Recent advances in Tourette syndrome research

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Tourette syndrome (TS) is a developmentally regulated neurobehavioral disorder characterized by involuntary, stereotyped, repetitive movements. Recent anatomical and neuroimaging studies have provided evidence for abnormal basal ganglia and dopaminergic function in TS. Basic research on striatal inhibitory mechanisms and dopaminergic function complements the recent neuroimaging and anatomical data. Parallel studies of basal ganglia participation in the normal performance and learning of stereotyped repetitive behaviors or habits has provided additional insight. These lines of research have provided new pieces to the TS puzzle, and their increasing convergence is showing how those pieces can be put together.

Introduction

Tourette syndrome (TS) is a neurobehavioral disorder characterized by motor and vocal tics beginning in childhood [1,2]. Tics are involuntary, repetitive muscle contractions that produce stereotyped movements (motor tics) or sounds (vocal tics). Approximately 50% of individuals with TS also exhibit obsessive–compulsive behaviors (OCBs); tics and OCBs have similar features and both are thought to arise from frontal-cortical–basal-ganglia–thalamo–cortical circuits. Recent advances in understanding the neurobiology of TS come from neuroimaging studies, from anatomical studies in post-mortem TS brains, and from physiological and behavioral studies in rodents and non-human primates. These advances provide exciting clues to the underlying circuit abnormalities in TS and point towards new therapies for this complex and fascinating disorder.

Clinical features of TS

Tourette syndrome is defined by motor and vocal tics that start during childhood, persist for more than one year, and fluctuate in type, frequency and anatomical distribution over time. A specific tic can be present for weeks, months or years and then suddenly cease. Other tics emerge and disappear with no predictable time course. The motor patterns of tics can involve individual muscles or small groups of muscles (simple tics), or more muscles acting in a coordinated pattern to produce movements that can resemble purposeful voluntary movements (complex tics). Many individuals with TS exhibit both simple and complex tics during the course of the disorder. Simple tics include eye blinking, nose twitching, head jerking, eye deviation, mouth opening, sniffing and throat clearing. Complex tics include head shaking, scratching, touching, throwing, hitting, gestures or uttering phrases.

Tics are preceded often by specific sensations, such a scratchy feeling in the throat before a grunt, or by a nonspecific urge [3]. There is a tendency for tics to occur in 'bouts' that wax and wane over hours, days, weeks or months [4]. It is common for tics to increase during times of stress, and to decrease when the individual concentrates on certain tasks. Tics start around school age, increase to a maximum severity on average during the pre-adolescent years, and typically decline in frequency and severity by the beginning of adulthood [5,6]. This worsening of tics during later childhood and early adolescence, and the fact that tics are more common in males than in females, suggest a role for gonadal hormonal influences in the pathophysiology of TS [2].

Obsessive-compulsive behaviors are strongly associated with TS both within individuals with TS and within families [7]. OCBs are characterized by repetitive thoughts that are involuntary, senseless and often associated with anxiety, coupled with repetitive ritualistic behaviors that are often performed in response to the premonitory thought or idea. There are striking similarities between tics and OCBs, and it is sometimes difficult to distinguish complex tics from compulsions. Both tics and OCBs include premonitory experiences such as sensations (tics) or thoughts (OCB) that precede involuntary repetitive movements (tics) or behaviors (OCB). Performance of the tic or compulsion typically terminates the premonitory symptoms, at least temporarily. Another feature common to both phenomena is impaired ability to inhibit unwanted actions [8]. The spectrum of simple tics, complex tics and compulsions suggests that similar or shared pathophysiological mechanisms, but separate neural circuits, might underlie these phenomena.

Epidemiology and genetics of TS

Recent epidemiological work has changed the perception that TS is rare. Newer studies have combined

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community-based surveys with more comprehensive ascertainment techniques [9–13]. Another important change is that the definition of TS in some recent studies has been 'relaxed' to include individuals with non-disabling tics. These studies suggest relatively high prevalence rates of tics and TS, with some studies reporting incidence of >1000 per 100 000 children. Many of these children have mild clinical features and might never come to medical attention.

