REVIEW

Pathophysiology of Tic Disorders

Dorin Yael, MSc, Esther Vinner, BSc, and Izhar Bar-Gad, PhD*

The Leslie & Susan Goldschmied (Gonda) Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat-Gan, Israel

ABSTRACT: Tics are the defining symptom of Tourette syndrome and other tic disorders (TDs); however, they form only a part of their overall symptoms. The recent surge of studies addressing the underlying pathophysiology of tics has revealed an intricate picture involving multiple brain areas and complex pathways. The myriad of pathophysiological findings stem, at least partially, from the multifaceted properties of tics and the disorders that express them. Distinct brain pathways mediate the expression of tics, whereas others are involved in the generation of the premonitory urge, associated comorbidities, and other changes in brain state. Expression of these symptoms is controlled by additional networks underlying voluntary suppression by the patient or those reflecting overall behavioral state. This review aims to simplify the complex picture of tic pathophysiology by dividing it into these key components based on converging data from human and animal model studies. Thus, involvement of the corticobasal ganglia pathway and its interaction with motor, sensory, limbic, and executive networks in each of the components as well as their control by different neuromodulators is described. This division enables a focused definition of the neuronal systems involved in each of these processes and allows a better understanding of the pathophysiology of TDs as a whole. © 2015 International Parkinson and Movement Disorder Society

Key Words: tics; Tourette's syndrome; neurophysiology; basal ganglia; animal model

Tics and Tic Disorders

Tics are sudden, rapid recurrent, nonrhythmic movements (motor tics) or sounds (vocal tics)[1] that are preceded, in most cases, by a premonitory urge.[2] Tics may be voluntarily suppressed for a limited period of time[3] and their expression is affected by different behavioral states.[4] Tics typically appear in early childhood, vary their frequency and severity over time, and, in most cases, decrease or even completely disappear in early adulthood.[5,6] Tic disorders are classified hierarchically into three types: provisional (transient) tic disorder (TD); persistent (chronic) TD; and Tourette syndrome (TS). The diagnosis of these disorders depends on tic type and persistence: Transient TD includes motor tics and, rarely, vocal tics that can appear together or alone in a period of less than 1 year. Chronic TD lasts over 1 year and includes the expression of motor or vocal tics, but not both. Finally, the diagnosis of TS must include multiple motor and one or more vocal tics over a period of at least 1 year.[1,6] Current studies have documented very few differences between the underlying pathophysiology of different TDs; hence, this review will relate to the unified results, under the general term TDs. Most individuals with TS (~90%) and chronic TD express additional comorbid symptoms. The most common comorbid symptoms are attention-deficit hyperactivity (ADHD) and obsessive-compulsive disorder/behavior (OCD/OCB), each of which affect ~50% of TS patients.[7] The cause of tic expression, as well as the appearance of comorbid symptoms, is unclear; however, multiple lines of evidence link basal ganglia (BG) deficits to TDs.

*Correspondence to: Dr. Izhar Bar-Gad, Bar-Ilan University, Gonda Brain Research Center, Ramat-Gan 52900, Israel; izhar.bar-gad@biu.ac.il

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The CorticoBasal Ganglia Pathway Pathology in TDs

The BG have two primary input structures, the gamma-aminobutyric acid (GABA)ergic striatum (subdivided into the caudate, putamen, and nucleus accumbens)

and the glutamatergic subthalamic nucleus. These structures receive excitatory glutamatergic input from the thalamus and cerebral cortex and project to the output structures, globus pallidus internus (GPi), and substantia nigra pars reticulata (SNr). This projection is either direct or indirect through the globus pallidus externus (GPe). Activity throughout the BG is modulated by dopaminergic input from the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) that is directed primarily to the striatum. The GPi/SNr return their information to the frontal cortical areas by projecting inhibitory output to the thalamus, which has excitatory connectivity with the cortex, thus forming the cortico-basal ganglia (CBG) loop.[8,9] Input to the BG is sent from cortical areas associated with motor, associative/executive, and limbic functions. These inputs reach different anatomical territories within the input structures of the BG. The segregation of the territories is maintained throughout the nuclei of the BG and in their projections back through the thalamus to the cortex, thus forming the motor, associative, and limbic CBG pathways.[10]

