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1. Introduction

1.1 Inhibitory motor control in health and movement disorders

The capacity to control our actions and guide them according to our goals is a fundamental characteristic of behavioural flexibility and a key aspect of volition ¹. For example, the ability to either refrain from executing a prepared action (e.g. not clicking the enter button to send an angry e-mail) or disengage from ongoing motor behaviours (e.g. stop pressing the gas pedal when approaching a red light) is intrinsically connected to our ability to thrive in a stimulus-rich environment. The importance of the capacity to inhibit actions is also a central theme of regulatory laws, which penalize consequences of impulsive actions in children and adolescents or people with structural brain damage, where this capacity is respectively underdeveloped or diminished, differently from healthy adults ²⁻⁴. Religious and moral codes ('no sex until marriage') and social campaigns ('just say no') frequently assume an entire range of action inhibition capacities, further emphasizing the importance of voluntary inhibitory motor control in social life. Crucially, effective inhibitory control early in life has been associated with better psychosocial measures, including educational achievements, stress-coping capacity and sense of self-worth ⁵.

However, despite the intrinsic importance of voluntary inhibition of actions in daily living, the effects of inhibitory control are difficult to observe, as the successfully inhibited behaviour never occurs. On the other hand, the consequences of insufficient behavioural inhibition can be readily exposed in a spectrum of neuropsychiatric and movement disorders ⁶. These disorders not only provide clear clinical examples of the relevance of voluntary inhibitory control in the successful fulfilment of life goals, but also offer a unique opportunity to experimentally explore the neural circuitry of inhibitory control ⁶. Among the wide range of movement disorders, several conditions known as *hyperkinesias* present with excessive involuntary motor output that is thought to reflect disinhibition at different levels of the motor system ⁶. For example, in cortical myoclonus, single, irregular and rapid bursts of involuntary muscle activation are viewed as the result of disinhibition of the primary sensorimotor cortex and possibly combined with cerebellar damage ⁷. In contrast, the brief jerks of brainstem myoclonus are suggested to reflect excessive brainstem excitability ⁸ and choreic movements are one behavioural consequence of neurodegeneration within the striatum, where there is severe loss of inhibitory Gamma-aminobutyric acid (GABA)ergic medium spiny neurons ^{9,10}. In dystonia, corticospinal disinhibition in motor and sensory systems is a key pathophysiological finding ^{11,12}. However, beyond the aforementioned examples, where inhibitory deficits lead to non-physiological

movement patterns, one particular neuropsychiatric movement disorder has long puzzled medical literature as a prototypical example of behavioural disinhibition due to the unique qualities of its abnormal motor behaviours known as tics.

1.2 Tic disorders and Tourette Syndrome

In current literature, tics are defined as movements or sounds that typically resemble voluntary actions, but appear repetitive, often exaggerated in intensity and are not bound to a certain social context¹³. Tics are categorized as either *clonic* or *tonic*, based on the duration of their occurrence, or *dystonic* if they lead to prolonged and abnormal body postures^{14, 15}. Tics are labelled as *simple*, to describe movements as a result of activation of individual muscles (e.g. eye twitching, head jerking) or brief sounds without meaningful content (e.g. sniffing sounds, simple vocalizations). In contrast, *complex* tics denote motor behaviours and sounds that may be misunderstood as having social intent, although by definition they do not (e.g. winking, sending kisses, shrugging shoulders). Other complex tics include palii- (the repetition of actions or sounds), echo- (the imitation of movements or sounds in the absence of explicit awareness) and coprophenomena (the execution of socially obscene actions or words without intent), although the question as to whether all these behaviours should be truly labelled as tics has more recently been disputed¹⁶. It is noteworthy that any possible movement or sound may be a tic-behaviour, and thus, among the entire range of hyperkinetic movement disorders, tics have the widest phenomenological variability. Tics that significantly interfere with the execution of ongoing voluntary actions are labelled as ‘blocking tics’¹⁷. The term ‘malignant tics’ refers to tics that may lead to serious injuries, as for example intense neck jerks leading to cervical myelopathy, or repetitive head banging as the cause of intracranial haemorrhage¹⁸. Malignant tics are not common.

Tics are prevalent in many different disorders, including neurodevelopmental syndromes and neurometabolic or neurodegenerative conditions¹³, but are most commonly documented in primary tic disorders. Tourette syndrome (TS) is the prototypical primary tic disorder encountered in clinics and affects up to 1% of school-age children¹⁹. It is defined as a syndrome, which occurs before the age of 18 and where at least two motor tics (i.e. tic movements) and one phonic or vocal tic (i.e. tic sounds) have been present for at least a year²⁰. Beyond TS, the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) of the American Psychiatric Association also recognises other primary tic disorders, to include ‘chronic motor/vocal tic disorder’, where the main presentation before

the age of 18 is that of isolated motor or vocal tics respectively, and ‘provisional tic disorder’, where tics have been present for less than a year’s period²⁰. Most likely, tics in all these disorders share the same pathophysiological underpinnings²¹. However, it should be noted that most research in tics stems from studies of patients with TS, as they the most prevalent clinical population.

Tics in primary tic disorders and patients with TS appear during early development and are typically first noted in children aged 4 – 6 years. However, they may already occur within the first years of life^{19,22,23}, parallel to the developing emergence of voluntary actions. The clinical course of tics is variable and longitudinal case-series have shown that tics persist in adulthood in the majority of cases²⁴⁻²⁶. However, worst-ever tic period is typically reported in early adolescence (ages between 12 – 14 years), after which the severity of tics most often improves. Unfortunately, large longitudinal studies to determine robust predictors of tic persistence into adulthood are missing. Of note, the distribution of tics in primary tic disorders and TS is not random, but systematic. Tics most commonly affect the face alongside the neck and shoulders¹⁵. Also, in the majority of patients with TS neuropsychiatric comorbidities often complicate clinical presentation and may further impact tic outcome¹⁵. Indeed, approximately 90% of patients with TS will also suffer from disorders, such as attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety disorders and depression^{15,27}.

1.3 The pathophysiology of tics

The pathophysiology of tics has a long history of misconceptions and confusion. Historically, tics were considered as signs of ‘hysteria’²⁸. The reasons behind that include both the phenomenology of tic behaviours, as they strikingly resemble voluntary actions but are often exaggerated and on occasion socially-inappropriate, and the often-challenging behavioural facets of people with tics due to the aforementioned range of neuropsychiatric comorbidities. However, Gilles de la Tourette’s seminal two-part study of “...*a nervous affliction characterized by motor incoordination with echolalia and coprolalia...*” placed tic disorders in a different context²⁹. According to Tourette, the *malady of tics* was a progressive and hereditary syndrome, which despite fluctuations in the expression of symptoms, was resistant to any treatment at the time. However, the profound overlap of tics with voluntary actions continued to create resistance in the acceptance of tic-behaviours as involuntary movements, which is largely ongoing today.

