RESEARCH PAPER

Are premonitory urges a prerequisite of tic inhibition in Gilles de la Tourette syndrome?

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ABSTRACT

Background Despite the common notion that premonitory urges facilitate tic inhibition, no studies have investigated this question systematically. We examined the relation of the trait of premonitory urges with tics and tic suppression. We hypothesised that patients with more urges would be more efficient at inhibiting tics.

Methods 15 adult (14 men, mean age 32.2±7.9 years) pure Gilles de la Tourette syndrome patients participated. Tic severity was evaluated using the modified Rush Video Scale and by employing the Yale Global Tic Severity Scale. Tic suppressibility was assessed from videos of additional periods where patients were instructed to maximally suppress their tics. Rush score based inhibition potency was synthesised by combining the scores in the two conditions. A measure of pure motor tic inhibition potency was also generated based on the number of motor tics alone. Premonitory urges were assessed by the Premonitory Urge for Tics Scale.

Results All participants reported urges preceding their tics and were able to voluntarily suppress their tics. However, there was no correlation between urge scores and the Rush score based inhibition potency or the pure motor tic inhibition potency. Scores of the Premonitory Urge for Tics Scale correlated with the interference subscale item of the Yale Global Tic Severity Scale.

Conclusions Urges and tic inhibition are not directly related. There seem to exist at least two distinct neurophysiological systems of urge/tic generation and tic control in adult Gilles de la Tourette syndrome patients.

INTRODUCTION

In 1980 Bliss, a physician and Gilles de la Tourette syndrome (GTS) patient, reported his awareness of unsatisfied bodily feelings[1] in association with his tics, which needed relief[1] and proposed the voluntariness of tics as habitual responses to these relentless preceding urges.[1] In the following years, the concept of sensory tics[2] was proposed.[3 4] This led to the acknowledgement that Bliss's initial report on sensory phenomena preceding tics was not just an isolated observation but probably a core feature of tics, with a prevalence of more than 90%.[3–5] Awareness of premonitory sensations gradually emerges over the years after the onset of tics,[3 4] suggesting that urges are a result of becoming aware of tics as extra movements escaping, at least partially, voluntary control. In other words, urges could be interpreted as a result of an adaptive process of increasing the gain for the perception of imminent movements. Increased perceptual gain might result in earlier awareness that the movement was about to occur, creating an opportunity for tic suppression.[1 4–7] In essence, GTS patients might learn to 'hyperattend' to somatic signals that precede movements but that go unperceived in individuals without GTS.

In addition, based on neurophysiologic evidence of studies addressing volitional movement control,[6 7] it was hypothesised that different neuronal mechanisms may be involved in the generation of tics preceded by sensory urges and those without, with the former stirring awareness and being considered 'voluntary' and the latter going unnoticed and thus conceptualised as 'involuntary'.[4 7]

The hypothesis that tics preceded by premonitory sensations could be inhibited more efficiently than tics without premonitory sensations has so far only been studied indirectly,[5] using questionnaires, and with negative results. Furthermore, two video based studies examining the effects of voluntary tic suppression on reported urge intensity led to equivocal results.[8 9]

Thus although the hypothesis, that premonitory urges act as 'sensitisers' in tic perception and may allow tic suppression, is plausible and appealing, there have been no studies addressing this.[10] To this end, we examined the relationship between premonitory urges and tic suppression in a sample of adult 'pure' GTS patients. We hypothesised that patients with stronger urges would be better at inhibiting tics.

MATERIAL AND METHODS

Eighteen adult GTS patients (three women) aged 20–46 years (mean age 31.9±7.28 years) and without clinically manifest comorbidities were recruited from the GTS outpatient clinic in the Department of Neurology, University Medical Center Hamburg-Eppendorf. All patients underwent a thorough clinical assessment (AM, CG) based on a semistructured neuropsychiatric interview. The diagnosis of GTS was made according to DSM-IV criteria.[11] Lifetime GTS associated symptoms were assessed using the Tourette syndrome Diagnostic Confidence Index.[12] Tic severity was evaluated with the Yale Global Tic Severity Scale (YGTSS).[13] Actual tic frequency was measured using the Modified Rush Video Scale (MRVS).[14] Patients were screened for comorbidities using the attention deficit hyperactivity disorder self-assessment scale (German version; ADHS Selbstbeurteilungsskala),[15] the Yale–Brown Obsessive

Compulsive Scale[16] and the Beck Depression Inventory.[17] Patients with symptoms or signs of attention deficit hyperactivity disorder, obsessive compulsive disorder or depression above the diagnostic threshold were excluded from the study. Thus, three patients were excluded because of psychiatric comorbidities (two with depression and one with obsessive compulsive behaviour). Of the remaining 15 'pure' Tourette patients, two were receiving neuroleptic medication (tiapride) and one had been diagnosed with idiopathic epilepsy in childhood (currently non-medicated).

