

Disease Focus

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Neurobiology of Tourette Syndrome: Current Status and Need for Further Investigation

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Tourette syndrome (TS) is a common, chronic neuropsychiatric disorder characterized by the presence of fluctuating motor and phonic tics. The typical age of onset is ~5–7 years, and the majority of children improve by their late teens or early adulthood. Affected individuals are at increased risk for the development of various comorbid conditions, such as obsessive–compulsive disorder, attention deficit hyperactivity disorder, school problems, depression, and anxiety. There is no cure for tics, and symptomatic therapy includes behavioral and pharmacological approaches. Evidence supports TS being an inherited disorder; however, the precise genetic abnormality remains unknown. Pathologic involvement of cortico-striatal-thalamo-cortical (CSTC) pathways is supported by neurophysiological, brain imaging, and postmortem studies, but results are often confounded by small numbers, age differences, severity of symptoms, comorbidity, use of pharmacotherapy, and other factors. The primary site of abnormality remains controversial. Although numerous neurotransmitters participate in the transmission of messages through CSTC circuits, a dopaminergic dysfunction is considered a leading candidate. Several animal models have been used to study behaviors similar to tics as well as to pursue potential pathophysiological deficits. TS is a complex disorder with features overlapping a variety of scientific fields. Despite description of this syndrome in the late 19th century, there remain numerous unanswered neurobiological questions.

In the 1880's, Georges Gilles de la Tourette published a two-part article in which he emphasized differences between tics and chorea. Although many of the descriptions about the disorder, which now bears his name [Tourette syndrome (TS)], have been revised, his belief that tics are a neurological movement disorder and not a psychiatric condition persists to the present (Goetz and Klawans, 1982). Nevertheless, despite multiple advances and widespread acceptance of TS being a biological disorder, the precise etiology and underlying pathophysiological mechanisms remain unknown. The goals of the present review are to briefly describe the clinical phenomenology of TS and related

tic disorders, to review current information on genetic and neurobiological mechanisms, and to identify areas in need of further investigation.

The Clinical Problem

The hallmark of TS is the presence of chronic, fluctuating motor and vocal tics. Best diagnosed by observation, tics are sudden, repetitive, involuntary movements or vocalizations with differing degrees of intensity and frequency, and unpredictable durations (Kurlan, 2010). Tics are currently classified as motor or vocal (phonic), although this separation has been questioned, and further subclassified into simple or complex categories. Simple tics generally involve fewer muscle groups, are briefer in duration, and tend to be more meaningless in their appearance/phonation. Common examples of simple tics are as follows: motor: eye blinking, head jerking, facial grimacing, or shoulder shrugging; and phonic: sounds

or noises such as throat clearing, sniffing, or grunting. In contrast, complex tics typically involve more elaborate manifestations and appear to have a more purposeful action or verbalization. Examples of common complex tics are as follows: motor: touching objects, clapping, obscene gestures, or body contortions; and phonic: the repetition of words including echolalia, palilalia, and coprolalia. Characteristics that help to differentiate tics from other paroxysmal movement disorders include a waxing and waning course, the presence of particular factors that exacerbate (stress, anxiety, fatigue) or reduce (concentrating or focusing) symptoms, a suggestible nature, the presence of a premonitory sensation, and brief suppressibility.

Tics are common in childhood, with epidemiological studies showing that ~20–30% of children exhibit brief, repetitive, involuntary movements or sounds in a classroom setting (Kurlan et al., 2001). The diagnosis of a tic disorder is based solely on

