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Voluntary tic suppression and the normalization of motor cortical beta power

in Gilles de la Tourette Syndrome: an EEG study.

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Abbreviations

ADHD: Attention deficit hyperactivity disorder
BDI: Beck Depression Inventory
fMRI: Functional magnetic resonance imaging
EEG: Electroencephalography
GTS: Gilles de la Tourette Syndrome
M1: Primary Motor Cortex
MS: Milliseconds
MRI: Magnetic resonance imaging
preSMA: Anterior portion of the Supplementary Motor Area
PET: Positron Emission Tomography
PUTS: Premonitory Urge Tics Scale
OCD: Obsessive-compulsive disorder
SD: Standard deviation
SMA: Supplementary motor area
SPM: Statistical Parametric Mapping
YGTSS: Yale Global Tic Severity Scale
YBOCS: Yale-Brown Obsessive Compulsive Scale

Abstract

Gilles de la Tourette Syndrome (GTS) is a neurological condition characterized by motor and vocal tics. Previous studies suggested that this syndrome is associated with abnormal sensorimotor cortex activity at rest, as well as during the execution of voluntary movements. It has been hypothesized that this abnormality might be interpreted as a form of increased tonic inhibition, probably to suppress tics; however, this hypothesis has not been tested so far. The present study was designed to formally test how voluntary tic suppression in GTS influences the activity of the sensorimotor cortex during the execution of a motor task.

We used EEG to record neural activity over the contralateral sensorimotor cortex during a finger movement task in adult GTS patients, in both free-ticcing and tic-suppression conditions; these data were then compared with those collected during the same task in age-matched healthy subjects. We focused on the levels of activity in the beta frequency band, which is typically associated with the activation of the motor system, during three different phases: a pre-movement, a movement, and a post-movement phase.

GTS patients showed decreased levels of beta modulation with respect to the healthy controls, during the execution of the task; however, this abnormal pattern returned to be normal when they were explicitly asked to suppress their tics while moving.

This is the first demonstration that voluntary tic suppression in GTS operates through the normalization of the EEG rhythm in the beta frequency range during the execution of a voluntary finger movement.

1. Introduction

Gilles de la Tourette Syndrome: a general overview

Gilles de la Tourette Syndrome (GTS) is a neurological movement disorder, characterised by motor and vocal tics that last longer than one year; tic onset typically occurs in childhood and symptoms can persist during the patients' entire life-span (Leckman *et al.*, 2001).

Tics look like voluntary actions, but they are "repetitive, seemingly uncontrollable, out of context, and exaggerated" (Ganos & Martino, 2015); they are usually preceded by a premonitory urge, typically described as a feeling of "urge to move" or a mounting internal tension which can be temporarily relieved by tic expression (Cavanna *et al.*, 2017).

Motoric manifestations in GTS are the core aspect of the syndrome, but they still lack a mechanistic explanation; indeed, the pathophysiology of GTS remains incompletely understood. GTS is most likely associated with aberrant activity in the basal ganglia and with functional changes in the cortico-striato-thalamo-cortical circuits (for systematic reviews, see Mink, 2006; Leckman *et al.*, 2010; Felling & Singer, 2011; Ganos *et al.*, 2013), linked to enhanced habit learning.

Interestingly, tics can be kept for a certain time under control through voluntary tic suppression, something that differentiates GTS from other movement disorders characterized by unwanted movements, such as Parkinson's disease or Huntington's disease.

In order to characterize the origin of tics or their suppression, and how they compare physiologically with voluntary actions, GTS has been studied with a variety of functional MRI (fMRI)/PET activation paradigms. In a recent meta-analytical summary of these studies, Zapparoli et al. (2015) showed how GTS was characterized by brain hyperactivations at the level of the premotor cortices of the medial wall (SMA/anterior cingulate cortex) in various aspects of voluntary motor execution and tic suppression (Zapparoli et al., 2015). These findings were further confirmed by another recent meta-analysis by Polyanska and colleagues (2017).

Abnormal activity of the primary motor cortex

Transcranial Magnetic Stimulation data integrated these results and provided a deeper understanding of the syndrome for what concerns the specific activity of the primary motor cortex, viewed as an important relay in the tic generation circuit (Ziemann *et al.*, 1997; Orth *et al.*, 2008; Orth, 2009). These studies showed decreased inhibition, or increased excitability, of the primary motor cortex in GTS patients that correlated with the severity of the motor symptoms (Ziemann *et al.*, 1997; Orth *et al.*, 2008; Orth, 2009). The abnormal activity at the level of the motor cortex in GTS has been confirmed also by MEG/EEG studies, showing augmented functional interactions between M1 and S1, prefrontal and fronto-mesial areas in GTS (Serrien *et al.*, 2005) or patterns of increased M1 activation in the domain of beta frequency during preparation and execution of voluntary finger movements in GTS patients (Franzkowiak *et al.*, 2010). Abnormal patterns of beta oscillations were also found in a recent MEG study conducted by Niccolai and colleagues (2016), where the authors reported a reduction of beta power on sensorimotor regions during pre-movement and actual movement phases in GTS patients during a go/no-go task.