TS pathology has been examined through a variety of postmortem, imaging, and genetics studies that have revealed associations with CBG pathways and, specifically, with the striatum. Postmortem anatomical studies indicate a 50% to 60% decrease in the number of GABAergic and cholinergic interneurons in the striatum of TS patients,[11] a decrease in the GPe and an increase in the GPi neuron count, compared to healthy controls.[12] Imaging studies support these finding and show a decrease in the volumes of the striatum and GP in TS patients.[13,14] In addition to gray matter changes, multiple alterations in structural connectivity were observed in CBG circuits.[15,16] An inverse correlation was reported between tic severity and the structural connectivity of the supplementary motor area (SMA) with the BG,[17] whereas motor cortex connectivity with the striatum and thalamus was positively correlated with tic severity.[16] Additional structural changes, correlated with tic severity, were found in multiple cortical areas, primarily in the frontal lobe and pre-/postcentral sulci.[18] Cytogenetic mapping has revealed rare changes in the SLITRK1 gene in association with TS.[19] SLITRK1 is expressed in projection neurons of the CBG circuits.[20] Circumstantial evidence for BG involvement in TD pathology comes from the emergence of tics consecutive to certain cases of BG stroke[21] and tic reduction post-DBS in multiple locations along the CBG pathway.[22] This converging evidence of changes in the CBG circuit points to this pathway as the key candidate for the abnormal pathophysiology of tics and TDs.

Pathophysiology of Tics and TDs

Over the last two decades, a growing number of studies have attempted to shed light on the underlying pathophysiology of tics and TDs. These studies point to the large number of brain areas involved in diverse functions, including the motor, sensory, limbic, and executive networks. This myriad of findings stems, at least partially, from the multifaceted properties of tics and the disorders that express them, which have led to a fuzzy definition of the term TD pathophysiology. Below, we break down the term TD pathophysiology into smaller, better-defined terms. This is done by disentangling the different factors related to the expression and modulation of tics and comorbid symptoms and examining the underlying functional changes associated with each factor.

The networks underlying the characteristics of TDs can be roughly divided into two main categories: (1) expression networks, which mediate the behavioral symptoms of the disorder, and, (2) control networks, which regulate their expression (Fig. 1). The expression networks include (1) the neural substrate underlying tic manifestation, (2) the networks underlying the comorbid symptoms, and (3) other alterations in brain state that result in different natural and experimentally induced behaviors. The control networks include (1) voluntary tic suppression and (2) a variety of behavioral states, such as stress and arousal, that influence symptom expression. Premonitory urges have properties common to both networks. If seen as a sensory phenomenon expressed in conjunction with tics, they should be categorized as one of the expression networks. Alternatively, they can be considered as the driving force leading to tic execution, which places them among the control networks.

Expression Networks

Tics and Tic-Related Neuronal Activity

One of the earliest questions regarding tic physiology is which part of their encoding differentiates them from normal, seemingly identical, voluntary movements. Obeso et al. identified differences between EEG signals preceding tics and the voluntary movements mimicking them.[23] During more than three decades of research since, the pathophysiology underlying tic expression has been studied using a variety of techniques. In line with the primary anatomical findings revealing BG abnormalities, converging evidence from these studies supports the involvement of the CBG pathway in the pathophysiology of tic expression.