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historical features and a clinical examination that confirms their presence and eliminates other etiological conditions. There is no reliable diagnostic test for TS or the spectrum of disorders that have tics as their cardinal feature. The formal criteria for TS require an age of onset before 18 years, the presence of multiple motor and at least one vocal tic (not necessarily concurrently), a waxing and waning course, the addition and subtraction of various tics, the presence of tic symptoms for at least 1 year, and the absence of a precipitating illness (e.g., encephalitis, stroke, or degenerative disease) or tic-inducing medication. Motor tics have a typical age of onset of ~5–7 years, and the course of TS can be quite variable. Most patients, however, have a decline in symptoms during the adolescence or early adulthood (Leckman et al., 1998; Bloch et al., 2006), leading to suggestions of a developmental disorder. In addition to tics, children with TS often have a variety of comorbid psychopathologies, including attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), learning difficulties, sleep abnormalities, anxiety, and other behaviors, all of which can have a significant impact on the individual's prognosis (Channon et al., 2003; Sukhodolsky et al., 2003; Cavanna et al., 2009). The frequent occurrence of ADHD and OCD in affected individuals has led to suggestions of overlapping pathophysiology between tic disorders and these conditions.

A discussion of treatment is beyond the scope of this review and has been described previously (Singer et al., 2010). In brief, there is no specific cure for tics. The indications for initiating tic-suppressing therapy include psychosocial problems, functional difficulties, disruptions in the academic or work environment, or physical discomfort. Available therapies include both behavioral (habit reversal, cognitive behavioral, and relaxation therapies) and pharmacological approaches. The beneficial response to medications affecting specific neurotransmitter systems is often used to support a pathological involvement, e.g., improvement of tics following the use of dopamine receptor antagonists.

Etiology

Numerous studies have confirmed Gilles de la Tourette's initial suspicion that tic disorders are inheritable, but the genetics underlying the disorders have proven complicated (State, 2010). Familial studies have repeatedly demonstrated significant increases in the incidence of TS or other tic disorders in first degree relatives of affected individuals (McMahon et al., 2003). Studies in twins

also support a genetic disorder with a concordance of chronic tics in 77–94% of monozygotic compared to just 23% in dizygotic twins (Price et al., 1985; Hyde et al., 1992). Despite these reports, the precise pattern of transmission and the specific genes involved remain elusive. Linkage analyses have suggested several chromosomal locations, but without a clear reproducible locus (Pauls, 2006; O'Rourke et al., 2009). Similarly, candidate gene studies have failed to yield consistent results for specific susceptibility genes. Much attention has been paid to dopaminergic candidates, and there is evidence of a significant association between TS and a dopamine transporter polymorphism (DAT1 *Ddel*) (Yoon et al., 2007b). Several recent candidate genes have included: a heterozygous loss of function mutation in L-histidine decarboxylase, which encodes the rate limiting enzyme in histamine biosynthesis (Ercan-Sencicek et al., 2010); functional variations of the *SLITRK1* gene, with homology to a known axon guidance molecule (Scharf et al., 2008); and DLGAP3, a postsynaptic scaffolding protein highly expressed in striatal glutamatergic synapses (Crane et al., 2011).

Multiple factors contribute to the ongoing difficulty in identifying a specific means of genetic transmission, including phenotypic heterogeneity, the variable expression of comorbid conditions, genomic imprinting [sex of the transmitting parent affecting clinical phenotype (Lichter et al., 1995; Eapen et al., 1997)], bilineal versus unilineal transmission (Hanna et al., 1999; Lichter et al., 1999), and epigenetic factors. Several studies have suggested that a variety of prenatal and perinatal risks may be associated with the subsequent development of TS, including the timing of perinatal care, severity of mother's prenatal nausea and vomiting, proband birth weight, the 5 min Apgar score, and prenatal maternal smoking (Leckman et al., 1990; Burd et al., 1999; Mathews et al., 2006; Young et al., 2008; Pringsheim et al., 2009). Further replication, however, is necessary before any significance can be attributed to these factors. The emergence of genomic methods that enable comprehensive investigation of both rare and common genetic variations and the availability of large patient cohorts is expected to provide valuable insights in the near future (Grados, 2010; State, 2010).

