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Correlates and clinical implications of tic suppressibility

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Purpose of review: Tic disorders are common in the pediatric population and are differentiated from other movement disorders by tic suppressibility. Understanding the mechanism of tic suppression may provide new insights to the pathophysiology of tic disorders. This article highlights clinical phenomenology and neuronal correlates of tic suppressibility.

Recent findings: Recent studies suggest that tic suppressibility exists in children shortly after onset of their tics. Moreover, those who are better able to suppress their tics have better tic outcomes. Interoceptive awareness and automatic action inhibition may be involved in tic suppression.

Summary: We illustrate a possible underlying mechanism of tic suppressibility and its clinical correlations and implications. New concepts such as interoceptive awareness and action inhibition may help explain tic disorders. Further study will be useful to fill remaining knowledge gaps.

Introduction

Tics, defined as "sudden, rapid, recurrent, nonrhythmic motor movement or vocalization" [1], are one of the symptoms of hyperkinetic movement disorders. Tics are prevalent in the pediatric population with at least 20-25% of elementary school children exhibiting motor tics [2–4]. The onset of tic disorders must occur before the age of 18 years to be considered primary (i.e., not explained by other disorders like Huntington's disease). Provisional Tic Disorder is diagnosed when the duration of tics is less than one year. After one year, Tourette's Disorder or Persistent Tic Disorder (collectively hereafter, Tourette syndrome: TS) can be diagnosed. Tics usually begin between 3 and 8 years of age and show a waxing and waning course with peak tic severity occurring around 8 to 12 years of age. Many patients experience improvement of their tics by early adulthood [5].

Hyperkinetic movement disorders (e.g., chorea, dystonia, and tic disorders) are conceptualized as disorders of the basal ganglia with abnormal inhibitory networks leading to a failure to inhibit unwanted movements [6]. Their various motor symptoms depend on the dysfunction of inhibitory networks. Unlike other hyperkinetic movement disorders such as dystonia or myoclonus, patients with tics frequently experience premonitory urges (PU),

defined as an unpleasant sensation or perceived need to move that precedes tics and is often temporarily relieved by the execution of tics [7–9].

Patients with tics can suppress their tics for variable periods of time, which has contributed to their being described by some as "un-voluntary" [10, 11]. This suppressibility can differentiate tics from other movement disorders and has therapeutic implications for behavioral therapies. A questionnaire survey regarding daily experience with tic suppression revealed that 58% of TS children and adults attempted to suppress their tics in daily life, but were not always successful [12]. Sometimes they felt uncomfortable or incomplete when they suppressed tics and found tic suppression difficult (i.e. requiring concentration or extra effort). Thus, unsuccessful tic suppression may lead to difficulty in schoolwork, negative responses from peers or teachers, a decline in self-esteem, and poorer quality of life [13]. Understanding the pathophysiology of tic suppressibility is clinically beneficial and may inform tic pathology and the natural course of tic disorders.

In this paper, we review the existing literature to describe clinical characteristics and brain correlates of tic suppressibility. In particular, we highlight recently published studies, aiming to create an up-to-date overview of tic suppressibility.

Clinical phenomenology of tic suppressibility

Generally, both motor and vocal tics are suppressible to a degree [14]. In clinical observation studies, children with tics were able to suppress their tics by nearly 70% in frequency for as long as 40 minutes [15–17]. Little is known about which types of tics are more suppressible, but one video analysis study of adolescents with TS showed that tic

suppression was most effective in body areas such as the trunk or proximal leg, and least effective in the hands and eyes, which had the most tics at baseline [18]. Although the sample size was small and types of tics were heterogeneous across the sample, this finding suggested that tic suppressibility follows a somatotopic pattern, whereby truncal and lower-body tics may be less suppressible [18].

Tic suppression usually requires effort [12]. However, tic suppressibility can also occur to some extent without conscious awareness. In an observational study of children and adolescents with TS who were videotaped in the clinic and at home in three situations (holding a casual conversation with a stranger, being seated quietly with a stranger, and being seated quietly alone), the intensity and frequency of tics were highest when participants were alone at home and lowest when they were quietly seated with a stranger in the clinic (without conversing) [19]. Other observational studies of adults with TS showed tic frequency increased when they paid attention to their tics compared to when they were distracted from their tics (e.g., watching a video or performing a fine motor task), even when they did not intentionally suppress their tics [20, 21]. These studies point to interesting characteristics of subconscious tic suppression. Individuals with tics may at times unconsciously suppress their tics to adapt to their situation without explicit thought or through modulation of attention to or distraction from the tics. The following paragraph describes evidence for unconscious situational tic suppression. This finding is important because it provides an explanation for the worsening or improvement of tics with changes in social context.