The tic suppression hypothesis

The majority of the cited studies suggested that the abnormal cortical activity recorded at the level of the motor system may represent a compensatory process needed to keep tics and premonitory urges under control. Even if patients were not told explicitly to suppress tics, they could have done it automatically, in order to achieve a performance comparable to the one of healthy controls (see for example Niccolai et al., 2016); indeed, tics can be seen as competing and to-be-suppressed motor acts that make the execution of tasks more demanding for GTS patients.

In an fMRI study, Zapparoli et al. (2016) showed how hyperactivations in premotor and prefrontal regions, recorded in GTS during the execution of a motor task, were positively correlated with the severity of tics: the more severe were the tics which have to be kept under control during the experiment, the greater was the activity in these regions. These data were further explored by the same authors using a Dynamic Causal Modelling analysis, a technique that measures effective brain connectivity between specific regions of interest (Friston *et al.*, 2003); the results showed how the prefrontal/premotor hyperactivations recorded with univariate analyses might be of compensatory nature, in response to multiple inputs according to task demands and the natural tendency of patients with GTS to generate tics (Zapparoli *et al.*, 2017).

However, this compensatory hypothesis has not been tested explicitly: indeed, none of the aforementioned studies formally compared experimental conditions with specific instructions of suppressing tics with free ticcing conditions, during the execution of the same task while measuring brain activity of the level of the cortical motor network.

Aims of the study

The present study was designed to specifically test how tic expression and tic suppression in GTS patients influences the activity of the sensorimotor cortex, during the execution of a concurrent voluntary motor task; in particular, we tested the hypothesis that tic expression and tic suppression might have a differential effect on motor cortex activity as a function of the phase of the movement.

To this aim, we took advantage of a previous work published by Kilner and colleagues (2000), where the authors investigated with MEG the task-dependent modulation coherence between motor cortex and hand muscles during a precision grip task. Their results showed significant levels of coherence between MEG signals and muscle activity in the 15–30 Hz range, suggesting a systematic relationship between coherence in this frequency range and the different features of the motor task they adopted.

Therefore, we focused our attention on the domain of beta-band oscillations and we tested GTS patients and healthy controls with a task with a similar structure of Kilner et al.'s (see below for the details); this was done in order (i) to reproduce a similar pattern of beta-modulation in our participants, (ii) to investigate whether such pattern was different in the GTS population in the different phases of the movement execution and (iii) to explore whether the potential abnormalities in the beta frequencies in GTS could be modulated by the active tic suppression.

Moreover, the chosen experimental motor paradigm standardizes the characteristics of the movement produced by the participants (i.e. the start and the end of each phase of the movement, as well as its duration and speed), in order to maximize the chances of having a similar performance in both GTS patients and healthy controls and to be sure that any possible neurophysiological difference between the two groups in the sensorimotor cortex could not be explained by a different explicit behaviour. Finally, we recruited GTS patients in a drug-free state, in order to focus our attention on the motoric symptoms of the syndrome not treated by medications.

2. Materials and methods

2.1 Subjects

We recruited 10 patients with GTS (6 M, 4 F; mean age: 34 +/- 7 years; mean educational level: 16 years), from the National hospital for neurology and neurosurgery (UCLH, London, UK, where EJ worked at the time of this study) and from the Lewisham & Greenwich NHS Trust (London, UK, where DM worked at the time of this study).

The criteria for GTS, as assessed during a neurological examination conducted by AM, were defined by the DSM-V.

Patients' data were compared to those of 13 healthy subjects, matched for age, with no history of neurological or psychiatric illness, and not related to GTS patients. All participants were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). The study protocol was approved by the Institutional Review Board (National Hospital for Neurology and Neurosurgery and Institute of Neurology NHS research ethics committee; Protocol: 08/H0716/27), and informed written consent was obtained from all of the patients in accordance with the Helsinki Declaration (1964).

The following psychopathological variables were also assessed in GTS patients, as suggested by the European clinical guidelines for Tourette Syndrome and other tic disorders (Cath *et al.*, 2011): the Baratt Impulsivity Scale (BIS) for impulsivity (Fossati *et al.*, 2001); the Yale-Brown Obsessive Compulsive Scale for obsessive-compulsive disorder (YBOCS, Goodman *et al.*, 1989), the Beck Depression Inventory for depression assessment (BDI, Beck *et al.*, 1961) and the Adult ADHD Self-Report Scale (ASRS, Adler *et al.*, 2006).

Tic severity was measured according to the Yale Global Tic Severity Scale (YGTSS, Leckman *et al.*, 1989) and premonitory urge was quantified using the Premonitory Urge Tics Scale (PUTS, Woods *et al.*, 2005).

The evaluation was performed by a certified neurologist (AM); clinical data are presented in Table 1. All the recruited patients were unmedicated since at least 6 months at the moment of the testing.

2.2 Experimental Paradigm

During the experiment, subjects performed an externally paced voluntary motor task with their right hand.