Another proposed theory is that tics can be an acquired consequence of autoimmune mechanisms following a Group A β -hemolytic streptococcal infection (GABHS) (Swedo et al., 1998; Snider and Swedo, 2003), a condition labeled as pediatric autoimmune neuropsychiatric disorder

associated with a streptococcal infection (PANDAS). Indirect support of such a theory includes a significantly higher incidence of autoimmune disease in the mothers of children with tics (Murphy et al., 2010). Nevertheless, the existence of this etiological entity is extremely controversial based on both epidemiological and autoimmune studies (Kurlan, 1998, 2004; Singer and Loisel, 2003; Kurlan and Kaplan, 2004; Singer et al., 2005b; Kurlan et al., 2008; Singer et al., 2008; Morris et al., 2009; Leckman et al., 2011).

Neurobiology of TS

Circuits

A series of parallel cortico-striatal-thalamocortical (CSTC) circuits that link specific regions of the frontal cortex to subcortical structures has provided a framework for understanding the interconnected neurobiological relationships that exist between TS and its multiple comorbid problems (Singer and Harris, 2006; Leckman et al., 2010; Mazzone et al., 2010). In classical models of movement disorders the basal ganglia was believed to influence behavior by changing cortical excitability through the interplay of the "direct" [striatum to globus pallidus interna (GPI)] and the multisynaptic "indirect" [striatum to globus pallidus externa (GPe) to subthalamic nucleus (STN) to GPI] pathway (Albin et al., 1989). According to this model, hyperkinetic disorders were the result of increased cortical excitability, due to either a reduction of direct pathway excitatory effect or an increase in the indirect inhibitory effect. Since this direct/indirect pathway approach failed to address the specificity of tics, other hypotheses have been developed that view the basal ganglia as performing a process of action selection, i.e., focused facilitation of selected movements and inhibition of competing motor patterns (Mink, 2003). Within this system, tics are viewed as a focal excitatory abnormality in the striatum that causes an erroneous inhibition of a group of neurons in the GPI and in turn a disinhibition of cortical neurons (Mink, 2001; Albin and Mink, 2006).

Animal models

Several animal models have been used to investigate TS on different bases: (1) face validity, i.e., behaviors or movements that have some characteristics resembling motor tics (e.g., motor stereotypies, sequential super-stereotypy, repetitive grooming, circling, and self injurious behaviors) (Dodman et al., 1994; Campbell et al., 2000; Berridge et al., 2005; Löscher, 2010; Taylor et al., 2010); or (2) construct validity, i.e., the

animal model has a pathophysiological or developmental neural circuit deficit that is consistent with current knowledge concerning TS. Examples in this latter category include the following: a psychostimulant-induced model; the D1CT-7 transgenic and dopamine transporter knockdown (DAT-KD) mutant mice; a monkey model with striatal disinhibition-induced tics; and rodent models with immunologically related basal ganglia dysfunction.

Psychostimulant model

The psychostimulant model derives some relevance based on the ability of dopaminergic enhancing medications to exacerbate tics and stimulate locomotor behavior. This rodent model has provided important understandings about the role of the basal ganglia, especially striasomes, and the activation of stereotypic behaviors (Canales and Graybiel, 2000; Graybiel, 2000).

D1 receptor cholera toxin transgenic model

The D1CT-7 transgenic mouse (produced using a transgene made by fusing the promoter region for the human D1 receptor with the intracellular A1 subunit of cholera toxin) clinically demonstrates compulsive behaviors (repetitive climbing, digging, and leaping), biting behaviors, and jerking movements (flurries of “twitches” of the head, limbs, and trunk) that begin as early as postnatal day 16 (Burton et al., 1991; Nordstrom and Burton, 2002). Jerky movements, similar to what occurs in TS, are reduced following treatment with clonidine and D2 antagonists. Animals have a reduced seizure threshold which is atypical for children with TS. The construct validity of this model for tics is based on hyperactivity within cortical, limbic, and corticostriatal circuitry, although its correlation to TS has been questioned (Swerdlow and Sutherland, 2005).