Tic suppressibility is also affected by the environment. A standardized tic suppression task (TST) was designed to characterize the effect of external environmental variables and quantify the ability to suppress tics under various conditions [16]. In this paradigm, participants are seated in front of a "tic detector" and are told either to tic freely or to suppress their tics. During the experiments, researchers in an adjacent room observe the participant's behavior through a one-way mirror or camera. They can then provide an immediate contingent reward for successful tic suppression in the form of a token dispensed from the tic detector remotely, which can be exchanged for money at the end of the study. Many studies using the TST paradigm in children with tics have demonstrated that adding rewards for tic-free periods to verbal instruction to suppress tics yielded greater reduction in tics than verbal instruction alone [14, 16, 17, 22, 23]. Further, contingency of the reward was important, as tokens delivered noncontingently did not show similar benefit on tic reduction [24]. A particularly clever study tested whether certain contexts could create an implicit stimulus for tic suppression [25]. Children with tics underwent the TST paradigm in the presence of different color lights (e.g., purple light presented when rewarded for tic suppression, orange light presented when verbally instructed to suppress tics without rewards). No explanation for the lights was provided, yet later, when participants were exposed to the light that had been associated with tic suppression during contingent reward, tic frequency was reduced even when no rewards or instruction to suppress tics were given. This study provides compelling evidence that implicitly learned environmental cues can affect tic suppressibility.

With years of experience suppressing tics, patients with tics may become better at tic suppression over time. Young children under 10 years old can suppress their tics but not as well as older children. Tic suppressibility is positively correlated to age (4-18 years) such that older children and adolescents can suppress their tics more effectively [23, 26]. Individuals with more frequent tics at baseline may better suppress their tics with the caveat of potential measurement artifacts [23]. These findings suggested that development and more real-life practice makes tic suppressibility more efficient. Still, somewhat surprisingly, children with recent onset of tics (i.e., within 6 months of tic onset) can suppress about 40% of their tics and do so more efficiently with immediate contingent reward [27]. Interestingly, those with better suppression in the presence of contingent reward showed better tic outcome (i.e., less tic severity) at a later timepoint, namely the one-year anniversary of tic onset [28]. Thus, tic suppressibility and its reinforceable nature may be inherent (or learned very early after the onset of tics), and this ability may be an important predictor of clinical outcomes.

Clinically, there has been a concern that volitional tic suppression might elicit more tics once efforts to suppress stop, which was referred to as a "rebound effect." In fact, the Diagnostic Confidence Index, which summarizes classic features of TS, lists "Rebound effect after suppression" as one of the characteristic features [29]. A questionnaire survey of health care professionals including physicians and psychologists showed that 77% of them believed the rebound effect existed [30]. However, a number of clinical studies have shown no evidence of tics worsening after voluntary tic suppression, including with behavioral therapies for tics [14, 15, 17, 22, 31]. These results support the safety of

behavioral therapies that employ tic suppression. However, tic suppression is not without potential negative consequences. More than 80% of TS patients reported that tic suppression caused fatigue, and 95% "felt uncomfortable or incomplete when they suppressed tics" [12]. Intentional tic suppression also re-allocates attentional resources, and many children with tics reported that tic suppression interfered with concentration at school [13]. A laboratory study supported this perception: children could suppress tics with or without a concomitant cognitive task, but performance on the task worsened during tic suppression [21]. Thus, effort expended suppressing tics may result in mental fatigue, which can affect social life, or may impair attention. Therefore, tic suppression needs to be advised judiciously, and ideally should be employed as part of an effective behavior therapy.

