Recent advances in Tourette syndrome
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Purpose of review
This review considers the recent literature pertaining to the neurobiology, genetics and treatment of Tourette syndrome.

Recent findings
Over the last several years, both neuropathological and genetic findings have further focused attention on long-standing hypotheses regarding the role of the basal ganglia in causing tics and Tourette syndrome. Moreover, although the field awaits the results of the first large-scale genetic studies, recent findings have already mirrored developments in the neuropsychiatric genetics literature more broadly, highlighting the value of the study of rare variation and the overlap of risks among seemingly disparate diagnostic categories. Finally, treatment studies have underscored the importance of cognitive–behavioral as well as pharmacological interventions for the treatment of tic disorders.

Summary
Recent findings have led to novel, testable hypotheses regarding the molecular and cellular mechanisms underlying Tourette syndrome. These, in turn, have begun to provide new avenues to conceptualizing treatment strategies. Although the development of additional medication options is a pressing need, recent data has demonstrated both the safety and efficacy of nonpharmacological approaches.

Keywords
habit reversal therapy, histaminergic neurotransmission, striatal interneurons, Tourette syndrome

Introduction
Tourette syndrome is a potentially disabling developmental neuropsychiatric disorder defined by the combination of persistent brief, repetitive, nonrhythmic movements and vocalizations. Despite long-standing interest in the neurobiology and genetics of the disorder, knowledge regarding specific cellular and molecular mechanisms has remained limited. Compared with other neuropsychiatric syndromes of similar prevalence, the volume of research into Tourette syndrome over the last decade has been relatively modest. Nonetheless, recent findings with regards to the neurobiology and genetics of the syndrome have begun to clarify etiological mechanisms and have pointed to unexpected opportunities for the development of novel therapeutics. In addition, recent data regarding nonpharmacological interventions are offering considerable hope to patients and their families.

Phenomenology, clinical course and epidemiology
Tourette syndrome typically begins in early childhood, with motor symptoms most often preceding vocal tics by several years. Tics wax and wane, tend to occur in bouts, fluctuate in frequency and intensity, and crescendo and then diminish through late adolescence. In fact, only approximately 20% of affected individuals endorse functional impairment as a consequence of tics at age 20 [1]. There is also a considerable population of individuals who suffer either from chronic motor or chronic vocal tics, but not both, and these individuals are considered as being on a Tourette syndrome spectrum of disorders.

The prevalence of Tourette syndrome is estimated at between 0.3 and 1% [2,3]. However, the epidemiological literature is limited, and characterizations of the natural history tend to reflect a strong ascertainment bias. Many individuals with vocal and/or motor tics do not seek medical attention. The vast majority who do also suffer from other neuropsychiatric symptoms. The vast majority who do also suffer from other neuropsychiatric symptoms. Upwards of 50% of Tourette syndrome probands seen in clinical settings have attention deficit hyperactivity disorder (ADHD) or obsessive–compulsive disorder [4–10]. Learning disabilities, mood and anxiety disorders are also quite common [11–13]. In fact, these comorbid conditions often dominate the clinical picture, and their occurrence along with tics, rather than tics in isolation, can present the most pressing challenges for clinical management.
Recent advances in neurobiology

Several lines of data provide compelling evidence that the basal ganglia, especially the striatum, are a locus of pathology in Tourette syndrome [14,15*]. The caudate and putamen are reduced in size in medication-naive patients with Tourette syndrome, relative to matched controls [16]; smaller volumes in children predict increased symptom severity in adulthood [17]. Functional imaging has shown that activity in striatum, as well as in prefrontal and premotor cortex, correlates with the frequency and intensity of tics [18]. Voluntary tic suppression leads to activation of the basal ganglia, as well as of afferent cortical areas. The magnitude of this activation correlates inversely with tic severity [19].

Despite a long-standing interest in the contribution of the basal ganglia to Tourette syndrome, it is only relatively recently that reproducible cellular abnormalities in these regions have been identified in post-mortem studies. Using unbiased stereological counts in brains from adult Tourette syndrome patients and matched controls, Flora Vaccarino’s laboratory at Yale [20] found a reduction in parvalbumin-expressing fast-spiking interneurons in the dorsal striatum of affected individuals. In contrast, the number and density of these neurons in the globus pallidus, in which they constitute the principal cell type, was increased in patients. This may indicate a developmental abnormality in cell migration, whereby an approximately normal number of parvalbumin-expressing neurons are generated but become abnormally distributed between striatum and globus pallidus.