Indeed, many of the neurophysiological characteristics of tics, such as the pattern of muscle activation and burst duration, can be indistinguishable from those of voluntary actions. Moreover, tics, similar to volitional movements, are often preceded by an impending urging somatic (interoceptive) experience³⁰, which is typically relieved upon the execution of a tic³¹. Consequently, people with tics often view their tic movements as partially voluntary responses to involuntary sensory (urge) signals³². This perception clearly differs from the perception of other hyperkinetic movement disorders, such as dystonia or myoclonus, where patients clearly describe their abnormal movements as purely involuntary and beyond their control³². Accordingly, some behavioural treatments view tics as reinforced stimulus-response associations, as result of negative reinforcement^{33,34}, where the occurrence of a tic provides temporary relief from the pressing experience of the premonitory urge. Evidence from reinforcement learning and habit formation studies in patients with TS further support this view^{35,36}.

However, the view of tics as purely repetitive/habitual volitional movements (“nervous habits”, “nervous dispositions” or “psychological tics”) is not in line with other key clinical and neurophysiological data. First, tics typically lack behavioural flexibility, which is characteristic for voluntary actions. That means that even though tic patterns may change over time, most tics characteristically lack contextual adaptation, and within a given time period (from days to years) their phenomenology typically remains unchanged (e.g. blinking, eye rolling, sniffing, head jerking). Second, different from voluntary actions which are normal constituents of our behavioural output, the occurrence of tics may actually interfere with ongoing voluntary motor output. Blocking tics are examples of such interference, which may on occasion even temporarily lead to complete cessation of any behavioural output¹⁷. We have previously explored the potential pathophysiological implications of blocking tics elsewhere¹⁷. Third, the subjective experience of tics - typically perceived as unpleasant - differs from that of voluntary behaviours³². Indeed, premonitory urges preceding tics are typically phenomenally intense and aversive somatic sensations³⁷. Finally, the neurophysiology of tics differs from that of voluntary actions. Although movement kinematics for most tic behaviours may be indistinguishable from volitional motor output, tics are only rarely preceded by movement-related cortical potentials (MRCP; Bereitschaftspotential)³⁸⁻⁴⁰. Crucially, the duration (shorter) and morphology of tic-related MRCPs differs from that of comparable volitional motor output³⁸. Taken together, these findings support the view that the generation of tics may have some

minimal involuntary component. Neuropathological studies of patients with TS and animal models of tic disorders further support this view ⁴¹⁻⁴⁵.

1.4 Voluntary inhibitory tic control

Perhaps one of the greatest sources of confusion in the pathophysiological understanding of tic disorders and their position within the voluntary-involuntary continuum is their characteristic susceptibility to volitional inhibitory control. This means that patients can voluntarily suppress their abnormal motor output for variable periods of time (typically from seconds to minutes). Voluntary tic suppression is both specific and selective. This means that during the ongoing inhibition of targeted tics, the performance of voluntary actions remains unaffected. At the end of the effortful inhibitory process, tics characteristically reappear ³¹. The strong effects of voluntary inhibition over tic behaviours is typically used in the clinical setting to distinguish tics from other jerky hyperkinesias, as the ones described above, that cannot be voluntarily suppressed. Most importantly, the capacity to voluntarily suppress tics on demand lies at the core of behavioural treatments of tics.

The two main behavioural interventions specifically designed for the reduction of tics are habit-reversal training (HRT) - either as standalone or together with its multiple component treatment package of comprehensive behavioural intervention for tics (CBIT)- and exposure-response prevention (ERP) ^{33, 34, 46}. These interventions are first-line recommendations of international treatment guidelines and pragmatic treatment approaches (reviewed in ⁴⁷). Both in HRT/CBIT and ERP, patients are provided with appropriate neurocognitive tools to enhance their volitional capacity to control tics. Here, the association of tics with premonitory urges is viewed as a key-component of tic pathophysiology and a central element to voluntary tic inhibition. This proposition stems from early clinical descriptions of tic disorders and the acknowledgment that premonitory urges are a driving force both for the emergence of tics, as well as their voluntary control ⁴⁸. However, the exact relation between premonitory urges, tic generation and voluntary tic inhibition remains unclear and several studies, which addressed this complex issue have provided conflicting results (reviewed in ⁴⁹). For example, data collected on the basis of phone interviews of 254 children and adolescents with TS (ages 8-19) revealed a striking dissociation between voluntary inhibitory tic control and presence of premonitory urges ⁵⁰. Indeed, 64% of study participants reported being able to voluntarily suppress their tics, but only 37% reported awareness of premonitory urges preceding their tics ⁵⁰. Most importantly, the intrinsic role of voluntary tic inhibition in the scientific study of the pathophysiology of tic disorders has been

largely overlooked. These questions are not only of academic interest, but have important implications, because understanding how voluntary tic inhibition temporarily reduces tics may profoundly impact the treatment of tics, which still remains unsatisfactory for a majority of clinical cases. Indeed, only about half of patients with tics respond to HRT/CBIT or ERP and tics are typically reduced by about 32% (range 25.8-37.5%; data for CBIT) ⁵¹.

The five studies comprising this Habilitationsschrift explicitly explore core qualities of behavioural markers and neural correlates of voluntary tic inhibition in adolescents and adults with TS with the ultimate goal of providing novel insights into tic pathophysiology and effective tic control.

1.5 Research topics

The first two studies presented here explore the behavioural associations of voluntary tic inhibition. Specifically, the first study explores the association of voluntary tic inhibition with premonitory urges. A key assumption of previous literature is that premonitory urges are a prerequisite of voluntary tic inhibition, i.e. a patient can only inhibit their tics as long as they are aware of their impending onset. Given a range of controversial evidence on the topic (reviewed in ⁴⁹) and a wealth of different methodologies to examine this, we here address this question and introduce a novel and simple measure of voluntary tic inhibition in patients with chronic tic disorders and TS. Specifically, we assess whether the capacity to voluntarily inhibit tics is related to the perceived intensity of premonitory urges.