Another potential negative effect of tic suppression is that a minority of children (<10%) paradoxically have more tics when trying to suppress them [23]. This paradoxical increase in tics may stem from attempts to control PU. In the words of Franklin et al [32], "attempts to control aversive private events [like PUs] tend to be ineffective and, paradoxically, increase the very thoughts and emotions that the individual was trying to avoid." Alternatively, "white knuckle" efforts to suppress tics may increase one's focus on the upcoming success or failure at tic suppression. Such a focus will often exacerbate anxiety, which in turn can exacerbate tics [33, 34]. In extreme cases, such internally-directed attention and worries about tics may lead to severe "tic attacks" [35]. Acceptance and Commitment Therapy [32] and cognitive-behavioral approaches to tics [36] address these internal factors. Current first-line behavioral interventions – exposure and response

prevention (ERP) and habit reversal therapy (HRT) or its descendent Comprehensive Behavioral Interventions for Tics (CBIT) – are tic-suppression-based treatments [37]. HRT employs awareness training and competing response training to encourage tic suppression for long durations of time [38]. ERP consists of exposure to stimuli that tend to induce tics, combined with practice to resist ticcing [39]. Although these therapies effectively decrease tic frequency and severity, finding a trained therapist can be difficult. Recently, internet-based training programs such as “TicHelper” (https://www.tichelper.com) [40] and "TicTrainer” (https://tictrainer.com) [41] are available. Since tics improve with distraction and worsen when focusing on them, distraction from tics may be an important part of such treatment.

Functional correlates of related symptoms

ADHD

Attention-deficit hyperactivity disorder (ADHD) is common in TS patients. Similar to TS, the pathophysiology of ADHD is thought to involve frontal-striatal networks, including the prefrontal cortex, cingulate cortex, and basal ganglia [42]. Previous studies support the idea that ADHD symptoms, especially attention problems, diminish tic suppressibility as well as the efficacy of behavioral therapy for tics. Laboratory-based studies using the TST paradigm, clinical data review, and a meta-analysis of inhibitory control in TS patients demonstrated that participants with comorbid tics and ADHD were capable of suppressing their tics, but those patients with more attention problems were less successful with this suppression and inhibitory control [15, 43, 44]. Moreover, TS patients with poorer response inhibition have been shown to respond less favorably to the

behavioral therapies for tics, which require repeated inhibition of tic expression [45]. Improvement of tics has been seen during the treatment of ADHD. Methylphenidate (MPH) is a stimulant medicine for the treatment of ADHD and inhibits the reuptake of dopamine and norepinephrine [46]. Enhanced dopaminergic and noradrenergic activity in the prefrontal cortex may contribute to its efficacy in ADHD [47]. Clinical trials showed that tics improved significantly in those treated with MPH alone [48, 49]. Intriguingly, tic suppressibility did not improve with the one-time administration of D-MPH although tics were decreased [49]. It is possible that improvement of tics with MPH is related to modulating the dopamine system as well as enhancing the ability to suppress tics with improvement in attention.

Premonitory urges and interoceptive awareness

Many TS patients report that unpleasant somatic sensations increase before a tic and during tic suppression, and are momentarily alleviated by the performance of a tic [9, 50, 51]. Studies using the TST paradigm showed that, acutely, the severity of PU was increased by tic suppression and decreased by discontinuation of tic suppression [37, 52, 53]. PU are closely associated with tics and have been considered as the driving force of tics [8]. The presence of PU also helps distinguish tics from other movement disorders. Studies using the YGTSS and the Premonitory Urge for Tics Scale (PUTS) demonstrated that the severity of PU was significantly correlated with tic severity in both adults and children with tic disorders [54, 55]. Reductions in the severity of PU by behavioral therapies correlate with a decrease in tic severity [56]. However, some research on the relationship between PU and tic suppression has demonstrated different results. For example, behavioral therapies [57],

cross sectional studies using questionnaires, rating scales such as YGTSS and PUTS, and video review [26, 43, 51, 58], and behavioral analyses using the TST paradigm [22, 59], showed no evidence of a correlation between tic suppressibility and PU severity. Thus, understanding the relationship between PU and tic suppressibility will be useful in improving current therapeutic approaches as well as developing new ones. In fact, identifying PU and separating them from tics is one component of behavioral therapies for tics [50]. Indeed, both HRT and ERP eventually lead to diminished urges to tic and decreased tic frequency and severity.

Interoceptive awareness is awareness of internal physiological processes of receiving, accessing, and appraising internal bodily signals (e.g., visceral, vasomotor events) [60]. Based on the similarity between interoceptive awareness and PU, some studies have examined these phenomena, finding that higher severity of PU was associated with higher interoceptive awareness [61, 62]. These results suggest that PU might represent enhanced or aberrant interoceptive sensations. However, no study has investigated the relationship between tic suppressibility and interoceptive awareness. Thus, future studies investigating such a relationship are clearly warranted.