TS has a strong heritable component, with a high percentage of TS patients having an affected first-degree relative [14,15]. Twin studies reveal high concordance rates in monozygotic but not dizygotic twins. TS genetics are complex with the available evidence favoring polygenic inheritance and linkage data pointing to several loci. The first association of a gene with TS was reported recently [16]. Abelson *et al.* identified a child with TS and a *de novo* inversion on chromosome 13, and found that the gene encoding Slit and Trk-like 1 (SLITRK1), a member of a family implicated in neurite outgrowth, was close to one of the breakpoints. Among 174 unrelated subjects with TS, two mutations in this gene were identified in three unrelated individuals, but no mutations were found at this locus in 3600 control chromosomes [16]. One of these mutations is a frame-shift event and another is a point mutation mapping to a microRNA-binding site in the $3'$UTR of *SLITRK1*. Both mutations are thought to cause haploinsufficiency. In primary neuronal cultures, wild-type *SLITRK1* enhanced dendritic growth, but a *SLTRK-1* mutant did not. SLITRK1 is expressed widely in developing and postnatal brain, and implication of a molecule regulating neuronal development opens an intuitively attractive pathway to explaining the pathogenesis and natural history of TS.

Clues from clinical pharmacology and neuroanatomy

Useful clues regarding the neurobiology of TS come from the clinical pharmacology of tics and OCBs. Tics are suppressed reliably by dopamine antagonists. OCBs are improved by selective serotonin-reuptake inhibitors (SSRIs), although in some subjects with TS, OCBs respond best to a combination of an SSRI and a dopamine antagonist [17]. These facts implicate the dopaminergic and serotonergic pathways and suggest that regions where dopaminergic and serotonergic neurons interact are candidate loci of abnormalities in TS. Three regions are prime candidates: the striatum, the substantia nigra and the prefrontal cortices. The dopaminergic complex of the substantia nigra and ventral tegmental area and the serotonergic dorsal raphe nuclei both send major projections to the striatum. There is dense dopaminergic innervation of all components of the striatal complex, whereas the serotonergic projections exhibit a ventral-to-dorsal gradient with more intense innervation of the ventral striatum (nucleus accumbens and ventral striatum proper) [18,19]. Serotonergic dorsal raphe cells also innervate the substantia nigra dopaminergic neurons [20]. In prefrontal cortex, dopaminergic and serotonergic terminals mutually contact both pyramidal neurons and non-pyramidal interneurons [21]. The striatum, prefrontal cortices and substantia nigra are further interlinked

by a web of pathways that form the cortical–basal-ganglia–thalamo–cortical circuits [22,23]. From clinical and anatomical considerations, it has been inferred that TS is a basal ganglia disorder and, based on the dense dopaminergic and serotonergic innervation of the striatum, is specifically a disorder of striatal organization and/or function. Some correlative data from other disorders supports the idea that striatal dysfunction is involved in TS. Tics are seen also in disorders with known striatal pathology, such as Huntington's disease [24]. Abundant data implicates ventral striatal dopaminergic neurotransmission in drug abuse and drug craving, attributes of which overlap with obsessive–compulsive disorder (OCD) [25,26].

Recent preliminary reports of surgical treatment of TS also link TS to basal ganglia dysfunction. High-frequency deep-brain stimulation (DBS) of the centromedian–parafascicular complex (CM–PF) in the thalamus or of the internal segment of the globus pallidus (GPi) ameliorates severe tics and possibly OCB [27,28]. The CM–PF is reciprocally connected with the basal ganglia, giving rise to robust projections to the striatum and receiving substantial inputs from the GPi.