Using this simple clinical measure of voluntary tic inhibition, the second study is informed by the clinical observation that patients with tics can selectively suppress a target tic behaviour, while other movements, as for example voluntary actions, remain unaffected. This implies that patients with tics have the capacity to selectively distinguish between neuromotor signals related to tic behaviours and those related to voluntary actions. The key research question of this second study, therefore, is how voluntary tic inhibition relates to the awareness of voluntary actions.

The third study explores the effector specificity of voluntary tic inhibition. Indeed, in the previous two studies, voluntary tic inhibition was assessed as the general capacity to suppress tics across individuals. However, patients can selectively target and suppress isolated tic behaviours, as for example those that may not be socially acceptable (e.g. inhibition of tic-

vocalisations during school classes, in the presence of ongoing blinking tics). This third study explores the spatial properties of voluntary tic inhibition and focuses on the concept of somatotopic selectivity of the inhibitory process.

The remaining two studies expand beyond behavioural methodology to address the neural correlates of inhibition in TS using functional magnetic resonance imaging (fMRI). Informed by the influential disinhibition theory in TS (reviewed in ²¹), the fourth study specifically assesses the neural underpinnings of voluntary action control in a sample of well-characterized adults with TS. The fifth and final study explores the neural events associated with voluntary tic inhibition.

2. Publications

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

Ganos C, Kahl U, Schunke O, et al. Are premonitory urges a prerequisite of tic inhibition in Gilles de la Tourette syndrome? *J Neurol Neurosurg Psychiatry* 2012;83:975-978.

URL: <http://dx.doi.org/10.1136/jnnp-2012-303033>

Classic literature of voluntary tic control suggests that the presence of premonitory urges facilitates tic inhibitory capacity. According to this view, premonitory urges would serve as triggers for a cognitive process of voluntary inhibition, which would reduce tic output. However, only few studies addressed this experimentally and produced conflicting results. Here, therefore, we systematically examined the relation between the trait of premonitory urges and the capacity to voluntarily inhibit tics in a sample of adults with TS. According to previous literature, we hypothesised that the presence of premonitory urges would facilitate voluntary tic inhibition. Fifteen adult patients with TS (14 men, mean age 32.2 years) with no relevant neuropsychiatric comorbidities participated in the study. Actual tic severity was captured by means of the Yale Global Tic Severity Scale and the Modified Rush Video Scale (MRVS). A novel measure of voluntary tic inhibitory capacity was computed based on video-captured tic scores during “free ticcing” and “voluntary tic inhibition” conditions. The Premonitory Urge for Tics Scale assessed the perceived trait measure of premonitory urges. All participants reported being aware of premonitory urges and being able to voluntarily inhibit their tics. The reported intensity of premonitory urges correlated with the interference subscale of the Yale Global Tic Severity Scale. This indicates that patients with stronger experience of premonitory urges preceding tics may also perceive that their actions are interrupted to a greater extent by the abnormal movements. However, there was no relation between the reported intensity of premonitory urges and the capacity to voluntarily inhibit tics. This result suggested that the capacity to voluntarily inhibit tics is largely independent from the perceptual experience associated with tics. This implies a dissociation between a putative urge and tic generator and voluntary tic control in adults with TS.

2.2 Volitional action as perceptual detection: Predictors of conscious intention in adolescents with tic disorders.

Ganos C, Asmuss L, Bongert J, Brandt V, Munchau A, Haggard P. Volitional action as perceptual detection: predictors of conscious intention in adolescents with tic disorders. *Cortex* 2015;64:47-54.

URL: <http://dx.doi.org/10.1016/j.cortex.2014.09.016>

Voluntary tic inhibition specifically targets tic behaviours, whereas ongoing voluntary actions remain unaffected. This suggests that in patients with tic disorders, motor signals related to tic behaviours are processed and classified separately from those related to voluntary actions. However, in light of the first study, which showed a clear dissociation between voluntary tic inhibition and premonitory urges, the behavioural correlates of this classification process remain unclear. In this study, therefore, we sought to explore the relation between awareness of voluntary actions with the perceptual experience of tics and voluntary tic control in a well-characterized sample of 27 adolescents with TS and 30 healthy controls. We used Libet's mental chronometry⁵². Here, study participants make judgments as to the timing of either their motor actions or, in different blocks, their motor intentions. First, we were able to replicate previous reports and showed that the conscious intention to act occurs several hundred milliseconds before a simple voluntary action (keypress). A multiple regression model between tic-specific factors, to include the intensity of premonitory urges, voluntary tic inhibitory control and tic severity revealed strong associations between the first two factors and intention awareness, but no effect of tic severity. Patients who reported stronger premonitory urges preceding their tics showed delayed intention awareness. In contrast, patients who were more able to suppress their tics made earlier judgements of their intention awareness of voluntary actions. Crucially, the capacity to voluntarily inhibit tics was not related to the reported intensity of premonitory urges. Taken together, these findings provided evidence that the experience of voluntary actions in patients with tic disorders relies on a perceptual discrimination process between competing neuromotor signals. In the presence of strong interference between these signals, as in patients with greater levels of premonitory urges, the detection of action intention might be more difficult and thereby delayed. On the other hand, patients who have earlier intention awareness might also have better capacity to distinguish between the different types of neuromotor signals and thereby greater capacity to voluntarily control their tics.

2.3 The Somatotopy of Tic Inhibition: Where and How Much?

Ganos C, Bongert J, Asmuss L, Martino D, Haggard P, Münchau A. The somatotopy of tic inhibition: Where and how much? *Mov Disord.* 2015 Aug;30:1184-9. URL: <http://dx.doi.org/10.1002/mds.26188>.

In the previous two studies voluntary tic inhibition was examined as the general capacity to suppress tics across individuals. However, one key feature of voluntary tic inhibition is effector specificity: Patients can suppress any given tic behaviour on demand. However, the somatotopic specificity of voluntary tic inhibition has not been previously explored. It, therefore, remains unclear whether the strength of voluntary tic inhibition varies across the different body parts. This finding could have important implications not only for therapeutic interventions, but also for the understanding of the neurocognitive mechanisms underlying the interaction between tic generation and voluntary tic inhibition. In order to address the somatotopic properties of voluntary tic inhibitory control, we, therefore, analysed video segments of 26 adolescents with TS during the different conditions of free ticcing and voluntary tic inhibition. We used two measures for our assessments: the distribution of tic counts across the different body parts of our studied population and the normalized ratios of voluntary tic inhibitory capacity for each body part. We then investigated the relation between body-part specific voluntary tic inhibition and tic frequency for that body part. First, we replicated the characteristic pattern of somatotopic distribution of tics across our sample. Ocular and other cranial tics were most common, followed by the neck/shoulders and the limbs. The trunk exhibited the fewest tic behaviours in our sample. Second, there was a significant negative correlation between tic frequency and voluntary inhibitory tic capacity across body parts. Voluntary tic inhibition was least effective for the body parts that were most affected by tics. These data indicate that voluntary tic inhibitory capacity is not random, but a somatotopically selective process. The specificity of voluntary tic inhibition to suppress tic behaviours without affecting voluntary motor output could explain these findings. We suggest that voluntary tic inhibition selectively targets weak motor signals such as those related to less frequent tics and is less efficient for strong neuromotor commands, as for example those related to frequently occurring tics or voluntary actions. Future behavioural intervention studies to treat tics should, therefore, factor somatotopic tic distribution in the design and analyses of their results.