DAT-KD mutant mouse

The DAT-KD mouse has a markedly reduced expression of DAT in striatal dopamine neurons, and extracellular dopamine levels are 170% of wild-type controls (Zhuang et al., 2001). Behaviorally the animals are hyperactive and have perseverative behaviors and a pattern of more stereotyped and syntactic grooming sequences that resist disruption (Berridge et al., 2005). This model lacks tic-like jerking movements and is more consistent with obsessive–compulsive-like behaviors.

Monkey focal striatal disinhibition

In two cynomolgus monkeys, focal disinhibition of the sensorimotor putamen, using the GABA_A antagonist bicuculline,

produced repetitive motor tics predominantly in the orofacial region (McCairn et al., 2009). Local field potential spikes, which correlated with tics, were identified throughout the cortico-basal ganglia pathway. Results suggest that output nuclei of the basal ganglia provide a temporally exact and spatially distributed release signal, but that the final activation of tics likely occurs downstream from basal ganglia output.

Autoimmune models

Primarily two types of models have been used to investigate immune mechanisms in tic disorders.

Passive transfer of antibodies. This approach evaluates behavioral effects following the infusion of sera or IgG from individuals with TS into rodent striatum. Results remain very controversial. Some investigations have shown that sera from TS subjects produced a significant increase in stereotypic behaviors (e.g., licks and forepaw shakes) as well as episodic utterances (Hallett et al., 2000; Taylor et al., 2002; Liu et al., 2008). In marked contrast, other studies infusing TS or PANDAS sera at the same coordinates showed no significant increase in stereotypic behaviors and no rat developed any audible abnormality (Loiselle et al., 2004). Negative studies were also confirmed in a blinded, collaborative three-center effort involving several of the previously reporting institutions (Singer et al., 2005a).

Immunization with GABHS. This model evaluates the appearance of autoantibodies and behavioral effects following immunization of mice with GABHS. Female SJL/J mice, immunized and boosted with a homogenate of GABHS in Freund’s adjuvant, developed immunoreactive antibodies against mouse cerebellum, globus pallidus, and thalamus (Hoffman et al., 2004). Rearing and ambulatory behavioral abnormalities correlated with IgG deposits in deep cerebellar nuclei. This model relates more to mechanisms for GABHS-mediated CNS damage than to either TS or PANDAS (Swerdlow and Sutherland, 2005).

Structural changes in TS

Basal ganglia

Volumetric MRI studies, used to identify neuroanatomical (particularly subcortical) changes in TS, vary extensively. In the largest cohort to date, Peterson et al. (2003) identified a mild but consistent decrease in basal ganglia volume in a cohort of >150 TS patients. Subdivided by age, the reduced volume was most apparent in the caudate of children, with adults showing reductions across all basal ganglia re-

gions. This finding is supported by a twin study that showed more severely affected siblings to have a smaller right caudate (Hyde et al., 1995) and a longitudinal study demonstrating that caudate volume in childhood varied inversely with tic severity in adulthood (Bloch et al., 2005). In contrast, a study using stricter exclusion criteria to control for confounders failed to demonstrate any changes in caudate volume, but did show increased volume of the putamen bilaterally in TS boys (Roessner et al., 2011). This finding was also identified using an automated image analysis technique capable of assessing differences throughout the brain rather than focusing on specific selected areas (voxel-based morphometry) (Kassubek et al., 2006). Asymmetry of the putamen, without any change in the absolute volumes, has been reported, but results were inconsistent and possibly affected by gender (Singer et al., 1993; Zimmerman et al., 2000). Diffusion tensor imaging (DTI), which measures the movement of water, provides several indices that can reflect microstructural changes. Using this technique, one group has demonstrated microstructural changes in the putamen compared to healthy controls (Makki et al., 2008). These findings were not replicated in a subsequent study, but a correlation was identified between the diffusion parameters and tic severity among TS patients (Neuner et al., 2011).