Striatal function, dopaminergic function, intralaminar thalamic function and TS

If striatal dysfunction is important in TS, then the clinical phenomenology of TS should reflect distortions of striatal function. Evidence from several disciplines is converging on a set of concepts exhibiting potential correlations with the phenomenology of TS. Tics are abnormal repetitive and stereotyped movements, but repetitive stereotyped behaviors also occur normally. For example, grooming chains are natural stereotyped behavioral sequences that are well characterized in rodents. Grooming chains are probably based on 'hardwired' motor patterns arising from the brainstem and/or spinal cord [29]. The dorsal striatum is crucial for the appropriate sequencing of these component movements [30,31]. Grooming chains are modified profoundly by dopaminergic agents [32,33], and D_1 dopamine receptor stimulation markedly increases grooming behavior and strengthens the stereotyped nature of grooming chains (super-stereotypy). These behavioral effects are consistent with the effects of D_1 receptor agonists on the response of medium spiny striatal neurons to stimulation [34,35]: D_1 agonists tend to potentiate the current state of striatal neurons and reinforce ongoing behaviors. The complex and perseverative behaviors caused by D_1 agonists differ from the effects of D_2 receptor agonists, which tend to cause simple repetitive stereotyped movements. Berridge and colleagues suggest that super-stereotypy is analogous to complex tics or OCBs [32,33]. Other stereotyped behavioral sequences are modulated by the basal ganglia include complex defensive behaviors and facial movements [36]. As pointed out by Darwin, many facial movements are stereotyped among mammals and important in non-verbal communication. [37] Because tics commonly involve involuntary head, neck and face movements, the importance of facial and related movements in social communication might explain the disruptive nature

of tics. There are suggestions that regulation of socially relevant forms of communication is a phylogenetically ancient function of the basal ganglia [38,39].

Another important concept is that the basal ganglia participate in brain circuits responsible for habit formation and maintenance. Habits are plausible physiological analogs of stereotyped, unconsciously executed behavioral sequences such as tics, obsessions and compulsions. The basal ganglia participate in circuits responsible for learning incremental stimulus–response associations epitomized by classical Pavlovian and instrumental conditioning [40,41]. Graybiel has emphasized that the basal ganglia might combine or 'chunk' individual stimulus–response associations into more complex behavioral sequences executed as stereotyped 'units' [42]. In addition, a recent functional magnetic resonance imaging (fMRI) study of a second-order pain learning task identified the ventral striatum as a key locus of such sequential learning [43]. Tics could represent a form of inappropriate habit formation in which inappropriate stimulus–response associations are formed. This interpretation might correlate with the fluctuating nature and 'sensory' component of tics. A corollary of this hypothesis, that TS subjects are impaired in forming desired habits, has experimental support [44]. Dopamine modulates corticostriatal transmission via long-term depression (LTD) and long-term potentiation (LTP) [45–47], and it regulates the efficacy of corticostriatal synapses and might mediate reinforcement of specific discharge patterns. LTP and LTD are thought to be fundamental to many neural mechanisms of learning and might underlie the hypothesized role of the basal ganglia in habit learning [48,49].

Work on dopamine function has been driven by interest in the key role of ventral striatal dopamine neurotransmission in the initiation and maintenance of addiction. The work of Schultz's group, in particular, has provided important findings related to the role of dopamine-mediated neurotransmission in positively reinforced behaviors [50,51]. Schultz's team has revealed a complex relationship between phasic dopaminergic neuron activity and reinforcing stimuli, with phasic nigral dopamine activity providing information about the difference between reward and expectation of reward. Some human fMRI data are consistent with this interpretation [52]. An attractive idea about phasic dopaminergic neuron signaling is that it might attach motivational significance or 'salience' to stimuli [53–55]; this notion represents a generalization of the reward-prediction interpretation of the data from Schultz group. Animal lesion data and some human fMRI data are consistent with the hypothesis that the ventral striatum has a key role in assessing the salience of various stimuli, including rewarding, relatively neutral and aversive stimuli [56,57]. In the specific context of TS, the salience hypothesis makes intuitive sense: TS patients commonly describe a subjective sense of feeling bombarded by unwanted sensations or urges, and some tics appear to be motor responses to these competing sensations [3].

