plasticity are unrelated to psychiatric comorbidity.[39–41] Adult patients account for only a minority of patients with GTS insofar as tic severity declines during late adolescence and early adulthood.[42–47] Therefore, our results, obtained in a cohort of adult patients

with relatively severe tics, cannot be generalized to young patients with GTS.

In GTS abnormal thalamocortical inputs[48–54] might alter LTP- and LTD-like plasticity in M1 cortical layers responsible for the TBS-induced aftereffects.[10] Basal ganglia also probably modulate the plasticity of the BR-R2 response by altering the inhibitory drive from the substantia nigra pars reticulata to the superior colliculus–nucleus raphe magnus–spinal trigeminal nucleus circuit.[48,49]

Given that we found no correlation between cortical and brain stem plasticity and severity of tics, altered LTP-like and LTD-like plasticity probably plays no role in generating tics but reflects a primary abnormality underlying impaired motor control. One hypothesis is that because LTP and LTD plasticity mechanisms in M1 play a role in motor control and motor learning,[19–21] the lack of plasticity in GTS might contribute to the impaired motor skills and motor learning previously reported in this disorder.[22–26] The abnormal brain plasticity in GTS might also reflect compensatory mechanisms to suppress tics. This hypothesis fits in well with several neuroimaging studies demonstrating compensatory plastic reorganization in various cortical and subcortical brain regions including the frontal cortex.[55–62]

A final comment is that the impaired plasticity in GTS might also explain the frequently reported weak symptomatic response to therapeutic repetitive TMS (rTMS).[63–65] The present findings should therefore be taken into account when considering rTMS for symptomatic treatment in patients with GTS. An interesting question for further studies is whether daily rTMS sessions improve motor symptoms in GTS[66] by restoring LTP-like and LTD-like plasticity.

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