A recent follow-up study from the same laboratory replicated this finding in a somewhat larger series of patients [21**]. In addition, a second population of striatal interneurons, the cholinergic tonically active neurons (TANs), was reduced in the dorsal striatum (both caudate and putamen). In contrast, neither medium spiny neurons, the predominant cell type in the striatum, nor medium-sized calretinin-positive interneurons were decreased.

These post-mortem findings provide a useful framework for conceptualizing the genesis of tics and their neurodevelopmental origins. Understanding the development of these defined populations of interneurons may lead to new insights into the manner in which genetic, toxic, infectious, hypoxic, or other environmental insults disrupt their division, migration, differentiation, or integration into local circuits and thus lead to the types of circuit-level abnormalities thought to underlie Tourette syndrome. Although certainly not yet conclusive, the combination of the characteristic ontogenic trajectory of symptoms [22] and the considerable evidence for a genetic contribution (see below) suggests that developmental disruption plays a key role.

The interaction of environmental factors and disrupted neurodevelopment is suggested by the finding that neonatal hypoxia is a predictor of tic severity in Tourette syndrome [22,23], though this finding has not been uniformly observed across all studies [24]. Maternal smoking, which can lead to a chronic hypoxic state, has similarly been associated with severity of Tourette syndrome in offspring. In experimental animals, developmental hypoxia appears to produce particular damage to interneurons, at least in cortex [25], though this phenomenon has not yet been documented in detail in the striatum. Moreover, these studies have not shown hypoxia to have a preferential effect on parvalbumin-expressing or cholinergic interneurons. It may be that environmental insults interact with genetic or other risk factors to engender the specificity suggested by neuropathological findings [21**].

The observed interneuronal pathology is consistent with a long-standing conceptualization of Tourette syndrome, at least in part, as involving excessive dopamine. This notion is supported by model systems data, neuroimaging studies (though these have not been entirely consistent in this regard) and the observation that neuroleptic medications, which block the D2 dopamine receptor, remain the most effective pharmacotherapy for Tourette syndrome [26]. Acetylcholine (ACh), which in the striatum derives exclusively from the TANs, is thought to exist in

Key points

- Recent neuropathological studies point to a relative reduction in parvalbumin-containing and cholinergic striatal interneurons in individuals with tics compared to controls.
- Tourette syndrome has long been known to have a strong genetic influence but investigations are just now reporting on cohorts of sufficient size to plausibly illuminate the contribution of common or rare genetic variation to tics and Tourette syndrome.
- Studies of rare copy number variation have highlighted the possibility of shared risks among Tourette syndrome and distinct diagnostic entities, including autism and schizophrenia.
- Over the last year, the study of a Mendelian form of Tourette syndrome has pointed to a previously unappreciated role for histaminergic neurotransmission in the genesis or modulation of tics.
- Dopamine receptor antagonists, the most effective current medications for treating tics, have increasingly been appreciated to carry significant side effects, particularly in the pediatric population. Notably, recent controlled trials have supported the use of nonmedication approaches to tic management, but broad dissemination of these specialized psychotherapies poses an ongoing challenge.
an antagonistic balance with striatal dopamine: ACh can reduce dopamine release in the striatum, at least at lower firing frequencies [27]; anticholinergic medications can treat the dystonic effects of D2 antagonism; and ACh and dopamine are oppositely regulated by reinforcement during certain learning tasks [28]. A reduction in TAN number in Tourette syndrome, therefore, may lead to disinhibited and excessive dopamine tone, producing a hyperdopaminergic state in Tourette syndrome.

**Recent advances in the genetics of Tourette syndrome**

The familial nature of Tourette syndrome has been well appreciated from its initial description by Gilles de la Tourette in 1885. Twin studies, though relatively modest in size, have long supported a high degree of heritability [29]. Nonetheless, after two decades of inquiry, there remains considerable uncertainty regarding the specific nature of the genetic contribution.