Action inhibition

Action inhibition is an ability to inhibit actions voluntarily. For example, in the Go/No Go tasks where participants are presented with a signal either instructing a predefined action or instructing no response, participants must inhibit a response deemed inappropriate on some trials [63]. Action inhibition for tics can be seen in competing

response training where patients with tics who learn to suppress their tics by performing actions incompatible with their tics. As TS is related to difficulties preventing unwanted tic movements, some have hypothesized that the ability to control goal-directed movements is similarly affected. In fact, impaired action inhibition has been proposed as a key mechanism in TS [64]. However, various laboratory studies investigating tic suppressibility and inhibition of intentional action have yielded inconsistent findings [44]. For example, some studies using fMRI and EEG found no overall deficit in action inhibition in TS [65, 66]. On the other hand, some behavioral studies showed a paradoxical enhancement of cognitive inhibition over voluntary actions in TS [67–69]. Cognitive inhibition is the ability to control cognitively demanding inhibitory tasks. For example, Mueller designed tasks to assess cognitive control where participants were cued by displaying either a green border or a red border on the screen and asked to switch predictably between moving eyes towards a visual target or to the opposite direction to the target depending on the cue [68]. Cognitive inhibition for tics can be seen when patients with tics consciously suppress their tics particularly in public to avoid social embarrassment [67]. This enhanced inhibition may be associated with compensatory adaptation to tics, including tic suppression.

Interestingly, a recent TMS study of adults with tic disorders found normal volitional movement preparation, execution, and inhibition, but impaired automatic (i.e., implicit or unconscious) action inhibition [70]. The authors suggested that tic disorders involve impairment of automatic action inhibition rather than volitional inhibition. However, a laboratory study using questionnaires (e.g., YGTSS) and a behavioral inhibition task showed no difference in automatic motor inhibition between patients with

tics and healthy controls [71]. Additionally, adults with TS had reduced ability to suppress blinks, yet blink suppression and tic suppression were not correlated [72]. Given these mixed findings, further research is needed to elucidate the relationship between tic suppressibility and action inhibition.

Mechanism/physiology of tic suppressibility

The pathophysiology of TS has been described as involving development-related atypical functional brain connectivity and impaired function of cortical-striatal-thalamic-cortical (CSTC) circuits with aberrant neurotransmitter function, including dopamine, serotonin, and GABA [9, 73–79]. Some structural and functional neuroimaging and neurophysiological studies have explored the neural correlates of tic suppressibility. An early functional magnetic resonance imaging (fMRI) study of adults with TS showed widespread signal intensity change (increases and decreases) during tic suppression in the basal ganglia, limbic system, thalamus, and a number of cortical regions, such as the frontal cortex, temporal gyrus, anterior cingulate gyrus, occipital cortex, and sensorimotor cortex [80]. The authors emphasized that subcortical-cortical circuits are involved in tic suppression. Although this study had limitations—*e.g.*, decreased brain activity during tic suppression could simply reflect increased brain activity with tics—it illustrated that tic suppression involves broad cortical and subcortical networks.

Multiple neural circuits have been suggested to contribute to tic suppressibility. In the CSTC pathway, the frontal lobe plays an important role in executive functions [81]. In particular, a network including the SMA, inferior frontal cortex, basal ganglia and primary

motor cortex has been suggested to be important for reactive stopping [82, 83]. Several tic suppression studies have focused on frontal regions. A task-based (suppression *vs.* free ticcing) fMRI experiment analyzed regional homogeneity (ReHO) in adults with TS [84]. ReHO is a measure of the functional connectivity of a region with its nearest neighbors. Tic suppression was associated with an increase in the ReHO of the inferior frontal gyrus, which was positively correlated with tic suppressibility [84]. An fMRI study comparing ocular tic suppression in TS adults and blink suppression in healthy adults showed the dorsal anterior cingulate cortex and associated limbic areas were activated during tic suppression, while the supplementary motor area (SMA), right ventrolateral prefrontal cortex and cingulate cortex were activated during blink suppression [85]. It is difficult to determine if these changes reflect brain activation of generating tics, performing tics, or suppressing tics. A novel event-related individualized model was designed recently that accounts for the transient decrease in PU after each accidental eye closure during blink tic suppression and allows for a tailor-made approach for future functional neuroimaging studies [72]. Applying this model to fMRI studies may help to identify BOLD activity specific to the urge to tic during tic suppression. Electroencephalography (EEG) studies of children and adults with TS suggest the involvement of premotor and prefrontal regions during tic suppression. Specifically, functional connectivity between the frontal and prefrontal cortices, and the sensorimotor cortex was noted during tic suppression [65, 86]. Another EEG study of adults with TS showed that abnormal beta activity in the sensorimotor cortex during the execution of tasks returned to its normal state during tic suppression [87]. These results could indicate that tic suppression exerts its effect by