Disease specific quality of life was assessed with the GTS-Quality of Life Scale (GTS-QOL).[18] The trait of premonitory urges was evaluated by means of an interview and quantified using the available German version of the Premonitory Urge for Tics Scale (PUTS).[19] This is a self-report scale with good internal consistency and easy applicability.[19 20] Although initially developed for children, the PUTS has already been applied in both paediatric and adult GTS populations.[19 21] Patients were also asked on the occurrence frequency (<25%, >25% and <50%, >50% and <75%, >75%, 100%) and the exact body location of premonitory sensations and tics.

Tic suppressibility was assessed in an additional sequence to the MRVS, where patients left alone in the room were instructed to inhibit their tics as best they could for 5 min of video recording (2.5 min head and shoulders and 2.5 min whole body view). Videos were evaluated by a rater experienced in tic rating (UK). Tic inhibition was expressed as inhibition potency (IP), which was defined as follows: IP = RF-RI/RF, where RF is the Rush score during 'free' ticcing and RI the Rush score during tic inhibition. Thus the higher the IP value, the more efficient the inhibition potency. Additionally, to evaluate the ability to inhibit motor tics only, corresponding motor tic inhibition potency (IP motor) was calculated from the count of motor tics during free ticcing (TF motor) and during tic inhibition (TI motor): IP motor = TF motor − TI motor/TF motor. All clinical assessment scales were employed immediately prior to the MRVS evaluations.

The study was performed in accordance with the Declaration of Helsinki and all study participants gave written informed consent prior to study attendance. This study was approved by the local ethics committee.

A Student's t test for dependent samples was applied to assess the differences between RF and RI. We tested the primary hypothesis that PUTS scores and IP as well as IP motor show a positive correlation using Pearson coefficients. We also explored the relationship between PUTS scores and the YGTSS subscores (YGTSS total and number of tics, tic frequency, tic intensity, tic complexity, tic interference and tic related impairment) as well as the GTS-QOL using Pearson coefficients. No correction for multiple testing was applied. A p value <0.05 was considered significant.

RESULTS

Patient characteristics and tic scores are given in table 1. All patients had premonitory sensations and 14 considered their tics as partially voluntary. Four reported premonitory sensations before each tic, one before more than 75% of tics, two before <75% but more than 50%, three before <50% (but more than 25%) and five before <25% of tics. Most common body areas affected by tics, determined on the basis of the Rush scores, and localisation of premonitory sensations, as reported by the patients, are presented in figure 1.

As expected, RF (8.1±2.7) differed from RI (4.9±3.0) (t (14)= 6.06, p<0.001) (table 1). TF motor (66.8±51.3) also differed from TI motor (22.6±24.6) (t (14)=5.35, p<0.001) (table 1).

Table 1 Patient characteristics (n=15)

Characteristic	Mean±SD
Age (years)	32.2±7.9
Sex (F/M)	1/14
Age at symptom onset (years)	7.3±2.7
DCI	50.3±11.1
YGTSS total	30.5±11.5
Premonitory sensations present	15/15
PUTS	25.1±4.6
GTS-QOL	6.5±6.4
Rush score during 'free' ticcing (RF)	8.1±2.7
Rush score during tic inhibition (RI)	4.9±3.0
Inhibition potency (IP)	0.4±0.3
Motor tics during 'free' ticcing (TF motor)	66.8±51.3
Motor tics during tic inhibition (TI motor)	22.6±24.6
Inhibition potential for motor tics (IP motor)	0.7±0.2

DCI, Diagnostic Confidence Index; GTS QOL, Gilles de la Tourette syndrome-Quality of Life Scale; PUTS, Premonitory Urge for Tics Scale; YGTSS, Yale Global Tic Severity Scale.

There were no significant correlations between PUTS and IP, IP motor, GTS-QOL values and YGTSS scores (total or subscales). There was, however, a correlation between PUTS and the interference subscale score of the YGTSS (r=0.546, p=0.035) (table 2).