The notion that Tourette syndrome is a single gene, autosomal dominant disorder is vestigial. Early studies focused on extended, densely affected multigenerational pedigrees that suggested Mendelian inheritance [30–33]. However, no Tourette syndrome locus was identified via studies of these pedigrees, and a single gene hypothesis has been abandoned. More recent segregation analyses [34–36] point to complex inheritance.

It is worth noting here that, in comparison to many other neuropsychiatric syndromes, the volume of data from genetic studies in Tourette syndrome remains quite limited. Given the increasing appreciation of the critical contribution of large sample size to the study of common disorders [37], many fundamental questions remain regarding the overall genomic architecture of Tourette syndrome, including the potential contribution of common polymorphisms, the relevance of transmitted and de novo submicroscopic copy number variation (CNV), and whether sporadic and familial forms of Tourette syndrome reflect distinct genetic mechanisms, as has been suggested in other developmental neuropsychiatric disorders [38].

The first phase of a large-scale genome-wide association study is reaching completion, promising to begin to illuminate these issues. Although the literature en toto is modest compared to studies of autism, schizophrenia, ADHD or bipolar disorder, very recent findings in Tourette syndrome genetics nonetheless reflect two important general trends in psychiatric genetics: the identification of shared genetic risks across diagnoses that have previously been conceptualized as entirely distinct; and an increasing appreciation of the importance of the study of rare variation in common disease.

Within the last year, the first study of CNV in Tourette syndrome was published by Sundaram and colleagues [39**], reporting on 184 individuals (111 probands). The authors used state-of-the-art methods to control for potential confounds and, even in this small sample, identified an overlap of genetic risks among diagnostically distinct syndromes, identifying rare CNVs previously implicated in autism spectrum disorders and schizophrenia, including the gene NRXN1 and a specific region of chromosome 1q21.

These findings echo several older studies showing a similar convergence. As convincing data have emerged with regard to the overlap of risks for specific CNVs in autism, schizophrenia, epilepsy and intellectual disability [40–42], these findings have been recast in a new light. Specifically, in 2003 a chromosomal insertion at 7q35–q36 was found to disrupt the CNTNAP2 locus in three affected individuals from a single family [43]. This was the first suggestion of a role for this gene in neuropsychiatric disorders, and subsequently, highly penetrant recessive mutations have been convincingly demonstrated in epilepsy, intellectual and social disability [44–48]. Similarly, a deletion involving coding segments of the gene NLGN4X (neuroligin 4X) was identified in a family with Tourette syndrome and autism, learning difficulties, anxiety and depression [49]. This gene has been strongly implicated in intellectual disability and autism spectrum disorders [50,51].

These studies highlight the increasing likelihood that specific genetic variations disrupting key molecular pathways underlying neurodevelopmental processes may manifest in a wide range of behavioral and cognitive phenotypes. They also point to the relevance of studying mutations found in less than 1% of the general population.

The value of the discovery of rare variants carrying large effect sizes has also been demonstrated this last year by our laboratory, through a parametric linkage study of a densely affected family, in which a father and his eight children were affected by Tourette syndrome and obsessive–compulsive disorder [52**]. Traditional linkage mapping revealed a single region of the genome reaching the maximum theoretical LOD score (LOD = 2.1) for the pedigree and sequencing of all known genes in the linkage interval revealed a single nonsense mutation, in the gene for L-histidine decarboxylase (HDC), the rate-limiting enzyme in histamine biosynthesis. Although this gene was not initially prioritized in our sequencing efforts, after the identification of the demonstrably functional, extremely rare mutation, its potential impact on dopaminergic function was of great interest, given hypotheses regarding the role of excessive dopaminergic activity in the genesis of tics (Fig. 1). Histaminergic neurotransmission in the brain is mediated by three of
the four known G-protein-coupled histamine receptors (H1–H4). Both histamine 2 (H2R) and histamine 3 (H3R) receptors are significantly enriched in the human and rodent striatum [53], and H3R acts as a presynaptic autoreceptor on histaminergic projection neurons, as a presynaptic receptor on non-histaminergic neurons that regulates a variety of neurotransmitters, including dopamine and serotonin, and as a postsynaptic receptor, particularly enriched in the striatum and colocalizing with both D1 and D2 receptors. HDC null mice show decreased brain histamine and increased sensitivity to the hyperlocomotor effects of dopamine agonists [54].