Reports that DBS of intralaminar thalamic nuclei ameliorates tics and OCBs suggest a role for these nuclei in the pathophysiology of TS. Electrophysiological studies of intralaminar thalamic nuclei in non-human primates indicate that they influence striatal attentional mechanisms and the processing of reward information [58–60]. These studies also suggest that intralaminar thalamic nuclei encode information complementary to the reward-prediction error information provided by the dopaminergic nigrostriatal projection. If initial reports of intralaminar thalamic DBS effectiveness in treating tics and OCBs are confirmed, this would represent additional evidence that basal-ganglia-supported mechanisms of learning are abnormal in TS.

Recent imaging findings

Magnetic resonance imaging (MRI) morphometry, functional imaging with MRI and positron-emission tomography (PET), and molecular imaging with PET have all been employed to explicate TS [61]. The resulting literature is contradictory (Table 1). This is likely to reflect the fact that many of the studies share defects. For example, many are small studies of adult TS subjects or mixed groups of adults and children – although the clinical phenomenology of adult TS subjects is identical to that of symptomatic children, individuals with tics persisting into adulthood might be an atypical group.

Table 1. Tourette syndrome: results from MRI morphometry

Number of TS subjects	Subject ages (years)	Results in TS subjects	Refs
14	18–49	Volumes of the caudate, pallidum and left lenticular nuclei were reduced	[64]
37	7–16	No differences in striatal, pallidal, lenticular or ventricular volumes Diminished asymmetry of putamen volume	[66]
14	18–49	Reduced corpus callosum area	[63]
20 (10 monozygotic twin pairs)	9–31	Reduced right caudate volume in the twin that had more severe behavioral symptoms. Ventricular volume asymmetry	[101]
27	6–16	Increased corpus callosum area	[62]
17	17–62	Increased corpus callosum area and loss of caudate volume asymmetry	[102]
19 (female)	8–15	No difference in corpus callosum area	[103]
155	5–65	Increased prefrontal and parieto-occipital cortical volumes. Diminished inferior occipital cortical volumes	[69]
19 (female)	7–15	Little difference from controls	[104]
35	7–16	Increased volume of right frontal white matter	[105]
154	5–65	TS children and adults had reduced caudate volumes. Lenticular nuclei volumes were reduced in adult TS and in TS children with co-morbid OCD	[67]
158	5–65	Children with TS had reduced corpus callosum size. Adults with TS had larger corpus callosum size. Tic severity correlated with corpus callosum size	[65]
43	<14 at MRI	Reduced caudate volume predicted tic and OCB severity in early adulthood	[68]

Some studies include subjects with tics alone and subjects with tics plus behavioral co-morbidities. Treatment might be another confounding variable, and the changing nature of TS with development means that studies obtained at one age or even a close group of ages might miss crucial developmentally regulated phenomena. There has also been considerable methodological improvement in imaging of all modalities, and findings obtained using older scanners and data analysis methods might be of limited resolution.

Anatomical imaging

Early volumetric MRI studies reported conflicting findings about basal ganglia and other CNS volumes [62–66]. In the most extensive study to date, Peterson and colleagues analyzed MRI scans from 150 TS subjects, both adults and children, and 130 control subjects [67]. TS adults, but not TS children, had smaller lenticular volumes. Both TS children and TS adults exhibited smaller caudate volumes than age-relevant controls. In a subsequent extension of this analysis, this group reported recently that smaller childhood caudate volumes predicted the severity of tics and OCBs in early adulthood [68]. Peterson *et al.* reported differences in some cortical volumes between TS and control subjects, and between adult and child TS subjects [69]. Given recent evidence that brain structure continues to change into the patients' 20s, a full-scale prospective study of TS subjects and controls from early childhood through their mid-20s would be necessary to characterize structural changes in TS completely. Thus, the relationship between size and function is complex, but reduced caudate volume supports the concept of basal ganglia abnormalities in TS.

Functional imaging

Studies of brain activity using PET or fMRI in TS subjects implicate the striatum, thalamus and related cortical regions [70–74]. Results from many of these studies overlap with similar studies of individuals with primary OCD, consistent with the idea that OCD and tics might be part of a spectrum [75–78]. A challenge with these studies is disentangling the contribution of motor activation *per se* from the mechanisms underlying tics. In a clever attempt to circumvent this problem, TS subjects were studied in their basal (tic) state and during conscious suppression of

tics. Tic suppression was associated with activity changes in the basal ganglia and in related cortical regions [4].