DISCUSSION

The main finding of the present study is that although GTS participants were able to voluntarily suppress tics when instructed to do so, there was no correlation between their tic inhibition capacity determined from video recordings and the trait of their preceding urges. There was also no relation between the severity of urges and GTS-QOL or YGTSS, apart from a positive correlation with the interference subscale score. This correlation suggested that patients with stronger urges feel that their actions are interrupted to a greater extent by tics.

These findings are in line with the reported results of Banaschewski *et al*.[5] Their cross-sectional survey study considered the

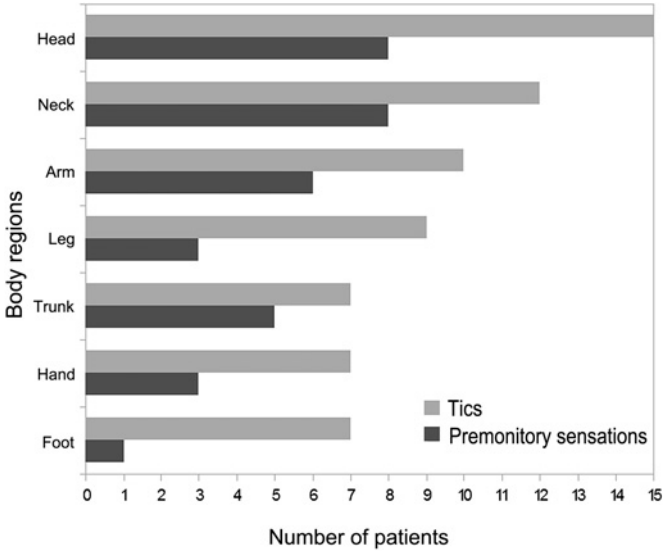

Figure 1 Localisation frequency per body region of tics, as determined on the basis of Rush video segments, and premonitory sensations, as reported by the patients.

Table 2 Correlation between PUTS and IP, GTS-QOL and YGTSS (subscale) scores

	R (p values)
Inhibition potential (IP)	−0.153 (0.586)
Inhibition potential for motor tics (IP motor)	−0.316 (0.251)
GTS-QOL	0.322 (0.242)
YGTSS Total	0.386 (0.155)
YGTSS: number of tics	0.175 (0.532)
YGTSS: frequency of tics	0.356 (0.192)
YGTSS: intensity of tics	0.155 (0.581)
YGTSS: complexity	0.319 (0.247)
YGTSS: interference	0.546 (0.035)*
YGTSS: impairment	0.215 (0.442)

*$p<0.05$.
GTS-QOL, Gilles de la Tourette syndrome-Quality of Life Scale; PUTS, Premonitory Urge for Tics Scale; YGTSS, Yale Global Tic Severity Scale.

capacity to suppress tics as a dichotomous trait, and found no correlation with premonitory urges. They concluded that despite the belief that premonitory urges may facilitate tic suppression of the impending tic, children without premonitory sensations are also able to inhibit tics by employing other behavioural strategies.[5] Furthermore, they hypothesised that tic suppressibility and premonitory urges are due to different neuronal mechanisms.[5]

On the other hand, a small case series of five adult GTS patients has reported a link between tic suppression and subjective intensity of premonitory urges[8] in three patients. This was interpreted as a result of a developmental conditioning process.[8 19] However, these results could not be replicated in a follow-up study by the same group, casting doubts on the reliability of these findings.[9]

Taken together, the view of urges as a prerequisite or 'prestage' of successful tic inhibition is probably no longer tenable. The present study, the first one to assess the relation between premonitory urges and tic inhibition in an adult pure GTS population, employing quantitative video measurements, lends experimental support to this notion. Furthermore, in light of the fact that we studied adult GTS patients, who by their age should have had more time to adapt to the process of 'sensory tic inhibition', any correlation between urges and tic suppression would have had the maximum possibility of appearing, if it existed.

Concerning the neural basis of urges related to tic elicitation, a subset of distinct cortical areas is likely to be involved. In particular, it has been demonstrated that direct electrical stimulation of the supplementary motor area can elicit a series of simple, regional and complex motor responses in a somatotopic order, but also of sensations of an 'urge to move' and a 'feeling of motion', in the absence of any motor response.[22] Additionally, direct electrical cortical stimulation of posterior parietal regions (Brodmann areas 39, 40) can produce a sensation of will/urge to move.[23] It was suggested that the former effects might reflect generation of motor output, and the latter prediction of the sensory consequences of movement.[23]