Although the identification of a very rare mutation in a single family may shed little light on the population genetics of Tourette syndrome, it nonetheless sets the stage for a number of interesting focused investigations of the histaminergic pathway, its role in striatal dopamine regulation and its relationship to the genesis or mediation of tics. These opportunities may be particularly timely given widespread interest in the pharmaceutical industry in the development of H3R compounds [55] for a variety of other neuropsychiatric indications.

**Recent advances in treatment**

Antipsychotics are the most-effective anti-tic medications currently available [56]. Medium to large effects in the treatment of tics, ranging from $d = 0.4$ to $d = 1.2$, have been identified in several randomized, placebo-controlled trials [56]. However, significant side effects [57,58], including weight gain and an increased risk of metabolic syndrome and diabetes, relegate these agents to second-line options, especially in pediatric populations.

Alpha-2 agonists are currently considered first-line treatment [56]. These show only modest efficacy in tic reduction (effect sizes from 0.1 to 0.5) but their side-effect profile is considerably more benign than that of the antipsychotics. They have also been shown to be quite effective in the treatment of comorbid ADHD symptoms [59**]. In particular, clonidine has similar efficacy to methylphenidate in the treatment of ADHD in children with tics [60]. Psychostimulants, although generally considered the fastest acting and most effective treatment for ADHD in isolation, are often not prescribed in individuals with...
Tourette syndrome because of an FDA warning listing tics or a family history of Tourette syndrome as a contraindication. This was based on a series of case reports published in the 1980s and 1990s highlighting the emergence or exacerbation of tics with psychostimulant use. However, a recent meta-analysis of four trials involving 193 children with ADHD and tics found methylphenidate was effective in reducing ADHD symptoms (effect size = 0.8) and had neutral-to-beneficial effects on tic symptoms (effect size = 0.3) [50**].

Several randomized, controlled pilot studies over the last decade have pointed to emerging pharmacological agents in the treatment of tic disorders, including pergolide, tetrabenazine and topiramate. Pergolide, a dopamine agonist that acts via both D1 and D2 receptors, is hypothesized to improve tics by inhibiting dopamine release. It has shown efficacy in reducing tic severity in children and adults [61,62]. Tetrabenazine inhibits the central vesicular monoamine transporter type 2, and case series have suggested that it may be an effective treatment for tics [63]. Topiramate is a broad-spectrum antiepileptic that acts by increasing central gamma-aminobutyric acid. A recent trial demonstrated a significant benefit of topiramate compared to placebo over 10 weeks in 29 patients with Tourette syndrome [63].

In contrast to the relatively modest progress in pharmacological treatments of tic disorders in recent years, there have been quite significant advances in behavioral treatments for tics. Habit reversal training (HRT) is the first psychotherapeutic intervention that has shown promise in reducing tic severity in patients with Tourette syndrome. HRT consists of awareness training and competing response practice. The former consists of four components designed to increase an individual’s awareness of tics; the latter involves teaching the individuals to produce an incompatible physical response (i.e. isometric contraction of tic-opposing muscles) contingent upon the urge to perform a tic. In recent, multisite trials, using blinded raters, HRT demonstrated efficacy compared to supportive therapy in both adults and children [64**]. The effect size of HRT was similar to that of antipsychotics.

Despite these very encouraging data, key challenges remain to the widespread adoption of HRT for the treatment of tics. Dissemination remains a significant issue, as there are few experienced HRT therapists. Further research into identifying the critical components within HRT and the use of the internet or telepsychiatry to provide more widespread access to treatment may be particularly helpful. At the same time, the development of more effective and safer pharmacological treatments is a pressing need. This effort will undoubtedly be aided by a progressively deeper understanding of the neurobiology and genetics of Tourette syndrome.

Conclusion

Recent advances in the neurobiology and genetics of Tourette syndrome have, in many respects, reinforced conventional wisdom by focusing attention on cortical–striatal circuits and dopaminergic neurotransmission. However, these studies have simultaneously offered potentially novel and important insights, with regard to specific deficits in subsets of striatal interneurons; convergent genetic risks underlying a range of developmental neuropsychiatric outcomes; and a possible role for histaminergic neurotransmission in the causation or regulation of tics. Recent controlled trials of habit reversal therapy support efficacy on par with the best current pharmacological alternatives. However, dissemination presents an important ongoing challenge. Further studies of these nonmedication approaches as well as the development of safer and more effective pharmacological agents remain a pressing need.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 184).