2.4 Action Inhibition in Tourette Syndrome

Ganos C, Kühn S, Kahl U, Schunke O, Feldheim J, Gerloff C, Roessner V, Bäumer T, Thomalla G, Haggard P, Münchau A. Action inhibition in Tourette syndrome. *Mov Disord.* 2014 Oct;29:1532-8.

URL: <http://dx.doi.org/10.1002/mds.25944>

The spatial characteristics of voluntary tic inhibition reveal somatotopic specificity. However, the overall inhibitory tone could be influenced by further factors, such as the general capacity to control any given motor behaviour, including voluntary actions. According to one influential account, tics represent disinhibited fragments of motor programs that escape voluntary control due to deficits in motor inhibitory tone⁵³. This view predicts that the capacity to inhibit voluntary actions is also impaired. However, literature on this topic remains unclear. Studies provided evidence for either deficient, normal or even enhanced motor inhibitory control over voluntary actions. This could be due to heterogeneity of studied populations (e.g. patients with TS with ADHD, OCD or other comorbidities vs patients without) and tasks to study inhibition (e.g. Go-NoGo, Simon task etc). Crucially, the neural correlates of action inhibition remain understudied. Here, we examined behavioural and neural correlates of action inhibition in a sample of 14 adults with TS without relevant comorbidities and a matched control sample. Action inhibition was examined using a classic stop-signal reaction-time task during event-related fMRI. In patients, clinical correlations were performed between stop-signal reaction-time task-related fMRI signal activations and clinical measures (e.g. motor tic frequency). We show that inhibitory task performance was comparable between the two groups. However, fMRI results revealed differences in the neural correlates of normal inhibitory performance. Although, healthy controls engaged the dorsal premotor cortex more strongly during the StopSuccess than in the Go condition, patients with TS showed the opposite pattern. Clinical correlations between action inhibition in the TS group and motor tic frequency revealed that patients who exhibited more tics engaged the supplementary motor area stronger during StopSuccess versus Go. Taken together, this pattern of results showed that deficits in inhibitory performance are not universal in patients with TS, specifically in the absence of clinically relevant comorbidities, such as ADHD. Aberrant patterns of brain activation in key areas involved in action control could facilitate normal inhibitory performance in patients. The supplementary motor area appears to represent a critical neural substrate both for the inhibition of voluntary actions and the suppression of tics.

2.5 The neural correlates of tic inhibition in Gilles de la Tourette syndrome

Ganos C, Kahl U, Brandt V, Schunke O, Bäumer T, Thomalla G, Roessner V, Haggard P, Münchau A, Kühn S. The neural correlates of tic inhibition in Gilles de la Tourette syndrome. *Neuropsychologia*. 2014 Dec;65:297-301. URL: <http://dx.doi.org/10.1016/j.neuropsychologia.2014.08.007>

The first four studies presented here examined the behavioural associations and key characteristics of voluntary tic inhibition, as well as the brain circuitry involved in voluntary action control in adolescents and adults with TS. However, the neural correlates of voluntary tic inhibition remain largely unknown. In this study, we sought, therefore, to examine the neural underpinnings of voluntary tic inhibition using a block-design voluntary tic inhibition paradigm during fMRI. For this purpose, the same sample of 14 TS adults with uncomplicated TS from the previous study was recruited. Tic severity and voluntary tic inhibitory capacity were first assessed outside the scanner, and subsequently during resting-state fMRI. Online and video-based tic-counts were performed. Regional homogeneity (ReHo) analysis was used to assess synchronization of spontaneous fMRI-signal between a given voxel and its immediate neighbours contrasting the two tic conditions (free ticcing vs voluntary tic inhibition). Clinical correlations of ReHo parameters with tic frequency, voluntary tic inhibitory capacity and the intensity of reported premonitory urges were also executed. Increased ReHo of the left inferior frontal gyrus (IFG) during voluntary tic inhibition vs the free ticcing state was found. Importantly, extracted ReHo values correlated with voluntary tic inhibitory capacity both during fMRI and outside the scanner underscoring the clinical specificity of findings. There was no correlation with the severity of reported premonitory urges. Taken together, these results emphasized the role of frontal cortical engagement during top-down voluntary inhibitory tic control. They also further highlighted the dissociation between the neural mechanisms involved in voluntary tic inhibition from premonitory urges.

3. Discussion

3.1 Voluntary inhibitory tic control

The current pathophysiological understanding of tic disorders is dominated by two influential pathophysiological accounts. On the one hand, tics are viewed as the result of abnormally enhanced stimulus-response associative learning^{36, 54, 55}. Here, tic behaviours represent pathologically reinforced motor programs (often referred to as habits), which occur due to abnormally enhanced dopaminergic neurotransmission³⁶. The efficacy of antidopaminergic pharmacological agents for the treatments of tics, and the comparable results achieved through behavioural interventions such as HRT lend further support to this view. On the other hand, tics represent disinhibited fragments of movements as the result of hyperexcitable cortico-basal ganglia-thalamo-cortical loops due to GABAergic dysfunction^{41, 56-58}. According to this view, some level of cortical control is possible, particularly related to the temporal onset of tic behaviours, even though their generation is the result of neuronal disinhibition⁵⁸. Neuropathologic investigations and animal models of tic disorders support the disinhibition theory⁴¹⁻⁴⁵.

The two different theories may in fact share common pathophysiological ground. Indeed, they both propose that tics are the result of pathologically enhanced neuromotor signals - either stimulus-response associations or disinhibited fragments of behaviour. They also suggest that the neural pathways that generate tics are also involved in the generation of voluntary actions. Crucially, they both introduce a concept of voluntary tic inhibition, either within the behavioural intervention of habit-reversal or as the neurophysiological manifestation of hierarchically arranged cortical top-down control. In-depth understanding of voluntary inhibitory tic control may, thereby, have important implications for the treatment of tics irrespective of the current views related to the tic generator.