The subject's right forearm was placed on the desk in front of them resting on foam padding with the arm bent at the elbow and the right index finger taped to a custom joystick peripheral device.

The experiment was programmed in MATLAB 2013b, by using the toolbox *Cogent* (http://www.vislab.ucl.ac.uk/cogent.php).

The task was organized in a ten-minute block of fifty trials. At the beginning of each experimental trial, a fixation cross was shown in the centre of the screen; after 1 second the fixation cross disappeared and a red circle with a small white circle inside was displayed on the right side of the screen (see Figure 1). During this "pre-movement phase", subjects were instructed to stay still and not move; after 3 seconds, the "movement phase" started: the red circle became green and it moved horizontally from the right side to the left side of the screen at the speed of 40 mm/s, subjects were instructed to keep the joystick-controlled white circle inside of the moving green circle.

After 3 seconds - once arrived on the left side of the screen - the green circle became again red and subjects were instructed to hold their index finger in place until the end of the trial ("post-movement phase"), when the screen turned blank; at this time, they could return their finger to the starting position in preparation for the next trial (see Figure 1 for a graphic example of one experimental trial).

The screen computer monitor was approximately 100 cm in front of the subject and it displayed the following instructions before the experiment: "*During the experiment, you will see a moving white circle. Try to move the small white circle to keep it into the green one by using the joystick with your right index finger.*" These instructions were explained verbally and also practice trials were used: each subject and each patient performed a 10-trials training before starting the experimental session.

To summarize, each trial comprised the following temporal intervals:
- 0-1000 ms fixation cross on screen;
- 1000-4000 ms red stationary circle on right side of screen ("pre-movement phase");
- 4000-7000 ms circle turns green and moves horizontally once from right to left side of screen ("movement phase");
- 7000-10000 ms red stationary circle on left side of screen ("post-movement phase").

The sampling rate of the behavioural data was 60 Hz; behavioural data were recorded by means of a custom-made joystick which was read by MATLAB as a standard computer mouse. The position of the joystick (and thus of the index finger) was then constantly monitored thanks to the Cogent's function "*getmouse*" which returns state of the cursor on the screen's axes.

We recorded 180 data points for each phase of the experiment (lasting 3 seconds each).

Healthy controls performed the task once, while for GTS patients, the task was repeated in two different conditions: in one block the patients were instructed to freely tic ("free-ticcing" condition), while in the other block the patients were asked to suppress their tics ("tic-suppression" condition). The order of the conditions (free ticcing/tic suppression) was counterbalanced between the patients: five patients performed first the free ticcing condition and then the tic suppression one, while the other five performed first the tic suppression task and then the free ticcing tasks.

All subjects were carefully monitored by one experimenter (LZ) who checked for the correct execution of the task; moreover, all the GTS patients were video-recorded (after their written consent, see below for further details).

2.3 EEG data acquisition

Recordings were obtained using a BioSemi Pin-type Active Electrode High Density 128 channel EEG amplifier and cap system (BioSemi, Amsterdam, Netherlands) at a recording rate of 2048 Hz. Each subject was seated in a height-adjustable chair at a computer desk and fitted with a dry, sanitized stretchy EEG cap.

2.4 Behavioural data

All the analyses were performed by using the software Jamovi (https://www.jamovi.org), based on R packages.

Number of tics

The video and the EEG recordings (which was synchronized with the behavioural procedure) were manually started in the same moment by the same researcher (LZ). Moreover, the video recordings permit to see the patient and the pc monitor as well (and thus to know the number of trial that the patient was performing in a particular moment). After the experiment, a researcher (LZ) carefully checked all the experimental trials recorded in the video and excluded from the analysis all the trials that were contaminated by tics.

Then, in order to check whether GTS patients were effectively able to suppress tics voluntarily, the total number of tics recorded during the two experimental sessions were combined by calculating a ratio (number of tics during the tic suppression / number of tics during the free ticcing) and then we tested whether this ratio was significantly different from the value 1 (indicating an equivalence between the number of tics in the two sessions). Given the non-normal distribution of such data (Shapiro-Wilk's p-value < 0.05), we applied a non-parametric one sample t-test (the one-sample Wilcoxon signed rank test).

Movement data: movement linear length and speed of the movement

The position of the joystick controlled by the right-index finger was recorded during the whole execution of the experimental task for both GTS patients and healthy controls.

We considered for each subject the linear length of the produced movements, by calculating the difference between the initial and the final position of the joystick for each phase (pre-movement; movement; post-movement) of each experimental trial. We assumed that this length during the "pre-movement" and the "post-movement phases" should have been around zero, since subjects were instructed to stay still.

We also calculated the speed of the movements performed during the "movement phase".

Before the data analysis, we checked for the normality of the data distribution for each variable considered, by means of the Shapiro-Wilk test; since some of the behavioural data collected were not normally distributed (Shapiro-Wilk's p-values < 0.05 for the following measures: amplitude in the pre-movement phase in GTS in the tic suppression condition, speed of the movement in GTS during the free ticcing condition, speed of the movement in GTS during the tic suppression condition), the data of the two groups were compared by means of a non-parametric independent sample test (Mann-Whitney U Test) for each condition, correcting the alpha level with a Bonferroni approach by taking into account the number of tests performed on the same data.