Neuropathological studies of TS patients are rare, but a few studies have provided evidence of cellular alterations in the basal ganglia to support imaging studies. In a small study (three TS patients and five controls), Kalanithi et al. (2005) found increases in the total number of neurons in the GPi with concomitant decreases in the number and density of neurons in the GPe and caudate. The distribution of parvalbumin-positive GABAergic interneurons was markedly different in TS patients, with a larger percentage residing in the GPi. This same group confirmed their findings in two additional patients and further demonstrated a decrease in striatal cholinergic neurons (Kataoka et al., 2010). Although the results are limited by a small sample size and multiple potential confounders, including possible effects of pharmacologic therapy, it is proposed that these findings strongly implicate the associative and sensorimotor regions of the basal ganglia in the pathogenesis of TS.

Cortex and subcortical white matter

Significant evidence exists for a primary cortical dysfunction in TS. MRI analyses have detected volumetric changes in the

cortex of TS patients including larger dorsal prefrontal and parieto-occipital regions, and a smaller inferior occipital region (Peterson et al., 2001). In a limited but well controlled male-only study that excluded medicated patients and those with comorbidities, voxel-based morphometry and magnetization transfer imaging (methods sensitive to tissue alterations and macrostructural integrity) have detected changes in prefrontal, frontal, sensorimotor, and anterior cingulate regions (Müller-Vahl et al., 2009). Using parcellation methods, variable changes have been reported in subcortical white matter, with increases in the right frontal region (Fredericksen et al., 2002) or decreases in left deep frontal white matter (Kates et al., 2002). Cortical thinning has been observed in frontal and parietal lobes, particularly in the sensorimotor cortex; the degree of thinning correlated with tic severity (Sowell et al., 2008). In another study of adults with TS, strength of premonitory sensations correlated with increased sensorimotor cortical volume (Draganski et al., 2010). Other reports evaluating subgroups of TS patients (e.g., those with simple tics, complex tics, and obsessive–compulsive symptoms) found a correlation between the location of cortical thinning and clinical symptoms (Worbe et al., 2010).

Interhemispheric connectivity abnormalities have been suggested by volumetric changes in the corpus callosum (Baumgardner et al., 1996; Mostofsky et al., 1999; Plessen et al., 2004; Cavanna et al., 2010; Roessner et al., 2011), abnormal functional [transcranial magnetic stimulation (TMS)] and structural (DTI) connections between the left and right motor hand areas (Margolis et al., 2006; Plessen et al., 2007; Bäumer et al., 2010), and altered performance on a modified verbal dichotic listening task (Margolis et al., 2006; Plessen et al., 2007; Bäumer et al., 2010) and the bimanual Purdue Pegboard (Margolis et al., 2006; Plessen et al., 2007; Bäumer et al., 2010). Diffusion-weighted imaging has revealed microstructural alterations in the corpus callosum and other white matter (Jackson et al., 2011). Additional support for frontoparietal network abnormalities are based on alterations of MRI resting-state functional connectivity (Church et al., 2009b), tic generation in association with coactivation of the supplementary motor area (Hampson et al., 2009), appearance of secondary tics after resection of the frontal lobe (Yochelson and David, 2000), and investigations on postmortem tissue showing a greater number of biochemical changes in pre-

frontal rather than striatal regions (Minzer et al., 2004; Yoon et al., 2007a).

Thalamus

Structural studies of the thalamus have yielded contradictory results. In two small studies of treatment-naïve boys with TS, one found larger left hemithalami (Lee et al., 2005), whereas a second showed bilateral decreases in volume as well as microstructural changes based on alterations in fractional anisotropy using DTI (Makki et al., 2008). A third study, using an automated computational anatomy technique, showed no difference in thalamic size between a small group of TS patients and healthy controls, although this study did not control for numerous variables (Wang et al., 2007). In the largest MRI analysis, including 149 children and adults, there was a 5% increase in thalamic volume, primarily the lateral thalamus (Miller et al., 2010). *Post hoc* testing suggested that the differences observed were not due to IQ, treatment history, or comorbid conditions.