Studies of striatal dopamine receptors and presynaptic dopamine terminal markers are inconsistent [79–83]. Both PET and single-photon-emission computed tomography (SPECT) have been used to target dopamine receptors and proteins associated with striatal dopaminergic terminals. Owing to small sample sizes and other problems, no definite statement can be made about striatal dopamine receptors in TS. Studies using presynaptic dopaminergic markers have also been inconsistent. (For a thorough summary of this literature, see [61].) Most recent studies seem to agree that expression of markers for striatal dopaminergic terminals is increased in TS. Two recent SPECT studies, including one involving untreated children <12 years of age, report significant increases in striatal dopamine transporter (DAT) density [84,85]. In one of the largest studies to date, [11C]dihydrotetrabenazine (DTBZ), a ligand for the type-2 vesicular monoamine transporter (VMAT2), was employed for PET imaging of 19 adult TS subjects. This study indicated increased VMAT2 density within the ventral striatum, particularly on the right (Figure 1), and suggested a ventral-to-dorsal gradient of increased striatal dopaminergic innervation; this raises the possibility that there is increased dopaminergic innervation throughout the striatum, but that within the dorsal striatum the differences between TS and control individuals are small [86]. The SPECT study of Cheon *et al.*, which is unique in examining untreated children of 6–12 years ($n = 11$), reported that DAT binding was increased throughout the striatum and was of greater magnitude than in the DTBZ-PET study [85]. Further support for the idea that TS is marked by increased striatal dopaminergic innervation comes from a study describing increased amphetamine-evoked striatal dopamine release in TS subjects [87].

Recent post-mortem data indicates that the density of the nigrostriatal projection changes during normal development, reaching a peak during the pre-adolescent period and then declining [88]. Some data from non-human primates suggests that neocortical dopaminergic innervation increases gradually until adolescence and then plateaus [21]. The suggested trajectory of human nigrostriatal innervation development correlates approximately with the natural history of tics, leading to the
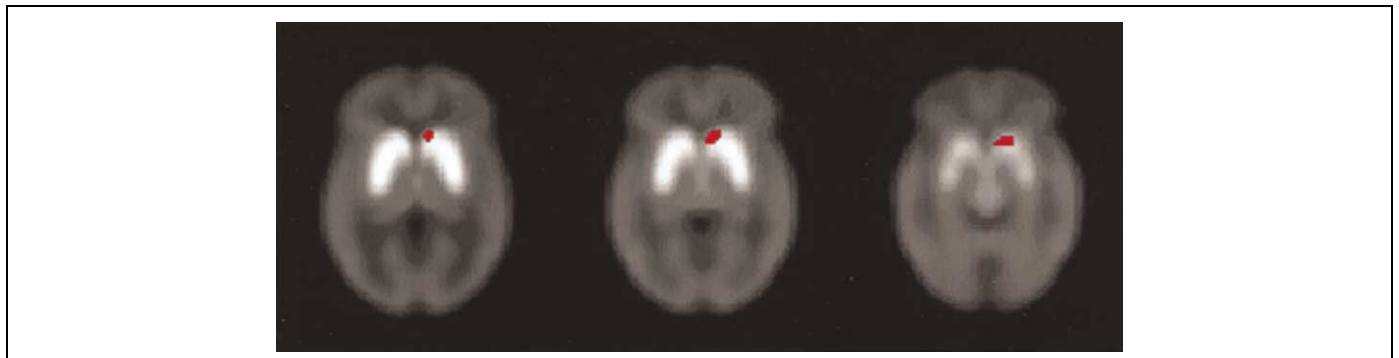

Figure 1. Transverse images of [11C]dihydrotetrabenazine (DTBZ) binding in subjects with TS compared with control subjects. The level of brightness indicates the degree of DTBZ binding and level of expression of the type-2 vesicular monoamine transporter (VMAT2). Images go left to right from dorsal to ventral striatal levels. Voxels with significantly increased DTBZ binding in TS subjects are represented in red. Reprinted, with permission, from [86].

simple hypothesis that changes in the extent or timing of development of the nigrostriatal dopaminergic projection might underlie tics and TS. Thus, nigrostriatal dopaminergic innervation is predicted to be increased in adult TS subjects and even greater in pre-adolescent TS subjects, which is consistent with recent imaging results [88].