Comparison of the neuronal circuits involved in expression of spontaneous tics and the voluntary imitation of these movements using functional MRI (fMRI) has indicated increased activity in multiple areas along the CBG pathway.[24] Specifically, activity in the sensorimotor cortex, putamen, GP, and SN is greater during the expression of spontaneous tics than in the execution of voluntary movements mimicking them.[24] Furthermore, the enhanced activity of these

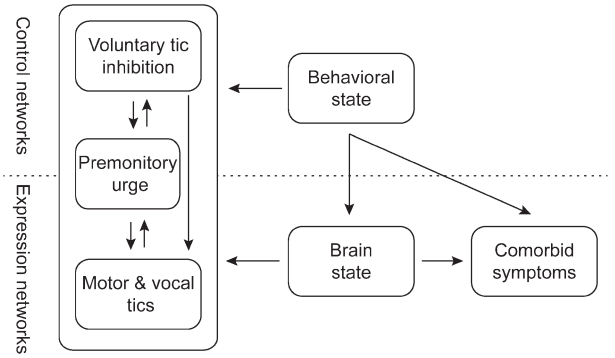

FIG. 1. Multiple aspects of TDs. Expression and control components involved in TDs and their interaction.

areas as well as in the STN, thalamus, and VTA is correlated with tic severity.[24,25] The temporal properties of tic formation have been studied by identifying transient tic-related activity using various imaging techniques. Multiple motor areas including pre- and primary motor cortices and putamen, and in limbic and sensory areas, showed tic-related activation preceding tic onset in an fMRI study.[26] During tic onset, enhanced activity was present mostly in motor areas such as thalamus and primary motor and somatosensory cortices.[26] The activity of premotor and primary motor cortices as well as striatal activity correlated with tic occurrence were also found in a PET study.[27] Evidence of tic-related activity of limbic, sensory, and executive areas was also present during tic onset. Transient changes in GPi neuronal activity preceding tic onset were identified using electrophysiological recordings in TS patients undergoing DBS implantation surgery.[28] This converging evidence suggests that tics are mediated by aberrant activity in motor CBG circuits. Additional motor systems, outside the CBG pathway, may be involved in tic formation, as was observed recently in the cerebellum of both human patients and animal models.[29-32] This motor system activity may be accompanied by secondary activity in the limbic, somatosensory, and associative systems.

The specifics of the pathophysiology of tics that show BG involvement in tic formation come from an animal model in which movements resembling motor tics are expressed. In this model, local disinhibition of the sensorimotor part of the striatum, using local $GABA_A$ antagonist injection, leads to the manifestation of motor tics in the contralateral side of the body. The striatal disinhibition model has been applied in multiple studies in both rodents[33-36] and non human primates.[37-41] Multiple studies that have revealed finely timed tic-related changes in neuronal activity throughout the CBG circuit, including the striatum, cortex, thalamus, GPe, GPi, and SNr.[37,38,42-44] Whereas each of the areas displayed tic-related modulations in neuronal activity in short (subsecond) time scales around tic onset, the modulation type differed substantially (Fig. 2). Tic-related activity in the primate motor cortex included bursting activity typically preceding the corresponding electromyography signal recorded from the tic-expressing body part.[37] The projection neurons of the striatum displayed an earlier bursty activity preceding tic onset.[38] GPe neurons expressed tic-related phasic modulations, primarily in the form of increases in their neuronal activity, and the GPi neurons mostly displayed transient decreases in firing rates.[37] Likewise, SNr neurons exhibited transient inhibition, whereas thalamic neurons were excited around tic onset[43] (Fig. 2). These physiological findings are in line with Mink's adaptation of the action selection model to tic expression.[45] The action selection model states that, in the normal state, the BG chooses a single action out of a large number of competing actions presented by the cortex.[9] According to this model, an aberrant activation of a subgroup of striatal neurons leads to expression of tics in addition to the expressed actions.[45,46]

The encoding of the location (i.e., the body part in which tic is expressed) poses another key question. In the rat, disinhibition of the anterior region of the dorsolateral striatum resulted mostly in forelimb tics, whereas disinhibition of the posterior part of the striatum led mostly to tics in the hindlimbs. These results