Other brain regions

Several additional brain regions have been implicated in TS. Based on the role of dopamine and known lesions associated with other disorders that involve tics, it was postulated that the midbrain and periaqueductal gray matter might be involved in TS (Devinsky, 1983). This hypothesis is supported by voxel-based morphometry demonstrating increased midbrain gray matter in 31 adult TS patients compared to controls (Garraux et al., 2006). Expanded perivascular spaces in the midbrain, usually considered a benign incidental finding on MRI, have also been correlated with stereotyped behaviors (Dávila et al., 2010). Disruption of corticocerebellar regulatory loops has been postulated based on MRI findings of reduced volumes of the cerebellum, primarily gray matter in crus I and lobules VI, VIIIB, and VIIIA (Tobe et al., 2010). Last, altered MRI volumes of the hippocampus and amygdala (Peterson et al., 2007) and DTI diffusion indices (Neuner et al., 2011) has led to suggestions of direct limbic involvement in TS. This hypothesis is supported by hippocampal and amygdala volumes that are larger in pediatric patients and significantly smaller in adult patients with persistent tics (Peterson et al., 2007). The latter suggests a possible failure of normal hippocampal plasticity in the minority of patients whose symptoms persist into adulthood.

Functional changes in TS

Transcranial magnetic stimulation

One pathogenic mechanism proposed for TS is decreased inhibitory control of the CSTC circuits. Using TMS to compare 20 adult TS subjects to healthy controls, investigators demonstrated normal motor thresholds but decreased intracortical inhibition and a shortened cortical silent period in TS patients (Ziemann et al., 1997). A similar shortening of the cortical silent period was observed in children with TS, but the changes in intracortical inhibition were not found in this group (Moll et al., 1999). Across a broad age range, the degree of reduction of intracortical inhibition appears to correlate with tic severity (Gilbert et al., 2004).

Functional neuroimaging

Event-related PET scanning has correlated tic occurrence with activity in a number of brain regions, including the prefrontal cortex, premotor and primary motor cortex, anterior cingulate cortex, putamen, and caudate (Stern et al., 2000). During active tic suppression, there is increased activity in the right frontal cortex and caudate with decreased activity in the globus pallidus, putamen, and thalamus using fMRI (Peterson et al., 1998). Several PET studies have also identified changes in regional blood flow consistent with increased activity in the sensorimotor cortices and decreased activity in the striatum and thalamus (Braun et al., 1993; Eidelberg et al., 1997). A small study using fMRI demonstrated increased activation of the motor cortex during voluntary motor tasks in TS patients, suggesting altered motor organization (Biswal et al., 1998). One study has also shown that tic severity correlated positively with activation of the substantia nigra and ventral tegmentum, lending credence to a dopaminergic role. This same study found that higher tic severity correlated with slower cognitive task performance, independent of comorbid OCD or ADHD symptoms (Baym et al., 2008). In two of the largest fMRI studies, age-related abnormalities in frontostriatal networks and in frontoparietal connectivity were identified, suggesting that TS patients do not undergo normal maturational changes (Marsh et al., 2007; Church et al., 2009a,b). These findings lend support to hypotheses suggesting that TS is a developmental disorder.

Neurotransmitter studies

Numerous neurotransmitters (dopamine, glutamate, GABA, serotonin, acetylcholine, norepinephrine, and opiates) are involved in the transmission of messages through