Premonitory urges in GTS do not seem to solely have the phenomenology of intentional action or will. Rather, they may resemble somatic sensations, often described as 'tension', 'impulsion', 'pressure', 'ache', etc.[3 4 24] To this end, the insula has been found to play a key role in somatosensory representation, tactile recognition and recall, and the generation of visceral sensations.[25 26] Interestingly, a functional MRI (fMRI) study, which addressed the question of brain activations 2 s prior to tic onset in GTS patients and reported premonitory urges, revealed a distinct network of cortical areas involving the supplementary motor area, the insula, the parietal operculum and the anterior cingulate cortex, mainly active prior rather than at tic onset.[27] Furthermore, a recent meta-analysis on fMRI studies addressing the question of urges preceding actions has proposed an anterior insular–cingulate motor area—mid insular loop, as a functional model of urges to act.[28] Finally, structural MRI studies suggested that the primary somatosensory cortex plays an important role in GTS pathology[29 30] with volumetric changes correlating with urge severity.[29]

With regard to tic generation, two fMRI studies in GTS patients with comorbid disorders have demonstrated activations in wider sensorimotor networks, implicating frontomesial structures (including the anterior cingulate cortex and the supplementary motor area).[27 31] These findings are corroborated by evidence of structural studies.[29 32 33] These regions can be considered auxiliary to the primary areas of motor control (basal ganglia–cortical and primary sensorimotor interhemispheric motor loops) which play a role in tic generation.[29 30 33] To summarise, brain activity prior to tic generation seems to include both voluntary motor circuits and circuits associated with somatic sensation.

Finally, concerning tic suppression and inhibitory motor control, neurophysiological[34] and neuroimaging[35 36] evidence has implicated prefrontal structures. For example, a neurophysiological study focusing on tic inhibition has found greater coherence of frontomesial activations during a Go/No-go task.[34] Interestingly, it has been shown that repetitive TMS over the supplementary motor area and not the primary motor cortex has been shown to be effective in tic reduction.[37]

Thus premonitory urges before tics do not seem to represent adaptively increased perceptual gain for the purposes of tic suppression. How then might such urges arise? We consider that two distinct functional systems may be implicated. The 'original' pathology would involve dysfunctional motor control pathways, as proposed by models of corticostriatal disinhibition.[38 39] This would produce parallel but distinct premotor[27 31] and sensory loop activations.[28] The former pathway would be responsible for tic generation and the latter for the premonitory sensations. From there on, separate control mechanisms may kick in, one related to tic suppression and the other related to urges. This notion is supported by evidence of altered functional connectivity implicating two separate neural systems, an adaptive online (frontoparietal) and a stable set (cingulo-opercular) control system.[40] It is therefore conceivable that tic state is an expression of the online motor control system and the trait of urges of a stable set modulatory system. These would constitute parallel manifestations of the same disorder.

A possible limitation (but also a potential strength) of this study is that we only included adult pure GTS patients without relevant comorbidities, so that the sample we studied is probably not representative of the whole GTS spectrum. Also, the sample size was small, although still larger than that of other studies on this topic.[8 9] Ideally, in a larger GTS sample, evaluation of patient subgroups according to their reported urge tic frequency and examination of the same correlation between PUTS and tic inhibitory capacity would provide more indepth information. Furthermore, with the development of online premonitory urges evaluation methods, such as those proposed by Himle and Woods,[8] not only is examination of their trait possible but also a one to one assessment of the state of urges and tic inhibition, which may provide deeper insights into their

relation. In addition, it would be of great interest to examine the interaction of the evolving tic inhibition and the developing premonitory urges in younger GTS populations. Tic control mechanisms appear to differ between age groups, presumably as a result of adaptive processes in the developing GTS brain.

In summary, this work shows that premonitory urges and tic inhibition in GTS are not tightly linked, as previously thought. This might be explained by at least two distinct neural systems of tic/urge generation and tic control in adult GTS patients. This sets the stage for future systems neuroscience research of tic generation and tic control.

Contributors All authors are listed along with their specific roles in the project and preparation of the manuscript. These included: (1) Research project: (A) conception, (B) organisation, (C) execution (data acquisition). (2) Video Evaluation. (3) Statistical analysis. (4) Manuscript: (A) writing of the first draft, (B) review and critique. CGa: 1A, 1B, 1C, 2, 3, 4A. UK: 1B, 1C, 2, 4A. OS: 1B, 1C, 4B. SK: 3, 4A, 4B. PH: 4B. CGe: 4B. VR: 4B. GT: 4A, 4B. AM: 1A, 1B, 4A, 4B.

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