Recent anatomical findings
Post-mortem analysis of TS brains has been hampered by a paucity of suitable brains for examination, and routine neuropathological analyses have revealed little about TS. To facilitate neuropathological studies, the Tourette Syndrome Association (http://www.tsa-usa.org/) has developed a brain collection program. Using material from this program, Kalanithi *et al.* found decreased numbers of parvalbumin-positive GABAergic interneurons in the striatum and increased numbers of parvalbumin-positive projection GABAergic neurons in the GPi [89]. Although this study was limited to three TS brains, the findings were consistent across the three brains and significantly different from controls. The authors suggested that their findings can be explained by a migration defect involving GABAergic neurons originating in the ganglionic eminence. This is an exciting idea although it would not, by itself, explain the natural history of tics and OCBs.

Basal ganglia circuitry and a neural circuit model of tics
Basal ganglia circuitry models have been fruitful in stimulating basic and clinical research in basal ganglia

disorders. A specific model for tic disorders has been proposed based on an elaboration of prior models of basal ganglia circuit function and dysfunction [8,23,90]. An important feature of this model is its specification of distinct abnormalities that would lead to tics. Such models view the normal, tonically active inhibitory output of the basal ganglia as a 'brake' on motor pattern generators (MPGs) in the cerebral cortex and brainstem [23] (Figure 2a). For a desired movement controlled by a particular MPG, a specific set of striatal neurons is activated; these neurons inhibit basal ganglia output neurons in the GPi and substantia nigra pars reticulata (SNr) that project back, via the thalamus, to the cortical MPGs. The removal of tonic inhibition from the GPi and SNr (the 'brake') enables the desired motor pattern to proceed. In parallel, neurons in the subthalamic nucleus (STN) excite the surrounding majority of GPi and SNr output neurons. These surround neurons project via the thalamus to competing MPGs, increasing their inhibitory output and applying the 'brake' to competing MPGs. The net result is facilitation of intended movement with inhibition of competing movements.