Table 1. Summary of TS studies with notes of methods and limitations

Reference	Technique	N (TS)	Primary results	Comments
Structural studies				
Peterson et al., 2003	Volumetric MRI	154	Reduced caudate volume in TS	<i>Post hoc</i> analyses by age, meds, comorbidity
Hyde et al., 1995	Volumetric MRI	10	Reduced right caudate volume correlated with symptom severity	Twin study; no control for age, treatment, or common comorbidities
Bloch et al., 2005	Volumetric MRI	43	Caudate volume in childhood varies inversely with tic severity in adulthood	Longitudinal design; includes assessment of OCD but not ADHD effects; no follow-up imaging
Roessner et al., 2011	Volumetric MRI	49	Enlarged putamen and corpus callosum in TS	Children/adolescents only, controlled for age and IQ; exclusion criteria included prior treatment and comorbid ADHD/OCD
Kassubek et al., 2006	Voxel-based morphometry	14	Enlarged putamen in TS	Children only; controlled for age and gender, not treatment; assessed ADHD but not OCD effects
Singer et al., 1993	Volumetric MRI	37	Altered hemispheric asymmetry of putamen and globus pallidus	Children only; controlled for age; <i>post hoc</i> analysis of ADHD comorbidity
Zimmerman et al., 2000	Volumetric MRI	19	No putamen asymmetry in girls with TS	Controlled for age; assessed for ADHD effect
Makki et al., 2008	Diffusion tensor imaging	23	Microstructural abnormalities in thalamus in TS	Controlled for age; no analysis of medication or comorbidity effects
Neuner et al., 2011	Diffusion tensor imaging	28	Correlation of BG diffusivity and symptom severity	Adults only; excluded comorbidities
Peterson et al., 2007	Volumetric MRI	154	Larger hippocampus and amygdala in TS	<i>Post hoc</i> analyses by age, meds, comorbidity
Peterson et al., 2001	Volumetric MRI	155	Enlarged dorsofrontal and parieto-occipital cortices; diminished inferior occipital cortex	<i>Post hoc</i> analyses by age, meds, comorbidity
Müller-Vahl et al., 2009	Voxel-based morphometry	19	Decreased prefrontal, sensorimotor, anterior cingulate, and left caudate gray matter; decreased white matter in right inferior frontal gyrus, left superior frontal gyrus, and anterior corpus callosum	Adult males only; untreated at least 1 year; no significant comorbidities in population
Müller-Vahl et al., 2009	Magnetization transfer imaging	19	White matter reductions in right medial frontal gyrus, inferior frontal gyrus bilaterally, and right cingulate gyrus	Adult males only; untreated at least 1 year; no significant comorbidities in population
Baumgardner et al., 1996	Volumetric MRI	37	Larger corpus callosum in TS	Children; controlled for age, gender, overall brain volume
Mostofsky et al., 1999	Volumetric MRI	19	No difference in corpus callosum	Girls only; assessed effect of ADHD comorbidity
Plessen et al., 2004	Volumetric MRI	158	Alterations of corpus callosum, variable with age	<i>Post hoc</i> analyses by age, meds, comorbidity
Cavanna et al., 2010	DTI	1	Lower fractional anisotropy of corpus callosum	Twin comparison
Draganski et al., 2010	Voxel-based morphometry and DWI	40	Cortical thinning diffusely, modulated based on comorbidity and symptom severity; increases in primary somatosensory cortex correlated with premonitory sensations	<i>Post hoc</i> analysis of comorbidities; infers ongoing structural plasticity based on a single study
Jackson et al., 2011	DWI	13	Diffuse abnormalities in white matter microstructure; enhanced motor control in TS patients	Adults; excluded comorbidities; wide range of tic severity
Functional studies				
Ziemann et al., 1997	Transcranial magnetic stimulation	20	Shortened cortical silent period and reduced intracortical inhibition	Adolescent/adult; <i>post hoc</i> analysis by age, sex, comorbidity, and treatment
Moll et al., 1999	Transcranial magnetic stimulation	21	Shortened cortical silent period	Children; <i>post hoc</i> analyses of age, OCD, neuroleptic treatment
Gilbert et al., 2004	Transcranial magnetic stimulation	36	Correlation of cortical disinhibition with tic and ADHD severity	Children and adults; assessed effects of ADHD and OCD comorbidities
Stern et al., 2000	PET	6	Tic correlation with activity in cortex, putamen, and caudate	Adults; no control for medication; no discussion of comorbidity
Peterson et al., 1998	fMRI	22	Increased cortical activity with decreased striatal and thalamic activity during active tic suppression	Adults; <i>post hoc</i> analyses of gender, treatment, and comorbidity
Braun et al., 1993	PET	16	Increased activity of sensorimotor cortex; reduction of activity in limbic cortex and striatum	Adults; nonmedicated
Eidelberg et al., 1997	PET	10	Increased activity in sensorimotor cortex; decreased in caudate and thalamus	Adults; nonmedicated; no assessment of comorbidity effects
Biswal et al., 1998	fMRI	5	Increased motor cortex activity during voluntary motor tasks in TS	Adults, few from same pedigree; variable severity and comorbidities
Church et al., 2009b	fMRI	33	Abnormal maturation of functional networks	Adolescents; included comorbidities
Marsh et al., 2007	fMRI	66	Abnormal age-related activation of neural circuits	Adults and children; <i>post hoc</i> analysis of medication and comorbidity effects
Baym et al., 2008	fMRI	18	Tic severity correlated with enhanced activation of dopaminergic nuclei and slower response time	Children; mostly medication-naïve; <i>post hoc</i> analysis of comorbidity;