2.5 EEG Data

EEG data analyses were performed in MATLAB 2013b (Math Works, Natick, MA, USA), using the software Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, London, UK). EEG data were rereferenced by deducting data from two external electrodes attached to the subjects' earlobes.

In processing our EEG data, we used a procedure very similar to Macerollo et al. (2018) and Palmer et al. (2016): after raw data conversion, high pass (1 Hz) and low pass (100 Hz) filters were applied and the signal was down-sampled to 400 Hz. The data were epoched relative to the onset of each experimental trial.

The experimental trials were then included in the time frequency analysis implemented in SPM; we first defined the time window of interest (the one covering the duration of each experimental trial) and the spectral estimation was performed by using the SPM multitaper option, with a time resolution of 400 ms (length of the sliding time window), a time step (to slide the time window) of 50 ms and a time bandwidth parameter set at 3.

The resulting power spectra were then averaged over trials, log-transformed and baseline corrected by subtracting the mean power corresponding to the 500 ms before the beginning of the experimental trial (corresponding to a "rest" period, when participants were observing a blank screen, with their hands still), by using the difference rescale method.

In order to focus our attention on beta frequencies, the time-frequency data were averaged over the 15–30 Hz frequency range (for each electrode).

Finally, we selected the electrodes covering the left sensorimotor cortex and we averaged the signal over electrodes D13-D14-D15-D16-D17-D18-D19, which correspond to CZ-C1-C3 electrodes in the 10-20 system nomenclature (*see also Supplementary Figure 1*).

The averaged signal intensity over left sensorimotor cortex was compared between GTS patient and healthy subjects group, using a standard general linear model approach. Three specific time intervals, each lasting 3 seconds, were analysed: the "pre-movement phase", the "movement phase" and the "post-movement phase" movements. Since the data were normally distributed (Shapiro-Wilk's p-value > 0.05 for all the measures collected, in each group), we performed two 2x3 repeated measures ANOVAs (one for each experimental condition: free ticcing/tic suppression), with "Group" (healthy controls/GTS patients) as a between factor and "Phase" (pre-movement/movement/post-movement) as within factor, to check whether there were between-group differences *in the beta frequency domain* and whether they were influenced by the suppression or the free expression of tics. Planned post-hoc comparisons corrected for multiple comparisons were then performed, in order to explore the significant interactions.

These last analyses were performed by using the software Jamovi (https://www.jamovi.org), based on R packages. For repeated-measures ANOVAs, the software uses the full Welch method for calculating the observed t, while it uses the Welch-Satterthwaite method for calculating the degrees of freedom of the post-hoc tests; post-hoc tests (and degress of freedom) are calculated on the actual model estimates and not on the observed values.

This method is particularly useful when comparing different groups' data, since it does not require the assumption of homoscedasticity (equal variance between populations).

2.6 EEG data – Relationship with clinical data

In order to explore the relationship between the level of beta power modulation and disease severity, we performed a correlation analysis between EEG data recorded in the three different phases of the experiment, with particular attention to the beta modulation in the three movement phases, and clinical scores. Our hypothesis was that the lower the degree of beta modulation observed during the three phases, the higher should have been the severity of the disease.

This was done first by calculating an index of the general beta modulation (Beta modulation=BetaPRE-BetaMOV+BetaPOST). We then correlated this value with the score obtained in the most used questionnaire to assess the severity of the disease in GTS (YGTSS, total score); since we had a strong a-priori hypothesis, we used a one-tail approach. We applied a non-parametric correlation analysis (Spearman rank correlation test), because YGTSS data were not normally distributed (Shapiro-Wilk test's $p<0.05$),

2.7 EEG data – Confirmatory analysis on neighbouring frequencies

In order to confirm the hypothesis that the crucial differences between groups in the two different conditions were focused in beta frequencies, we performed a confirmatory analysis on neighbouring frequencies. This was done by first looking at the average time-frequency plots for the time windows of interest for healthy controls, GTS patients suppressing their tics and GTS patients freely ticcing.

We then focused our attention on alpha frequencies (8-12 Hz): as for the beta frequencies analyses, three specific time intervals were analysed: the "pre-movement phase", the "movement phase" and the "post-movement phase" movements. Two different analyses were performed. Since the data were normally distributed (Shapiro-Wilk's p-value > 0.05 for all the measures collected, in each group), we performed two 2x3 repeated measures ANOVAs (one for each experimental condition: free ticcing/tic suppression), with "Group" (healthy controls/GTS patients) as a between factor and "Phase" (pre-movement/movement/post-movement) as within factor, to check whether there were between-group differences and whether they were influenced by the suppression or the free expression of tics. Post-hoc tests corrected for multiple comparisons were then performed, in order to explore the significant interactions.

3. Results

3.1 Number of tics

In the free ticcing condition GTS patients had an average of 6.3 +/- 4.8 tics, while during the tic suppression condition they had an average of 1.5 +/- 3.3 tics; the average tic ratio was 0.11 +/- 2.4.