In the medical literature the term of voluntary tic inhibition has also been synonymously used with tic control. However, the latter term has also been used to describe a range of different processes related to tic reduction not relevant to the specific designation that is suggested here (summarized in table 1). Voluntary tic inhibition (or voluntary tic control) denotes a specific cognitive effortful process of tic suppression. The inhibitory process is an intentional and goal-directed activity, which is specifically decided and initiated by the patient themselves. Voluntary tic inhibition is also amenable to reinforcement⁵⁹. Voluntary tic inhibition thus

resembles willed action, even though its consequence is to reduce motor output, and not promote it.

Table 1. Different forms of tic control as used in Tourette syndrome literature.

Forms of tic control	Description
Voluntary inhibitory tic control	Inhibition of tics on demand; an active, effortful form of tic inhibition
Tic control through behavioural interventions	Tic control through behavioural training in programs such as “habit reversal training” or “exposure response prevention”; an active, effortful form of tic control
Tic control through pharmacological or surgical interventions	Therapeutic interventions that lead to the reduction of tics; a passive, effortless form of tic control
Tic control through modulation of attention	Reduction of tics through attentional bias or distraction; a passive, effortless form of tic control
Age-related tic control	Tic control as a result of aging; also considered an effect of brain maturation; a passive, effortless form of tic control

Adapted from ⁴⁹ and used with publisher permission.

3.2 The interplay between premonitory urges and voluntary tic inhibition

Premonitory urges are an integral element of tic pathophysiology. Their presence is documented in the majority of patients and, indeed, most tics are reported to emerge as responses to preceding urge sensations ⁶⁰. Although, the exact language to describe premonitory urges – as any other interoceptive experience - lacks precision (e.g. often vaguely referred to as “muscle tightness”, “the need to do something” or a “just right” sensation ³⁷, there is a surprising specificity of the tic events that occur subsequent to their perception. Indeed, patients typically report that there appears to be only a very specific type of tic-movement (or sound) that can satisfy any given premonitory urge. Based on this observation, Bliss, who was both a clinician and a TS patient himself, and others suggested that tics may represent voluntary responses to involuntary premonitory urges ^{48,61}. Bliss also proposed that the cognitive process of voluntary tic inhibition is mediated through the perception of the urges, which signal the impending occurrence of a motor event to be suppressed. According to Bliss’ model, patients with stronger premonitory urges should also be able to voluntarily inhibit their tics most efficiently.

However, literature has provided conflicting results (summarized in ⁴⁹), perhaps owing to the absence of validated measures to capture state measures of premonitory urges and voluntary tic inhibitory capacity. Crucially, explicit state assessments of any of the two measures could influence performance in the other. For example, asking patients to attend to their urges could lead to a baseline increase of tic behaviours through shifting attention towards involuntary neuromotor signals. Conversely, patients who focus on voluntary inhibitory tic control may be less able to monitor their premonitory urges. These examples show that the explicit assessment of either premonitory urges or voluntary tic inhibition could be influenced by the effects of a third factor, namely the cognitive capacity of attentional allocation and processing.

One way to overcome this difficulty is to capture premonitory urges as a trait measure. Although, there is a surprising absence of longitudinal assessments of premonitory urges in literature, a validated scale has been devised to reflect the overall perceived trait intensity of premonitory urges ⁶². In our first study of this submitted work, we used assessments using this established rating scale and examined their relation to a state measure of voluntary inhibitory tic control we introduced. Importantly, this measure reflects a normalized ratio of voluntary tic inhibition, taking into account actual tic severity ⁶³. The surprising absence of a relation between perceived premonitory urges and voluntary inhibitory tic control in our study suggests a clear dissociation between the two measures and shows that voluntary tic inhibition does not reflect a conditioned response to premonitory urges, against Bliss's original suggestion. Importantly, our results were replicated in all subsequent studies, which employed similar conceptual methodologies ⁶⁴⁻⁶⁶.

How can this result be reconciled with the practice of the main behavioural intervention of HRT/CBIT ^{34, 46}? The main focus in HRT/CBIT is attracting patient awareness to premonitory urges and instructing patients to use these as early triggers of voluntary tic inhibition ⁴⁷. Our results do not nullify this practice but rather highlight an important distinction. Classic voluntary tic inhibition is an intentional process mediated through an internally triggered intention "not to tic". HRT/CBIT adds a further quality to the inhibitory process by using premonitory urges as external signals of motor inhibition. Although it remains unclear how baseline voluntary tic inhibitory capacity may influence results of HRT/CBIT, a clear prediction would be that patients who are able to voluntarily inhibit their tics on demand before behavioural training would also have the best outcome after HRT/CBIT. The role, however, of

voluntary tic inhibition as a moderator or predictor of any kind of behavioural intervention has not been yet explored ⁶⁷.

3.3 The association of voluntary tic inhibition and action awareness

One of the fundamental qualities of tic behaviours is their phenomenological and neurophysiological overlap to willed actions ¹³. Tics frequently involve well-structured motor actions, including gestures, gait patterns and utterances and in most cases, any given single tic cannot be distinguished from a voluntary action ⁶⁸. This raises an intriguing question of how the developing nervous system classifies each individual movement as voluntary or involuntary. This approach first requires working models of how voluntary actions arise, and how they are classified as voluntary in the healthy motor system. Most views of voluntary action are based on a model of threshold-crossing ^{69, 70}. Voluntary actions occur when an internal signal within the motor system reaches a threshold, generating a perception-like experience ^{69, 70}. These models imply a clear, categorical experience of volition, yet people with tics are often unable to report whether a given tic is voluntary or involuntary ³². This suggests that the perceptual experience of tics could interfere and/or partially overlap with neurocognitive signals related to voluntary actions. In line with this suggestion, one previous study demonstrated that adults with TS have difficulties in monitoring their own intentions ⁷¹. However, it remained unclear whether these difficulties are the result of a perceptual adaptation to the chronic occurrence of tic-related signals, or a primary deficit of an action monitoring system. Also, the limited sample size of this study did not allow to include several important tic-specific variables, as the capacity to voluntarily control tics.

People with tics are typically able to selectively control their tic behaviours without suppressing voluntary motor output. This suggests an intact neurocognitive capacity to distinguish between neuromotor signals related to tics from those related to voluntary actions. Elucidating the interaction between the voluntary motor system with involuntary tic behaviours and voluntary tic control is, therefore, crucial in providing an overall understanding of the pathophysiology of tic disorders and the mechanisms underlying successful tic inhibition.