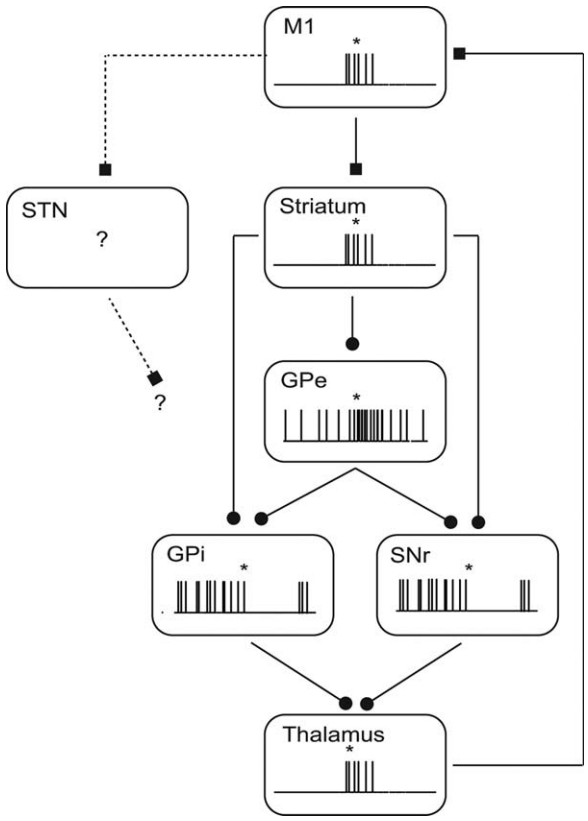

FIG. 2. Tic-related neuronal activity. Scheme of neuronal activity (each spike is marked as a line) in different areas of the CBG pathway. Interaction between the areas is marked by symbols (square, excitatory; circle, inhibitory connections).

suggest that the tic-expressing body part is determined by the location of activity disruption within the striatum.[35] Support for this hypothesis derives from recordings of the tic-related neuronal activity in the primate model of motor tics, which indicated that neurons displaying tic-related activity modulations are located in the striatal region somatotopically associated with the tic-expressing body part.[38] Finally, the evoked, primarily orofacial, tics in the nonhuman primate striatal disinhibition model are in line with the distribution in human patients, who most commonly display facial tics corresponding to the broad somatotopic representation of face muscles in both species. This relationship between the somatotopic representation and the probability of tic expression in the associated body part has recently been supported by studies of TD patients.[47]

Although the neuronal mechanism underlying tic manifestation is not fully understood, multiple evidence from both human studies and animal models converges to support the hypothesis that tic formation is associated with an aberrant function of motor parts of the CBG circuit. Based on experimental evidence, the abnormal function of these nuclei was suggested to be correlated with tic severity and location. Additional evidence emerging from multiple imaging studies indicates tic-related activity in limbic, sensory, and executive systems. These systems are thought to be involved in different tic-related conditions, which are discussed below.

Premonitory Urge

Premonitory urges are reported by the vast majority of TD patients.[2] Tic expression is commonly accompanied by a feeling of relief of this urge.[2,48] Although premonitory urges are a prominent symptom expressed alongside tics, the nature of the relationship between the two symptoms is unclear. In particular, it remains unclear whether tics and premonitory urges maintain a causal relationship in which one elicits the other, or whether they share a common input that mediates coexpression of two independent phenomena. It has been suggested that premonitory urges may be the involuntary component of tic expression, whereas the movement itself is the volitional response to it.[2,48] Conflicting evidence complicates this picture. First, not all patients experience premonitory urges, and even in patients who do, in some cases tics occur without any preceding sensations.[2,49] In addition, premonitory urges are mostly reported in patients above 10 years of age, creating a lag of 3 years, on average, between onset of tics and their premonitory sensations.[2] This dissociation between the existence of premonitory urges and tic expression hints that these two symptoms are governed by different neuronal mechanisms, but share a common input mediating their coexpression.