The ratio resulted significantly higher than 1, indicating a difference between the two sessions in the number of tics and therefore a successful inhibition during the suppression session (D<0.001; p=0.008). See Figure 2a.

3.2 Behavioural data

We had to exclude the behavioural data of one patient, due to recording issues during the experiment. The speed of movement was not significantly different between the two groups, in both the experimental conditions (free ticcing: U=49, p=0.336, Cohen's d=-0.166; tic suppression: U=51, p=0.402, Cohen's d=-0.034). See Figure 2b.

The amplitude of the movement of the finger was not different between GTS and controls in any of the phases, during the free ticcing condition (pre-movement: U=36, p=0.077, Cohen's d=-0.682; movement: U=49, p=0.336, Cohen's d=-0.166; post-movement: U=46, p=0.251, Cohen's d=-0.547); similar results were found for the tic suppression condition: (pre-movement: U=51, p=0.402, Cohen's d=-0.396; movement: U=54, p=0.515, Cohen's d=0.035; post-movement: U=41, p=0.145, Cohen's d=-0.494). See Figure 2c.

3.3 EEG data

Analysis of EEG recordings in the free-ticcing condition showed a significant effect of the factor "Phase" ($F(2,42)=34.78$, $p < 0.001$, $\eta^2=0.577$), with an expected modulation of beta oscillations during the different phases of the trial, and a significant interaction "Phase x Group" ($F(2,42)=4.45$, $p=0.018$, $\eta^2=0.074$); the factor "Group" was not significant ($F(1, 21)=0.104$, $p=0.219$, $\eta^2=0.071$).

The significant interaction was further tested by means of planned Bonferroni corrected post-hoc tests, showing that there was a significant difference between the two groups only during the movement phase ($t(44.1)=-2.536$, $p=0.015$), but not during the pre-movement ($t(44.1)=-1.077$, $p=0.287$) or during the post-movement phase ($t(44.1)=0.530$, $p=0.599$). In other words, during the free-ticcing condition, a significant modulation in beta band oscillations was observed between the different movement phases in all the subjects (reflecting the general pattern of beta modulation associated with the different phases of the movement), but this modulation was significantly less marked for GTS patients than for control subjects, especially during the movement phase (see Figure 3).

Analysis of EEG recordings in the tic-suppression condition showed a significant effect of the factor "Phase" ($F(2, 42)=63.91$, $p<0.001$, $\eta^2=0.43$), with an expected modulation of beta oscillations during the different phases of the trial; however, the interaction "Phase x Group" ($F(2, 42)=2.59$, $p=0.09$, $\eta^2=0.017$) and the factor "Group" were both not significant ($F(1, 21)=0.077$; $p=0.784$, $\eta^2=0.002$). In other words, during the tic-suppression condition, we observed a significant modulation in beta band oscillations between the different movement phases in all the subjects and this modulation was similar in the two groups, since the effect of the interaction term "Phase x Group" did not reach the threshold of statistical significance (see Figure 4).

All the different conditions are shown in Figure 5.

3.4 EEG data – Relationship with clinical data

We found a significant negative correlation between the beta power modulation during the different phases of the movements in the free ticcing condition and the *YGTSS total score* (motor tics severity subscore + vocal tics severity subscore + perceived impairment; Rho = -0.56; p = 0.046).

The lower the level of the beta power modulation during the three phases of the movement, the higher the severity of the disease (see Figure 6).

3.5 EEG data – Confirmatory analysis on neighbouring frequencies

The analyses performed on alpha frequency data showed that the alpha modulation recorded across the three phases of the task was not significantly different between HC and GTS, in both tasks: in the free-ticcing condition there was a significant effect of the factor "Phase" ($F(2,42)=56.01$, $p < 0.001$, $\eta^2=0.518$), with an expected modulation of alpha oscillations during the different phases of the trial, while the interaction "Phase x Group" was not significant ($F(2,42)=1.18$, $p=0.316$, $\eta^2=0.011$); the factor "Group" was not significant as well ($F(1,21)=1.18$, $p=0.289$, $\eta^2=0.015$).

The pattern of GTS patients in the alpha frequency was similar to the one of HC also during the tic suppression task, since there was a significant effect of the factor "Phase" ($F(2,42)=49.54$, $p < 0.001$, $\eta^2=0.443$), with an expected modulation of alpha oscillations during the different phases of the trial, while the interaction "Phase x Group" was not significant ($F(2,42)=2.82$, $p=0.08$, $\eta^2=0.025$); the factor "Group" was not significant as well ($F(1,21)=0.323$, $p=0.859$, $\eta^2=0.001$).

Finally, the average time-frequency plots for the time windows of interest showed that the power was modulated on average as a function of the task throughout both the alpha and the beta band. However, only during the free ticcing condition GTS patients showed less modulation in the power in the beta band compared with when they were suppressing their tics (see Figure 7).