In the generation of tics, it is hypothesized that an aberrant focus of striatal neurons becomes inappropriately active, causing unwanted inhibition of a group of basal ganglia output neurons, which in turn disinhibit an MPG leading to an involuntary movement. Repetitive over-activity of a given specific set of striatal neurons would result in repeated, stereotyped, unwanted movements (i.e. tics; Figure 2a). Multiple tics would result from
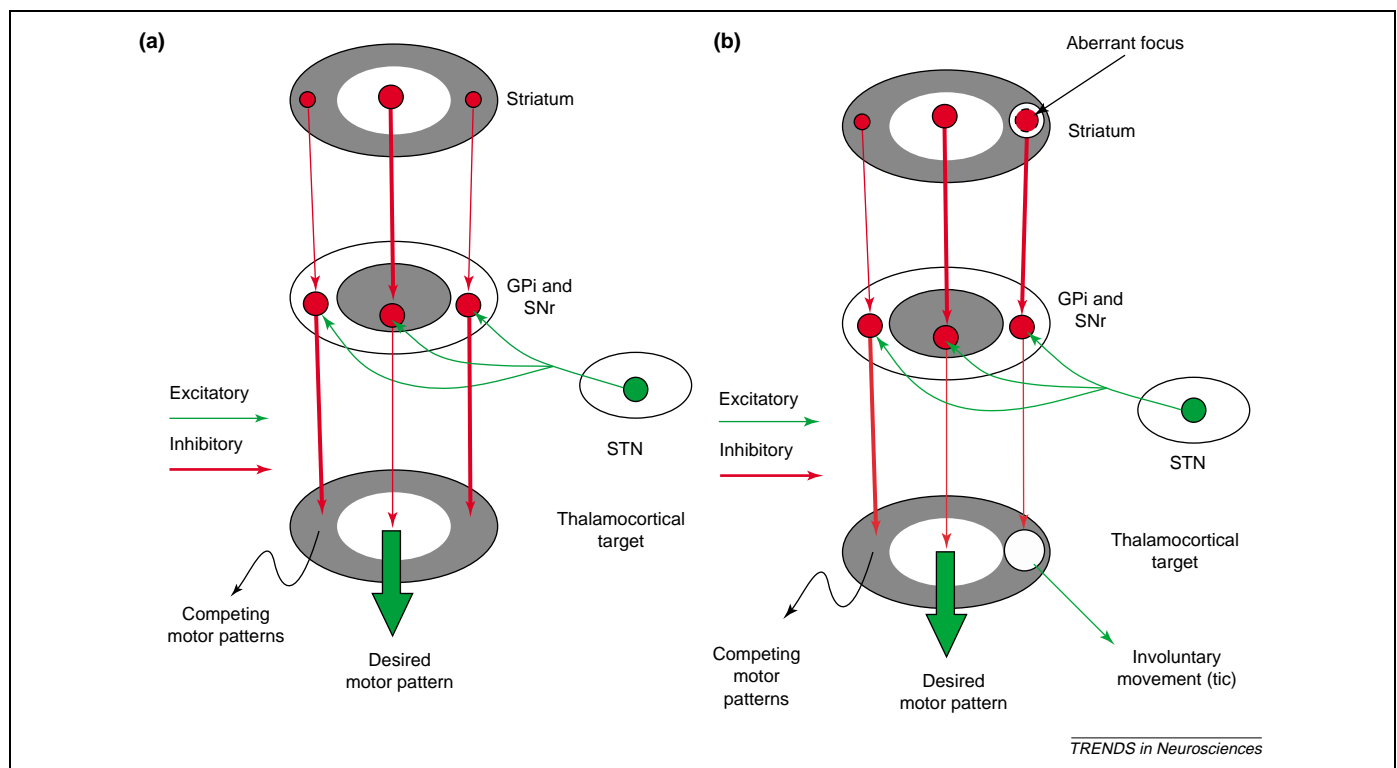

Figure 2. Organization of basal ganglia output under normal conditions and during TS. **(a)** Normal functional organization of the basal ganglia output. Relative magnitude of activity is represented by line thickness. Within the annuli, white indicates increased activity and gray indicates decreased activity. At the thalamocortical target, the center represents neurons involved in the desired motor pattern and the surround represents competing motor patterns. Abbreviations: GPi, globus pallidus pars interna; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus. **(b)** Hypothetical reorganization of basal ganglia output in TS. When a discrete set of striatal neurons becomes active inappropriately ('aberrant focus'), this leads to aberrant inhibition of a discrete set of GPi or SNr neurons. This inhibition disinhibits thalamocortical mechanisms involved in a specific unwanted, competing motor pattern, resulting in a stereotyped involuntary movement (tic).

abnormal excessive activity of multiple discrete sets of striatal neurons.

According to this hypothesis, each tic corresponds to the activity of a discrete set of striatal neurons [8], possibly within striatal matrisomes [91]. Matrisomes are thought to be zones of functional homogeneity defined to a large extent by the pattern of corticostriate inputs. Although no data exist regarding what determines the temporal pattern of spontaneous activity in matrisomal neurons, it is tempting to speculate that the intrinsic membrane properties or afferent activity patterns lead to the temporal pattern of tics that is seen clinically [92].

What would cause aberrant striatal activity in TS? In the normal waking state, striatal medium spiny neurons fire infrequently, averaging 0.1–1.0 spikes per second [93]. The low firing rate is determined in large part by membrane properties [94], and also by tonic inhibition from fast-spiking striatal interneurons [95]. It takes substantial spatial and temporal convergence of cortical afferent activity to activate medium spiny neurons [96], and any factor that increases the sensitivity to these inputs could lead to aberrant activity. Although there are several potential factors, decreased intrastriatal inhibition and/or abnormal dopamine neurotransmission could have a role. As already described, recent post-mortem work has found decreased numbers of parvalbumin-immunoreactive striatal interneurons in TS brains [89]. Parvalbumin immunoreactivity is the anatomical marker for the fast-spiking inhibitory interneurons, suggesting that there might be decreased intrastriatal inhibition in TS brains. Dopamine signaling modifies corticostriate synapse strength and is crucial for the learning functions of the basal ganglia.