11 Casey MB, Cohen M, Schuerholz LJ, et al. Language-based cognitive func-
tioning in parents of offspring with ADHD comorbid for Tourette syndrome or
12 Robertson MM, Orth M. Behavioral and affective disorders in Tourette
13 Coffey BJ, Biederman J, Smoller JW, et al. Anxiety disorders and tic severity in
14 Frey KA, Albin RL. Neuroimaging of Tourette syndrome. J Child Neurol 2006;
21:672–677.
15 Leckman JF, Bloch MH, Smith ME, et al. Neurobiological substrates of
17 Bloch MH, Leckman JF, Zhu H, Peterson BS. Caudate volumes in childhood
18 Stern E, Silbersweig DA, Chee KY, et al. A functional neuroanatomy of tics in
Tourette syndrome. Arch Gen Psychiatry 2000; 57:741–748.
resonance imaging study of tic suppression in Tourette syndrome. Arch
Kalanithi PS, Zheng W, Kataoka Y, Esbenshade TA, Fox GB, Cowart MD. Histamine H3 receptor antagonists:
Language-based cognitive func-
21 In this post-mortem study, a follow-up to [20], confirmed a reduction in fast-spiking
interneurons and documented, for the first time, that cholinergic tonically active
interneurons are also reduced in number in patients with Tourette syndrome,
focusing attention on this key interneuronal population.
low-birth-weight children at age 6 years: relation to neonatal cranial ultrasound
smoking and increased symptom severity in Tourette syndrome. Arch J
25 Kataoka Y, Kalanthi PS, Grantz H, et al. Decreased number of parvalbumin
and cholinergic interneurons in the striatum of individuals with Tourette
26 Fagel DM, Ganat Y, Cheng E, et al. FGFR1 is required for cortical regeneration
27 Singer HS, Tourette’s syndrome: from behaviour to biology. Lancet Neurol
28 Torrell S, Clements MA, Khodai T, et al. Striatal muscarinic receptors
promote activity dependence of dopamine transmission via distinct receptor
subtypes on cholinergic interneurons in ventral versus dorsal striatum. J
29 Konrad MD, Tourette’s syndrome: from behaviour to biology. Lancet Neurol
distribution in basal ganglia of individuals with Tourette syndrome. Proc Natl
33 Singer HS, Tourette’s syndrome: from behaviour to biology. Lancet Neurol
34 Torrell S, Clements MA, Khodai T, et al. Striatal muscarinic receptors
promote activity dependence of dopamine transmission via distinct receptor
subtypes on cholinergic interneurons in ventral versus dorsal striatum. J
35 Konrad MD, Tourette’s syndrome: from behaviour to biology. Lancet Neurol
36 Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. Physiol
38 Ercan-Sencicek AG, Stillman AA, Ghosh AK, et al. The l-histidine decarboxylase
39 Matsumoto A, Quach H, Chugani HT. Tourette syndrome is
associated with recurrent exonic copy number variants. Neurology 2010;
74:1583–1590.
40 Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. Physiol
42 Ercan-Sencicek AG, Stillman AA, Ghosh AK, et al. The l-histidine decarboxylase
43 Martin A, Scabill L, Anderson GM. Weight and lepi problem changes among
risperidone-treated youths with autism: 6-month prospective data. Am J
44 Bloch MH, Panza KE, Landeros-Weisenberger A, Leckman JF. Meta-analysis:
treatment of attention-deficit/hyperactivity disorder in children with comorbid
45 Fagel DM, Ganat Y, Cheng E, et al. FGFR1 is required for cortical regeneration
46 Konrad MD, Tourette’s syndrome: from behaviour to biology. Lancet Neurol
48 Ercan-Sencicek AG, Stillman AA, Ghosh AK, et al. The l-histidine decarboxylase
49 Martin A, Scabill L, Anderson GM. Weight and lepi problem changes among
risperidone-treated youths with autism: 6-month prospective data. Am J


Piacentini J, Woods DW, Scahill L, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA 2010; 303:1929–1937. This large, multisite study demonstrated a behavioral therapy had efficacy in reducing tic severity for adults with Tourette syndrome. The effect size demonstrated was equal to the best pharmacological treatments available.

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