In the current study, we employed the same methodology as Moretto et al. (Fig. 1A) ⁷¹ and examined the capacity to monitor voluntary actions in a relatively large sample of adolescents with TS and healthy, age-matched controls. First, we showed that there were no differences in action monitoring between the two groups ⁷². This highlights that the perceptual delay of

intention awareness, which was demonstrated in adults with TS ⁷¹, should most likely be the result of perceptual adaptation. Chronic exposure to the continuous occurrence of involuntary tic behaviours would be related to increased levels of neuromotor noise. Over time, this would in turn lead to an adaptive increase of perceptual thresholds for voluntary actions in order to reduce perceptual uncertainty (Fig. 1C). Our multiple regression model for the TS sample further supported this hypothesis. The strongest predictors of intention awareness were two tic-specific, independent factors: premonitory urges and the capacity to voluntarily inhibit tics. Patients who experienced stronger premonitory urges and, thereby, had greatest interference with their experience of volition, were also less able to detect their intentions early. In contrast, patients who had greater capacity to voluntarily control their tics, thereby being able to distinguish between different types of neuromotor signals, also had earlier experience of volition (Fig. 1B).

These results underline three important issues in the study and treatment of tic disorders. First, they provide a framework, whereby the interaction between voluntary actions, involuntary tic behaviours and voluntary tic inhibitory control is explained. Patients who are better able to distinguish the different premotor signals within the wide range of neuromotor noise are the ones with a better capacity to control their abnormal motor behaviours. Second, the long-standing presence of tic behaviours could lead to perceptual adaptations of action monitoring. Although, the malleability of such adaptive processes and their reversibility have not been yet explored, these results suggest that early interventions in the treatment of tics, as for example during childhood or adolescence – before perceptual adaptations occur – could provide important tools to improve prognostic outcome. It is noteworthy, that similar perceptual adaptations of action monitoring have already been reported in people with functional neurological disorders, a range of conditions often treatable with behavioural interventions ⁷³. Finally, these results highlight one key-issue of current behavioural interventions for the treatment of tics. The ultimate goal of HRT/CBIT is to reduce tics. As aforementioned, this is achieved through the direction of attention towards premonitory urges and tics. Our results here demonstrate that an increase in the perception of premonitory urges is associated with impairments of action monitoring ⁷². Perhaps, alternative treatments, such as those that distract attention away from tics and focus improving the perception and honing of voluntary actions (summarized in ⁴⁷) could be more beneficial for the long-term outcome and prognosis of people with tic disorders and TS.

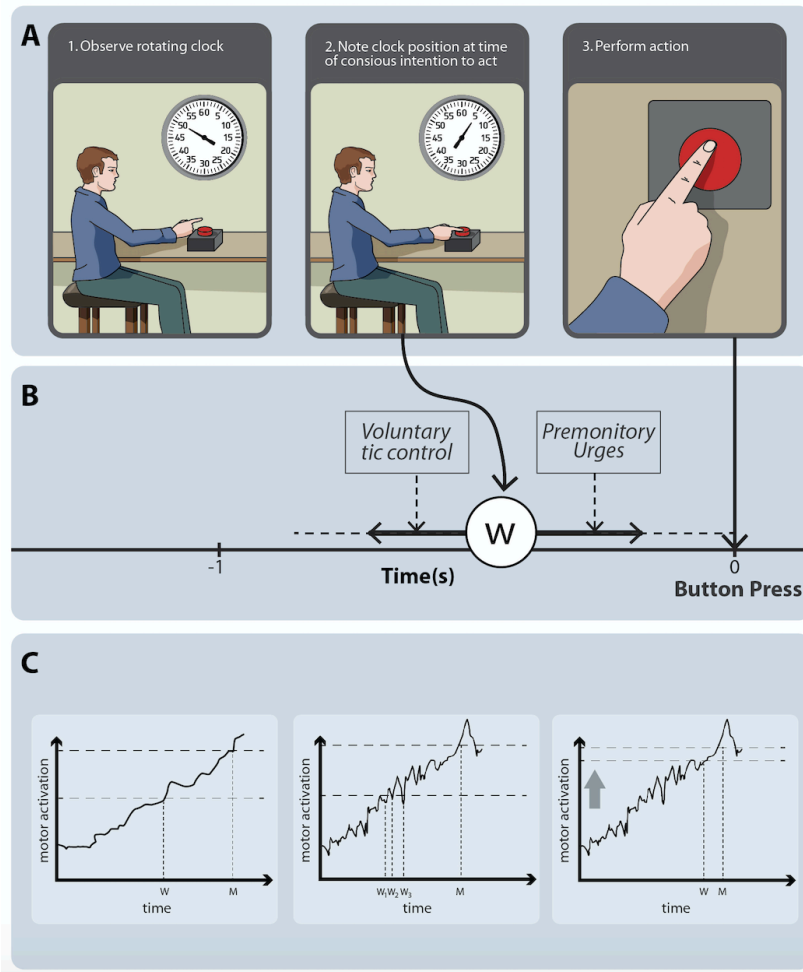


FIG. 1. (A) Representation of the Libet clock task. Participants view a rotating clock hand on a screen. At a time of their own choosing they press a button with their right hand. The clock stops at a random interval following the button press and participants provide a time estimate when they first “felt the urge” to perform their voluntary action - “Will” or “W” judgment – suggested to reflect the timing of their “intention awareness.” (B) Schematic representation of W-judgment estimates from 25 adolescents (10-17 years old) with chronic tic disorders. Patients with better voluntary tic inhibitory capacity experienced earlier W-judgements. In contrast, patients who reported stronger premonitory urges preceding their tics had later W-judgements. (C) A graphic representation model of conscious intention as a signal detection problem. Intention is perceived when motor signal activation surpasses a first threshold (corresponds to W). Further motor signal activation leads to actual movement (M) upon exceeding a higher threshold. In tic disorders, less noisy motor signals are associated with a better capacity to voluntarily inhibit tics (left plot). Conversely, the presence of noisier motor signals, as in patients with strong experience of premonitory urges, may produce a wide range of intention (W1-W3) and be associated with perceptual uncertainty. Adaptive increase of the threshold level prevents perceptual uncertainty but also delays experience of W (right reproduced from ⁴⁹ and with permission from the publisher).