Although the neural circuit hypothesis for tic production was developed specifically for the motor circuits of the basal ganglia–thalamo–cortical system, it is likely that the fundamental principles of function in the somatomotor, oculomotor, limbic and cognitive basal ganglia circuits are similar. The segregation of basal ganglia outputs to the frontal lobes via the thalamus described here might provide the anatomical substrate for production of simple tics, complex tics and compulsions [97,98]: abnormal activation of motor cortex via basal ganglia–thalamo–cortical circuits would cause simple motor or vocal tics; abnormal activation of premotor, supplementary motor and cingulate motor areas would cause complex tics; and abnormal activation of orbitofrontal cortex would cause more elaborate motor patterns such as compulsions.

We have emphasized, demonstrated and hypothesized about abnormalities within the basal ganglia, but it should be noted that other brain areas might also be abnormal in TS. It is clear that the basal ganglia are directly influenced by cortical neurons and that basal ganglia output influences cortical activity. Abnormal cortical function can cause basal ganglia function, and vice versa. Recent transcranial magnetic imaging studies have revealed abnormalities of intracortical inhibition in TS [99,100]. However, it is not clear is whether the neurophysiological abnormalities in the motor cortex are primary or are secondary to basal ganglia abnormalities.

Future research directions in TS

Inferences from clinical phenomenology, basic neurobiology of the basal ganglia, recent imaging data and the few post-mortem results converge to support the hypothesis that the clinical phenomena characteristic of TS are due to an abnormality of basal ganglia development. This hypothesis does not preclude the idea that the structure, function or development of other brain regions is abnormal in TS. It is possible that there are differences between TS and normal brains in different brain regions at different phases of development. The emerging evidence that TS involves basal ganglia dysfunction suggests several possible avenues for research on TS. fMRI studies of frontal lobe activation patterns associated with simple and complex tics and with compulsions might reveal a caudal-to-rostral gradient of different circuits responsible for this spectrum of behaviors. Studies of basal ganglia development with MRI morphometry in TS and control subjects from early childhood to adulthood might be revealing. Similarly, establishing the normal course of development of the nigrostriatal projection and examining whether its developmental trajectory differs in TS would be a difficult but potentially valuable experiment. Clinical research regarding the utility of intralaminar thalamic DBS might be revealing, as might further basic research on intralaminar thalamic function.

As genetic research on TS progresses, it might be possible to relate relevant polymorphisms and mutations to aspects of basal ganglia structure or development. Correlation of identified TS polymorphisms and mutations with morphometrically assessed brain changes might be fruitful. Although mutations of *SLITRK1* are not likely to account for a large percentage of TS cases, future research on the neurobiology of SLITRK1 might provide important insights into the pathogenesis of TS. *Slitrk1*-knockout mice might provide a relevant model for TS, SLITRK-1-interacting proteins and molecules regulating SLITRK1 activity might provide candidates for TS loci, and studies of the developmental role of SLITRK1 actions might help to identify the relevant circuits in TS. Polymorphisms associated with loci related to nigrostriatal neuron development might also help in identifying alleles associated with TS.

If natural sequential movements such as rodent grooming behavior are analogs of tics, then D_1 receptor antagonists might prove to be useful for symptomatic treatment of tics. That D_1 receptors are key molecules in the neuronal plasticity underlying addiction reinforces this hypothesis. Finally, the plausible relationship of the clinical phenomenology of TS with striatal regulation of naturally occurring behavioral sequences and habit formation emphasizes that further investigation of the basic neurobiology of the basal ganglia is likely to be indispensable for improved understanding of TS pathogenesis and pathophysiology.

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