The neuronal correlates of premonitory urges have rarely been investigated explicitly and have mostly been deduced from studies exploring the neuronal correlates of tic generation, which limits the ability to dissociate the origins of the two symptoms. Multiple fMRI studies have reported increased activity attributed to the premonitory urge, including: (1) enhanced activation in the somatosensory and posterior parietal cortices, putamen, and amygdala/hippocampus complex during spontaneous tic expression compared to simulated tics[24]; (2) activity in paralimbic areas, including the anterior cingulate cortex and insular cortex, and sensory areas, including the parietal operculum, preceding tic onset[29]; and (3) enhanced activity in the parietal operculum, anterior cingulate, insula, and amygdala preceding tic onset.[26] Further evidence for brain activity correlated with tic occurrence in the anterior cingulate and insula was reported in a PET study.[27] Using resting-state fMRI and graph theory-based neural network analysis, Tinaz et al. reported higher connectivity of the anterior insula with frontostriatal areas in patients, compared to the control group. The functional connectivity between the right dorsal anterior insula and the left dorsomedial prefrontal cortex correlated positively with urge severity. They suggested that these networks exhibit different patterns in TD patients, even in the absence of tic expression.[50] These data suggest the involvement of sensory areas (i.e., the parietal operculum), along with limbic and paralimbic areas, such as the anterior cingulate, insula, and amygdala, in the formation of premonitory urges.

Comorbid Conditions

The vast majority of TD patients suffer from additional comorbid symptoms, primarily ADHD and OCD/OCB.[7] The high rates of co-occurrence hint that these disorders have underlying mechanisms in common with TD. Indeed, all of these disorders have been associated with CBG pathway abnormalities: Imaging studies have reported smaller GP,[51] caudate,[52,53] and putamen[53] volumes in ADHD patients. In the case of OCD comorbidity, MRI studies have shown that the caudate[14] and putamen[13] volumes were reduced, in comparison to TD patients without comorbid OCD. The caudate nucleus volume in these patients was negatively correlated with tic severity[14] and OCD symptoms,[14,54] demonstrating the involvement of striatal pathology in the symptoms of both disorders.

Recent animal models lend weight to the hypothesis of a shared pathophysiology in TD, ADHD, and OCD. Local disinhibition of the sensorimotor part of the striatum induces motor tics. The same procedure induces symptoms of hyperactive behavior when

applied to the central associative-limbic part of the striatum of nonhuman primates,[39,55] or to the nucleus accumbens of rats.[56,57] Furthermore, OCD-like stereotypy is expressed when disinhibition is applied in the central and ventral parts of the anterior striatum of nonhuman primates.[39] Similar behavioral consequences were reported in a study of electrical microstimulation in the striatum of primates.[58] Manipulation of downstream BG targets had the same influence: Disinhibition of the associative part of the primate GPe induced ADHD, whereas disinhibition of the sensorimotor or limbic parts resulted in abnormal movements or stereotypic behaviors, respectively.[59-61] Another animal model that has underscored the common pathophysiology of TD and OCD is a genetic mouse model with an altered cortical-limbic subset of neurons that leads to hyperactivation of striatal circuits. These mice express OCD-like behaviors as well as juvenile-onset tics.[62] Using two different approaches, these models have shown that disinhibition/hyperexcitation of striatal circuits leads to tics as well as OCD-like and ADHD-like symptoms, which are dependent on the manipulated functional pathway within the CBG loop. These behavioral outcomes suggest that the comorbid conditions of TD with its associated disorders may be explained by an expansion of the pathophysiology from the motor areas of the CBG circuits toward the associative and limbic parts of these nuclei.[63]

Brain States

Several lines of evidence indicate that the state of the TD patient's brain is different from the healthy brain, even at times when tics are not expressed. Various experimental paradigms have investigated this difference to understand whether it is a result of the same deficit that causes tic expression, or whether it is a prior state that enables tic generation. The best-studied changes in TD patients' brain state are the abnormalities in the motor and sensory systems.