3.4 Somatotopic selectivity of voluntary tic inhibition

Beyond the associations of voluntary tic inhibitory control, little is known with regard to its spatial characteristics. Indeed, one key characteristic of voluntary tic inhibition is that patients

can selectively suppress a target tic behaviour on demand (e.g. vocalizing in classroom, or clapping hands while driving a car). Importantly, behavioural treatments such as HRT/CBIT capitalize on the selectivity of the inhibitory mechanism to further enhance control over specific unwanted tic behaviours. However, only about half of participants undergoing HRT/CBIT will respond to treatment and prognostic factors or moderators of treatment response still remain underexplored⁶⁷. Crucially, the question as to whether the clinical distribution of tics might influence treatment outcome remains unanswered.

In our study we determined tic frequencies for individual body parts across participants and calculated, for the first time, body part specific indices of voluntary tic inhibition⁷⁴. We could demonstrate that voluntary tic inhibition was not random but somatotopically selective and was most efficient for the least affected body parts. This finding provides important insights into the neurocognitive mechanisms of voluntary tic inhibition and treatment research.

Tics are generated within the cortico-striato-thalamo-cortical loops, presumably as a result of aberrant, sensorimotor activation within these circuits^{13, 75, 76}. Importantly, tic generation engages the same neural structures that are also involved in the formation of voluntary actions and shares characteristic qualities of this circuitry, such as the disproportionality of somatotopic representation⁷⁷. Body parts with large corresponding cortical representation, such as the face, are also most frequently affected by tics. In contrast, areas with small cortical representations, such as the feet or trunk, tic the least. An increase of sensorimotor activity within these circuits as a result of a putative tic generator would thereby lead to a disproportional increase in tic frequency over the different body parts (e.g. face vs feet). Voluntary tic inhibition specifically suppresses tic behaviours but does not affect voluntary motor output (also see ‘The association of voluntary tic inhibition and action awareness’ section). Our results suggest that the inhibitory specificity is achieved through the preferential attenuation of weak motor signals (i.e. those corresponding to smaller portions of cortical activity). In contrast, strong motor signals related to more frequent tics, and also voluntary actions, remain unaffected. Of note, this theory predicts that voluntary tic inhibition acts at a common motor command centre within the cortico-striato-thalamo-cortical circuitry, most likely at the level of the primary motor cortex as the final motor output relay. A neurophysiological study we more recently performed indeed confirmed this prediction. During voluntary tic inhibition motorcortical excitability over the primary motor cortex was reduced⁷⁸.

A final comment relates to behavioural treatment studies and clinical practice. To date, predictors and moderators of response to behavioural treatments such as HRT/CBIT have focused on few tic-specific characteristics, such as tic severity, tic complexity and the intensity of premonitory urges, and several non-tic specific factors, as the presence of neuropsychiatric comorbidities or the intake of pharmacological anti-tic medication ⁶⁷. However, the spatial characteristics of voluntary tic inhibition have not been previously explored. Our results suggest that future studies should also capture the somatotopic distribution of tics. Indeed, sample sizes of comparable tic severity and complexity may only differ in their somatotopic tic distribution, which may in turn bias treatment results due to differences in the baseline strength of voluntary tic inhibition.

3.5 The neural correlates of action inhibition and voluntary inhibitory tic control in Tourette syndrome

One key-pathophysiological assumption in tic disorders and TS literature is that tics represent disinhibited fragments of voluntary actions, possibly as a result of deficient motor inhibitory control ²¹. This hypothesis stems from two clinical observations. First, the resemblance of tics to voluntary actions and the capacity to voluntarily control tics on demand evokes the idea that tics are voluntary motor behaviours, which escape tonic inhibitory control ⁵³. This view assumes that the same neural circuitry that generates voluntary actions also generates tics. It also deems that all motor behaviours are subject to continuous tonic voluntary inhibition. Indeed, classic neuropsychiatric disinhibition disorders, such as the anarchic hand syndrome offer support to this view ⁷⁹. However, tics in primary tic disorders and TS do not share hallmark qualities of such disinhibition behaviours. For example, although involuntary movements in the anarchic hand syndrome are typically triggered by immediate environmental stimuli (also called “affordance”) ⁸⁰, tics are characteristically not stimulus-bound behaviours and are not driven by environmental affordances. Second, people with tic disorders and TS often exhibit impulsive behaviours, to include hyperactivity, rage attacks and socially inappropriate behaviours ^{81, 82}. However, many of these behaviours are often associated more strongly with the presence of comorbid ADHD than with tics ⁸¹⁻⁸³. Therefore, the role of disinhibition as the core deficit of tic pathophysiology remains disputed.

In line with this, our study on action control in a sample of adults with TS and no relevant comorbidities, such as ADHD or OCD, revealed no deficits of inhibitory performance (Stop-signal reaction time task) compared to an age-matched healthy control group ⁸⁴. However, the

neural circuitry related to inhibitory performance differed between patients and healthy controls, thus highlighting the differential role of two neural areas during action inhibition in tic disorders: the dorsal premotor cortex and the supplementary motor area⁸⁴. Both these areas are involved in the inhibition of motor actions in healthy volunteers, both during proactive tonic inhibitory control (dorsal premotor cortex) and reactive, global inhibition (supplementary motor area)⁸⁵. Crucially, a meta-analysis of fMRI studies in tic disorders and TS revealed a key role both for the lateral premotor cortex and the supplementary motor area in the expression of tic behaviours further confirming the disorder-specific significance of these findings⁸⁶.

Our study also investigated the relation between the inhibition of voluntary actions and the voluntary suppression of tics and found no association between the two measures. This, together with the previous two studies reported here^{63, 72} provides an additional insight into the correlates of voluntary tic control. The capacity to voluntarily inhibit tics does not relate to classic forms of voluntary action control. It most likely represents a distinctive cognitive process of top-down motor inhibitory control specifically to address and modulate tic behaviours. However, the exact neural underpinnings involved in voluntary tic inhibition remain unclear.