4. Discussion

The present study was designed to formally test how voluntary tic suppression in GTS patients influences the activity of the sensorimotor cortex during the execution of a voluntary motor task. In particular, we focused our attention on the role of beta oscillations measured over the contralateral sensorimotor cortex, taken as an indicator of motor regulation, and we investigated whether motor activity was sufficient for the normalization of EEG beta power (as suggested by previous studies) and/or whether voluntary tic suppression had a further modulatory effect on this process.

Our study presents a few strengths: first, the recruitment of a clinical sample of GTS patients in a drug-free state; then, the use of a new experimental motor task that allowed us to standardize and control each phase of the movements and, finally, the enrollment of the same GTS sample executing the same motor task during a free ticcing condition and during an intentional tic suppression condition.

We will start this section discussing the behavioural data of the experiment; we will then address the EEG differences between GTS and healthy controls, showing how they are different on the basis of the instructions given by the experimenter about what to do with their tics. Finally, we will discuss how these differences are specific for the beta frequency domain and how they are related to the severity of the disease.

Behavioral findings

GTS patients and controls show a similar behavioural performance across the experimental trials, as confirmed by the absence of any group main effect nor interaction in the behavioural statistical analyses.

Voluntary motor behavior has been studied in GTS with a number of different experimental paradigms, showing partially different results; Georgiou et al. (Georgiou et al., 1995), for example, reported that GTS patients were more reliant than controls on external visual cues during a visually cued button press motor task, as they required an external sensory cue to program a motor sequence efficiently (Georgiou et al., 1995). Recent studies with simple motor paradigms (e.g. simple hand movements) suggest that GTS patients perform like healthy controls when the motor act is simple (Heise et al., 2010; Werner et al., 2011; Zapparoli et al., 2016). Other studies reported an altered behavioral performance, but only in particular demanding conditions (Niccolai et al., 2016).

These discrepancies in the literature could be explained by the adoption of extremely different motor tasks, ranging from internally paced finger movements (Franzkowiak et al., 2010; Franzkowiak et al., 2012), to simple reaction time tasks (Heise et al., 2010), or go no-go tasks (Niccolai et al., 2016; Thomalla et al., 2014). Indeed, the complexity of task could have a direct effect on the behavioral performance in GTS in a proportional manner, as already been suggested by Heise and colleagues (2010), where the slowing of GTS in a simple reaction time task was approaching the significance level (Heise et al., 2010).

The use of an externally triggered simple motor task such ours might have helped in standardizing each phase of the task and the ensuing similar performance of two groups allowed us to test the EEG data, taking in mind that any possible neurophysiological difference between the two groups at the level of the sensorimotor cortex could not be explained by a different behavioural performance.

Beta suppression during externally paced movements in GTS in a free ticcing condition
Our results show a reduction of beta modulation over the contralateral sensorimotor cortex in GTS patients during the execution of the movement with their dominant hand.

This reduced modulation is directly correlated with the severity of the disease: the lower the modulation across the different phases of the motor task, the higher the severity of the disease, as already found in previous studies investigating GTS during the execution of a voluntary motor task with different techniques (Zapparoli et al., 2016; Franzkowiak et al., 2010). This result confirms the strict relationship between the severity of the motoric symptomatology and the abnormal activation of the motor system, directly involved both in the syndrome and in the experimental task.

Crucially, we show that the abnormal modulation of the EEG rhythm in GTS is specific for the beta frequency, as shown by the time-frequency spectra and by the analyses conducted on the alpha frequencies. Indeed, it has been hypothesized that beta oscillations may represent the specific tendency of the sensorimotor system to maintain the "status quo", representing an 'idling rhythm' of the motor system (Engel and Fries, 2010). Following this hypothesis, beta oscillations may allow the processing of feedback signals (such as the proprioceptive ones) required for monitoring the status quo and recalibrating the sensorimotor system (Engel and Fries, 2010).

Strong support for this hypothesis is provided by studies in movement disorders such as Parkinson's disease, in which sufferers find it difficult to initiate or change movements, is notably associated with higher levels of beta oscillations (Schnitzler et al., 2006), suggesting that the enhanced beta activity is preventing changes from the "status quo". The opposite pattern is shown here by GTS data.

Our findings are in line with previous fMRI/MEG studies showing decreased motor cortical activity during movement tasks (Heise et al., 2010; Niccolai et al., 2016; Thomalla et al., 2014).

Thomalla et al. (2014), for example, administered in an fMRI context a go no-go motor task to GTS patients and they found a reduction in the recruitment of primary motor regions during the execution of the task; this was true, however, only in the context of go trials (Thomalla et al., 2014).

Similarly, Niccolai et al. (2016) found a reduction of beta power over sensorimotor regions during pre-movement and movement in GTS patients (Niccolai et al., 2016).