reorganizing abnormal overactivity of CSTC circuits that cause tics. In other words, tic suppression may involve mechanisms of top-down control operated by cortical regions connecting to and normalizing aberrant activity in subcortical structures. The pathophysiologic difference in tic suppression for adults and children has not been investigated yet and is an important avenue for research.

The SMA may play a key role in the processes involved in suppressing tics. Previous human and animal fMRI studies suggested that the SMA is important for intended movement preparation and execution, but also for inhibitory motor control during motor imagery by suppressing premotor cortex activity when the movement is not to be performed [88–93]. Clinically, low frequency repetitive transcranial magnetic stimulation (rTMS) over the SMA significantly improved tic symptoms, measured by the Yale Global Tic Severity Scale (YGTSS) [94]. A number of neuroimaging studies in TS suggest a role of the SMA in tic suppression, even though they did not directly investigate tic suppression *per se*. For example, a magnetoencephalography (MEG) study with TS patients showed that the primary motor cortex was activated more during preparation and execution and then inhibited more after movement termination, which the authors argued might be influenced by tic suppression [95]. Subsequently, the same group provided evidence of augmented interactions between the SMA and primary motor cortex in TS patients [96]. An fMRI study using a stop signal reaction-time task showed that activation of the SMA was associated with successful stopping and correlated with tic frequency [66]. The authors proposed that the SMA is an important region for a global inhibitory mechanism for both voluntary motor control and tic suppression in TS. Another fMRI study using a Go/No Go

task showed less activation in the primary motor cortex and secondary motor areas including the SMA during the Go condition, which the authors interpreted as reflecting modulation of frontoparietal brain networks for motor and behavioral control in TS [97]. GABA concentration in the SMA was found to be inversely correlated with cortical excitability in the primary motor cortex and was associated with motor tic severity [98]. The authors suggested increased GABAergic tonic inhibition in the SMA results in enhanced control over volitional movements and suppression of tics [98]. Taken together, these studies revealed differences between individuals with and without TS that may relate to the control of tics.

Therapeutic considerations

Clinically, tic suppressibility seems to include both voluntary and involuntary components and can be modified by rewards or other environmental stimuli. Further understanding of tic suppressibility hopefully will provide more personalized behavioral therapy to match their variables. Pharmacological treatment should be considered when the behavioral interventions fail, or are not available (e.g., lack of access to behavioral therapies), or when patients exhibit severe violent tics that need immediate treatment. Various medications such as alpha-2 adrenergic agonists or dopamine receptor blocking agents have been used to lessen tic symptoms by targeting neurotransmitter modulation but they are not aimed at boosting tic suppressibility [99]. MPH might increase tic suppressibility by improving inattention, but one time D-MPH administration did not

improve tic suppressibility [49]. Developing pharmacological treatments that can increase tic suppressibility may provide a novel approach to developing new tic treatments.

Conclusions

This article discusses clinical features and neural correlates of tic suppressibility. As tic suppressibility is a distinct feature of tic disorders, a better understanding of it could provide new insight into the pathophysiology, prognosis, and treatment of tics. Tic suppressibility is present at the beginning of the onset of tics, even at very young ages. Tic suppression has been shown to predict future tic severity [28]. Thus, it is possible that early tic suppression can predict prognosis of tic disorders and/or response to treatment, a promising direction for future research. While neurophysiological and neuroimaging research has demonstrated the involvement of different brain systems in tic suppression, there is little known about how these systems change over time. Longitudinal studies are necessary to improve our understanding of the natural course of tic suppressibility. Thus, additional measures of tic suppressibility may need to be developed for consistent assessment of the ability to suppress tics over development.

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Compliance with Ethics Guidelines

Conflict of Interest

The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent

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