Cortical motor inhibition (i.e., the ability to suppress unwanted movement) is thought to be related to the abnormal release of tics in TD. This hypothesis has been partially supported by a number of behavioral[64] and transcranial magnetic stimulation[65,66] studies. Another suspected change in the TD brain has to do with sensory hyperawareness,[67] subsequently termed interoceptive awareness.[68] Interoceptive awareness is associated with enhanced activity of the insula, motor, and cingulate cortices.[69] This ongoing change in interoceptive awareness may cause the transient sensation of premonitory urges.[67,68] In line with this hypothesis, Ganos et al. recently found that interoceptive awareness was a strong predictor of premonitory urges.[70] TD patients also experience sensory-motor gating deficits.[71] Sensory motor gating is examined by testing for a suppressed startle effect after a presentation of a stimulus preceded by a prepulse. TD patients show prepulse inhibition (PPI) disruption, which may persist even in cases of tic disappearance in adulthood.[72] Rat models demonstrate PPI modulation by norepinephrine and dopamine,[73] both of which are neuromodulators associated with the control of tic expression (see section on Behavioral States).

Control Networks

Tic Suppression

Tics can be voluntarily suppressed by patients for a limited period of time.[3,74,75] Tic suppression is hypothesized to involve frontal-cortex–mediated modulations of BG activity. This claim was supported by an fMRI study showing that frontal cortex activity is correlated with increased activity in the caudate nucleus, which, in turn, was associated with decreased activity in the GP, putamen, and thalamus.[76] A correlation was apparent between tic suppression and increased regional homogeneity of the signal from the left inferior frontal gyrus,[77] which has been previously associated with inhibition of motor responses.[78] These activity increases were correlated with patients' ability to suppress tics. A recent magnetic resonance spectroscopy study suggested that tic suppression may result from a localized tonic inhibition mediated by extracellular GABA within the SMA.[79] Ganos et al. showed, in a recent study, that the ability to suppress tics is not equal for all body parts.[47] Whereas tic distribution across body parts is consistent with the proportions of their representation in the brain, tic inhibition is negatively correlated with it. Based on these findings, they suggested that tic suppression and tic generation involve two different mechanisms. The tic generation mechanism involves activation of an area that differs in proportions according to representation of the tic-expressing body part, but the mechanism governing tic inhibition sends relatively constant input to it. Accordingly, highly represented body parts should be less influenced by the inhibition process than body parts with a smaller representation on somatotopic maps.[47] Although the neuronal mechanism governing tic suppression is still largely unknown, these findings suggest that it involves frontal-cortex–mediated modulations of BG activity.

Behavioral States

TD patients self-report that contextual factors may cause involuntary fluctuations in tic frequency and severity.[4,80] These tic attenuation factors include focused concentration and relaxation, whereas tic exacerbation is induced by factors such as stress and anxiety.[4,80,81] However, a comparison of tic frequency during stress manipulation to baseline levels found no differences. Only when the subjects were asked to suppress their tics was tics frequency larger during stress manipulation.[82] Therefore, it has been suggested that