On the other hand, Franzkowiak et al. (2010, 2012) documented an augmented pattern of beta power during self-paced voluntary movements. However, these studies adopted a task that was different from both our task and the other tasks associated with reduced recruitment of the sensorimotor cortex, since patients were asked to perform a self-paced index finger flexion. This type of motor task could be labelled as internally guided, since subjects chose freely when to move their finger and the speed of the finger tapping movements. On the other hand, go/no-go tasks, as well as our task, are examples of externally triggered movements, because the characteristics of the movement are guided by external stimuli (for a detailed discussion about this topic see Jahanshahi & Frith (1998). There is a rich body of fMRI literature showing how internally and externally triggered actions are sub-served by partially different neural patterns. Studies comparing conditions in which subjects have to press a button at a moment of their own choice (internally triggered actions) to conditions in which subjects are prompted to press the button by a visual or acoustic cue (externally triggered actions) report greater activation of the SMA/preSMA associated with internally triggered actions (see Zapparoli et al., 2017, 2018). On the contrary, externally triggered actions seem to be more associated with the activity of visual or auditory cortices, depending on the type of external trigger signal (Cunnington et al., 2002; Jenkins et al., 2000).

The different recruitment of high-level motor regions in internally and externally triggered movements, such as preSMA and SMA, known to have an important influence on the sensorimotor cortex, might explain the different results described here on the electrophysiological activity in the sensorimotor cortex in GTS patients in motor tasks.

Previous EEG studies support this hypothesis, reporting differences in beta oscillatory activity on the contralateral sensorimotor cortex in self-initiated movements when compared with externally triggered actions (Wang et al., 2017).

Abnormal level of beta suppression as a compensatory mechanism to suppress tics?
Even if the experiments by Niccolai et al. (2016) and Franzkowiak et al. (2010,2012) showed opposite results, the authors of both studies hypothesized that the abnormal activation of the sensorimotor cortex was related to tic suppression: even if patients were not told explicitly to

suppress tics, they could have done it automatically in order to achieve a behavioural performance comparable to the one of healthy controls.

In our study, we were able to test this hypothesis, since we explicitly asked our patients to let their tics occur during one experimental session and to actively suppress them in the other one; the significant decrease in the number of tics recorded during the two sessions suggests that patients performed the task as instructed and that they were able to successfully suppress their tics during the experimental session (approximately 10 minutes).

The results of this second part of the experiment show that the level of beta modulation during the tic suppression condition is approximately the same of the healthy controls, as demonstrated by the absence of a significant interaction phase by group.

Thus, the abnormal rhythm recorded over the contralateral motor cortex during the execution of a voluntary movement cannot be considered as a result of tic suppression processes, since it returns to be normal during tic suppression.

An alternative hypothesis might derive by taking into account a recent dynamic causal modelling analysis on fMRI data collected on GTS patients (Zapparoli et al., 2017b): here the authors found a pattern of perturbed intrinsic connectivity patterns in the motor networks of GTS patients, with two competing forces operating in a tug of war-like mechanism: aberrant subcortical afferents to M1, compensated for by inputs from the premotor cortex recruited during the execution of a voluntary motor task (Zapparoli et al., 2017b). This top-down control operated by premotor cortices would override the abnormal subcortical inputs, thus guaranteeing adequate behavioural performance (see also Heise et al., 2010).

As mentioned before, the movements of our experiment were externally triggered; giving what discussed above, we can speculate that during a voluntary but externally triggered movement, the contribution of high-order motor areas such as SMA on the activity of the motor system could be only partial and the sensorimotor cortex might still show an abnormal oscillatory pattern, because of the underlying GTS pathology. Indeed, the structures involved in tic generation are in direct competition with the ones that are responsible of movement production, since we explicitly asked our patients to let their tics occur during the experiment.

When the instructions change and patients are explicitly asked to suppress their tics, a "sum of forces" of premotor regions involved in the motor task and high level prefrontal areas known to be involved in tic suppression (Ganos et al., 2014) might have successfully counterbalanced the aberrant input from the subcortical structures, resulting in a normal oscillatory activity in the sensorimotor region associated with the voluntary movement produced.

This is a hypothesis that might be tested in future, studying in the same sample of patients the primary motor cortex activity during the production of externally and internally triggered movements, during both free ticcing and tic suppression conditions.

Take-home message, limitations of the study and future directions

With this study, we were able to demonstrate for the first time that voluntary tic suppression in GTS is associated with changes in fundamental EEG rhythms, that are linked to motor behaviour in the primary motor cortex. In particular, we showed that the motor activity associated with a voluntary movement, even if externally triggered, is not sufficient to the

normalization of EEG beta power, as hypothesized by previous studies; indeed, successful voluntary tic suppression had a further modulatory effect on this process and operates through the normalization of the beta EEG rhythm during the execution of movements.

It is worth mentioning that we recruited a sample of patients not treated with any of the pharmacological therapies typically used for GTS; such patients would perhaps be from a milder part of the GTS spectrum, and this aspect should be taken into account in the interpretation of the data, with respect to their generalizability.

Another important limitation of our study is related to the spatial resolution of the adopted EEG technique and to our averaging over electrodes approach: indeed, we cannot be sure whether the recorded activity was specifically related to the contralateral primary motor cortex functioning or, more probably, to a wider cortical network involving premotor, motor and somatosensory regions.