One of the first studies to systematically address the differences in neural activity between the states of free ticcing and voluntary tic inhibition was performed by Peterson and colleagues, who in the early days of fMRI employed a block-design study⁸⁷. The results of this study revealed a wide range of cortical and subcortical blood-oxygen-level dependent (BOLD) signal changes between the two different states, to involve primary and secondary sensorimotor areas⁸⁷. Importantly, an increase of signal change in cortical structures and a reduction in respective subcortical areas was documented during voluntary tic inhibition and was suggested to reflect top-down motor inhibitory control. However, this study did not provide online tic-measures between the different states and, therefore, the relevance of these signal changes to the specific cognitive instruction of voluntary tic inhibition remains unclear. Following, two further studies assessed neural correlates of voluntary tic suppression in children and adults with TS by using electroencephalography (EEG) and demonstrated prefrontal cortical involvement during the tic-inhibitory process^{88, 89}. Our results, based on ReHo analysis, revealed increased local connectivity also in the prefrontal cortex, specifically in the left inferior frontal gyrus⁹⁰. Crucially, there was a strong correlation of the extracted ReHo values with our behavioural measures of voluntary tic inhibition both during the rs-fMRI scan and also prior to the scanning

session, but not with the trait intensity of premonitory urges. This suggests that our finding of increased ReHo of the left inferior frontal gyrus most likely reflects a specific neural event associated with voluntary tic inhibition. Unfortunately, no further structures or connectivity profiles were identified during the two states, perhaps owing to the limited sample size of the study. However, the results of the studies cited here support the view that during voluntary tic inhibition frontal cortical areas are preferentially recruited. Clearly, larger well-designed studies that monitor tics online and employ multimodal-assessments, as for example combined EEG with fMRI ⁹¹, or neurophysiological measures (e.g. TMS/EEG ⁹²) can further help elucidating the neural mechanisms involved in the voluntary inhibition of tics.

3.6 Limitations and future directions

Our concept of voluntary tic inhibition refers to the specific cognitive process of tic suppression on demand. In most of our studies we used a video-based measure to capture this inhibitory capacity in temporal segments of 2.5 minutes each. This was based on the previously validated and widely employed modified Rush-video rating scale ⁹³. Although, our methodology provided novel and important insights into the behavioural associations and neural correlates of voluntary tic inhibition in patients with tic disorders and TS, it remains unclear whether different time periods of voluntary tic inhibition could provide more accurate measures of this capacity.

Also, the sample size of patients we studied was relatively small (14-27 individuals per study). However, the range of our sample size is comparable to most other pathophysiological studies of tic disorders and Tourette syndrome (for example reviewed in ^{21, 94}). Given the wide clinical heterogeneity of the disorder and the broad range of associated neuropsychiatric comorbidities, which may influence voluntary tic inhibition, future research should aim to include larger study populations. Obviously, this can only be achieved through organized national and international collaborations, as for example through organizations such as the ‘European Society for the Study of Tourette Syndrome’ or the newly formed ‘Tic Disorders and Tourette syndrome Study Group’ of the Movement Disorders Society.

Moreover, all of the studies reported here were based on cross-sectional data-collection. Given the dynamic character of neurodevelopmental tic disorders and the shift in the clinical characteristics of tics in time, as well as the related profiles of neuropsychiatric comorbidities ^{24, 26} prospective studies should focus on the acquisition of robust datasets with a focus on longitudinal evaluations. On the one hand, this will provide key insights into the developmental

pathophysiology of the disorder and will ultimately allow to identify predictive markers of future tic outcome and response to treatments. Based on the data we presented here, a strong capacity to voluntarily inhibit tics at a young age may, in fact, constitute a positive predictor of either response to pharmacological and/or behavioural treatments and ultimately overall tic outcome. However, this hypothesis has not been yet studied.

Finally, studies in Tourette syndrome and voluntary tic inhibitory control provide a unique opportunity to bring together scientists from the entire tenor of neural disciplines, to include neurophysiology, neuroimaging, neuropharmacology, cognitive psychology, neurology, neuropsychiatry and psychiatry. Indeed, only through scientific cross-talk between the different disciplines can an in-depth understanding of the multifaceted disorder be reached. A holistic view of tic disorders and TS may then, in turn, provide novel and meaningful treatments in order to improve the quality of life of our patients and their families.

4. Summary

Tics are a hyperkinetic movement disorder. They are defined as movements or sounds that typically resemble voluntary actions, but appear repetitive, often exaggerated in intensity and are not bound to a certain social context. Tics are typically preceded by a phenomenally strong sensory experience known as the premonitory urge. Crucially, and different from most other hyperkinesias, tics can be voluntarily inhibited on demand. Tics are prevalent in many disorders, including neurodevelopmental syndromes and neurometabolic or neurodegenerative conditions, but are most commonly documented in primary tic disorders. Tourette syndrome (TS) is the prototypical primary tic disorder encountered in clinics and affects up to 1% of school-age children.

The predominant pathophysiological models of tic disorders view the abnormal motor behaviours as the result of pathological gain increase of neuromotor signals within the circuitry that also generates voluntary actions. Crucially, they introduce a concept of voluntary tic inhibition, as the capacity to exert top-down inhibitory control to temporarily suppress the pathologically increased neuromotor activity. In-depth understanding of voluntary tic inhibition may, thereby, have important implications for the regulatory control of tics, including the development and implementation of more efficient treatment interventions.

In the medical literature, the term of voluntary tic inhibition has also been synonymously used with tic control. However, the latter term has also been used to describe a range of different processes related to tic reduction not relevant to the specific designation that is suggested here. Voluntary tic inhibition (or voluntary tic control) denotes a specific cognitive effortful process of tic suppression. The inhibitory process is an intentional and goal-directed activity, which is specifically decided and initiated by the patients themselves, and, thereby, is also amenable to reinforcement.

In a progression of five consecutive studies, we here explore the behavioural associations and neural correlates of voluntary tic inhibition in adolescents and adults with tic disorders and TS. First, we explore the putative association between premonitory urges and voluntary tic inhibition. Importantly, we provide experimental evidence to support the view that the two processes are not directly related. We then examine the characteristic capacity of voluntary tic inhibition to specifically suppress tic movements without affecting motor performance for

voluntary actions. We assess the relation between the voluntary motor system and voluntary tic inhibitory control and introduce the concept of neuromotor noise in the pathophysiology of tic disorders to explain our findings. We also discuss the spatial characteristics of voluntary tic inhibition and provide a model of somatotopic-specificity of voluntary inhibitory tic control. Finally, we review the pathophysiological concept of deficient action control underlying the manifestation of tics and provide experimental evidence against it. We also examine the neural correlates of inhibitory control both over voluntary actions and involuntary tic behaviours. Current limitations in the research of voluntary tic inhibition are discussed and future directions of the scientific study of voluntary tic inhibitory control are suggested.

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6. Abbreviations

TS – Tourette Syndrome

MRCP – Movement-related cortical potential

GABA - Gamma-aminobutyric acid

DSM-5 - Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

ADHD- Attention-deficit hyperactivity disorder

OCD - Obsessive-compulsive disorder

HRT – Habit-reversal training

CBIT - Comprehensive behavioural intervention for tics

ERP - Exposure-response prevention

FMRI - functional magnetic resonance imaging

MRVS - Modified Rush Video Scale

ReHo – Regional Homogeneity

IFG – Inferior frontal gyrus

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