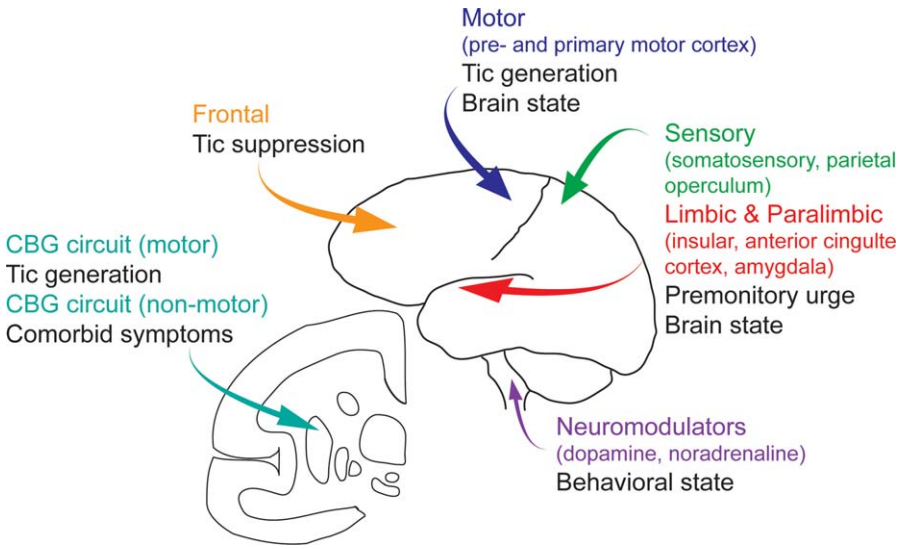

FIG. 3. Brain pathways involved in TDs. Schematic diagram of the primary brain areas underlying the expression and control networks in TDs. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

stress and, potentially, other factors do not affect tic expression directly, but rather indirectly by affecting the ability to voluntarily suppress tics.[4,82] Stress leads to enhanced dopamine levels in the striatum and frontal cortex.[83] Thus, the pathophysiology of tic fluctuations may comprise of a dopaminergic modulation of the basic impairment of the CBG loop. Another line of evidence links the modulation of tics with different states of arousal, leading the idea that tics can be suppressed by reducing sympathetic autonomic arousal,[84,85] which is regulated by the noradrenergic system.[86] Along these lines, both α2 noradrenergic agonists and the D2 dopaminergic antagonist are used to treat motor tics.[87] Aberrant activity of the histaminergic system, which is involved in multiple physiological functions, such as wake-sleep cycle, has been implicated in several neuropsychiatric disorders, including TDs.[88] An analysis of linkage in a two-generation TS pedigree revealed a rare functional mutation in the histidine decarboxylase (HDC) gene encoding L-histidine decarboxylase.[89] The interaction between disruption of the histaminergic system and dopamine modulation in TD was demonstrated in a study reporting tic-like stereotypies expressed in Hdc knockout mice after administration of D-amphetamine.[90] These data suggest that tic expression is, at least partially, controlled indirectly by different behavioral states by two neuromodulators: dopamine and noradrenaline, which may be regulated in turn by additional neuromodulators, such as histamine.

Conclusion

Tics are the defining symptoms of TDs; however, they are only one of many symptoms experienced by TD patients. Tics are accompanied by other phenomena, such as the premonitory urge and a multitude of comorbid conditions. Their expression is highly influenced by different behavioral states and they emerge from a global network malfunction that is present even when tics are not expressed. Thus, it comes as no surprise that the study of TD pathophysiology reveals an intricate picture of spatial and temporal activation involving multiple brain areas at multiple time scales. In this review, we sought to simplify this picture by partitioning TD pathophysiology into the different components comprising it. The separation of TD symptoms helps disentangle their underlying networks (Fig. 3). Thus, the motor pathway of the CBG loop is the primary network involved in the formation of motor tics. Premonitory urges, which can be seen as either a symptom expressed alongside tics or as part of the mechanism leading to their manifestation, are mediated by sensory, limbic, and paralimbic brain areas. Comorbid conditions, and, specifically, ADHD and OCD/OCB, can be viewed as an expansion of the pathophysiology that can lead to tics into the associative and limbic parts of the CBG circuits. In addition to the transient activation of the above-mentioned networks, there are changes in baseline brain activation that are present in the frontal cortical areas that lead to disrupted motor inhibition, as well as in the sensory areas that lead to aberrant sensory gating. Finally, the behavioral-state–dependent modulation of the expression of these symptoms is mediated by different neuromodulators, especially dopamine and noradrenaline (Fig. 3). This puzzle of interacting neuronal pathways jointly forms the complex pathophysiology of TDs. The assignment of the different networks to the different symptoms makes it possible to break down the system into smaller subsystems that can be both

studied and treated more efficiently. Subsequently, this will enable a study of the interaction of these subsystems that can shed light on the ways they coalesce to form the complete underlying pathophysiology of TDs. ■

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