Finally, we chose a particular experimental task with long time windows for each movement phase of interest; as already mentioned in the introduction section, this was done on the basis of previous results that guided our a-priori hypotheses. We are aware that this choice leaves the possibility of interesting findings when looking on a more fine-grained scale, which could be the starting point of new studies on the same topic.

Conflict of interest

All the authors do not have any potential sources of conflict of interest.

Author contributions

LZ, AM, EJ, DM, JK designed the experiment; EJ and DM recruited GTS patients; LZ and AM recruited HC participants; LZ and AM collected the data; LZ and JK analysed the data; all the authors contributed to the writing of the present version of the manuscript.

Data accessibility

Our data are available for consultation upon specific request to the corresponding author (LZ).

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Table 1a. Clinical and medical data of GTS patients (pathological scores are marked in bold).

# GTS	Age	BIS	BDI	ASRS	Y-BOCS	YGTSS-m	YGTSS-v	YGTSS total	PUTS	Medication
1	32	**73**	**10**	**6**	2	15	14	49	25	---
2	22	**59**	**14**	**8**	**11**	12	30	42	27	---
3	28	**71**	**12**	**5**	**11**	18	17	65	25	---
4	37	**70**	9	1	6	19	17	56	34	---
5	44	**65**	8	1	**12**	19	4	63	28	---
6	38	**59**	0	**9**	**11**	14	14	28	20	---
7	35	**75**	0	**7**	5	25	25	90	18	Baclofen
8	32	**69**	2	2	0	12	0	32	9	---
9	45	**63**	1	**7**	2	22	19	91	9	---
10	30	**63**	**11**	0	**11**	10	7	47	29	---

Table 1b. Clinical and medical data of HC controls.

# HC	Age	BIS	BDI	ASRS	Y-BOCS	Medication
1	29	20	0	0	0	---
2	40	29	0	1	0	---
3	25	21	1	0	0	---
4	35	10	0	1	0	---
5	34	25	2	1	0	---
6	32	29	0	0	0	---
7	40	25	0	0	0	---
8	25	29	1	0	0	---
9	31	23	0	1	0	---
10	38	19	2	2	0	---
11	30	24	1	0	0	---
12	36	27	0	0	0	---
13	28	31	0	1	0	---

Figure Legends

Figure 1. Graphical illustration of an experimental trial. (a) At the beginning of each experimental trial, a fixation cross was shown in the centre of the screen (duration: 1s). (b) Pre-movement phase: the fixation cross disappeared and a red circle with a small white circle inside was displayed on the right side of the screen; subjects were instructed to stay still and not move (duration: 3s). (c) Movement phase: the red circle became green and it moved horizontally from the right side of the screen to the left side at the speed of 40 mm/s; subjects were instructed to keep the joystick-controlled white circle inside of the moving green circle (duration: 3s). (d) Post-movement phase: once arrived on the left side of the screen - the green circle became again red; subjects were instructed to hold their index finger in place until the end of the trial. (e) When the screen turned blank, subjects could return their finger to the starting position in preparation for the next trial.

Figure 2. Behavioural results.

Figure 3. Beta power modulation (mean values ± standard errors; rescaling method: log transformation and baseline subtraction) during the free ticcing condition in healthy controls (HC) and Gilles de la Tourette patients (GTS), in the three phases of the experimental task (pre-movement, movement, post-movement).

Figure 4. Beta power modulation (mean values ± standard errors; rescaling method: log transformation and baseline subtraction) during the tic suppresion condition in healthy controls (HC) and Gilles de la Tourette patients (GTS), in the three phases of the experimental task (pre-movement, movement, post-movement).

Figure 5. Average beta power (mean values ± standard errors; rescaling method: log transformation and baseline subtraction) during the three phases of the experimental task, in both groups.

Figure 6. Relationship between clinical and EEG data: on the x-axis we reported the level of beta-modulation during the three phases of the task, while the y-axis represents the values of the YGTSS scale (Total score): the lower the level of beta modulation, the higher the severity of the disease as measured by means of the YGTSS scale (Total score). The x-axis ranges from -0.265 to 0.50, while the y-axis ranges from 25 to 93.

Figure 7. Average time-frequency plots in 0-40 Hz frequencies for the time windows of interest (white rectangles) for healthy controls, GTS patients suppressing their tics and GTS patients freely ticcing (rescaling method: log transformation and baseline subtraction).

Supplementary Figure 1. Scalp map of beta oscillations across our participant population (healthy and GTS patients) during the second hold period of the task, compared with background. The scalp map is facing up with the left on the left and right on the right. The white circles show our electrodes of interest. This scalp map shows that the beta power was increased over the contralateral sensorimotor cortex during the second hold period and our a-priori selected electrodes of interest overlap with this area of increase.

a) Number of tics

b) Movement speed during free ticking (left) and tic suppression (right)

c) Movement linear length in each phase of free ticking (left) and tic suppression (right)

Free Ticcing Condition

Tic suppression Condition

Average beta power

Spearman's rho = -0.56
p = 0.048

A
GTS Tic Suppression

B
GTS Free Ticcing

C
Healthy Controls