Table continued

Table 1. Continued

Reference	Technique	N (TS)	Primary results	Comments
Neurotransmitter studies				
Wong et al., 2008	PET	16	Increased phasic dopamine release in ventral striatum	Adults; included assessment of OCD comorbidity
Steeves et al., 2010	PET	8	More widespread phasic dopamine release compared to controls	Adults; controlled for medication exposure and comorbidity
Liu et al., 2010	SPECT	18	Higher dopamine transporter expression	Adolescents and adults; drug-naïve; no discussion of comorbidities
Behen et al., 2007	PET	29	Abnormal tryptophan metabolism in dorsolateral prefrontal cortex and thalamus	Children; subgroup analyses of medication and comorbidities
Haugbøl et al., 2007	PET	20	Increased serotonin receptor binding in TS	Adult; no assessment of medication or comorbidity effects

CSTC circuits, and each has been proposed as a potential pathophysiologic mechanism (Singer and Minzer, 2003). Dopamine dysfunction is considered a prime abnormality in TS based on tic suppression with the use of dopamine antagonists (antipsychotics), results from various nuclear imaging protocols (Wolf et al., 1996; Wong et al., 1997, 2008; Singer et al., 2002; Albin et al., 2003; Serra-Mestres et al., 2004; Liu et al., 2010), CSF analysis (Singer et al., 1982), and post-mortem studies (Singer et al., 1991, 1995; Minzer et al., 2004; Yoon et al., 2007a). One hypothesis is that either an overactive dopamine transporter or central abnormality leads to an alteration in phasic dopamine release, which in turn, results in a hyper-responsive spike-dependent dopaminergic system (Singer et al., 2004; Wong et al., 2008). This dopaminergic tonic-phasic hypothesis could potentially involve either the cortex or striatum. Although most neurotransmitter-related studies have focused on the striatum, support for an extrastriatal dopaminergic dysfunction includes PET findings of decreased cortical receptor binding potentials and increased dopamine release (Steeves et al., 2010) and post-mortem identified cortical dopaminergic abnormalities (Minzer et al., 2004; Yoon et al., 2007a).

Recognizing the various clinical manifestations seen in TS, it is highly likely that this disorder involves a dysfunction of more than one neurotransmitter system or a second messenger defect (Singer and Minzer, 2003). An altered modulatory effect of serotonin in TS has been suggested by the combination of diminished levels of the serotonin transporter and elevated serotonin 2A receptor binding (Wong et al., 2008), as well as PET studies identifying abnormalities of tryptophan metabolism in cortical and subcortical regions (Behen et al., 2007; Haugbøl et al., 2007; Wong et al., 2008). Glutamate has an essential role in pathways involved with CSTC circuits and an extensive interaction with dopaminergic systems (Harris and Singer, 2006). Several lines of evidence support a possible role of the glutamatergic system in TS including results of

familial genetic studies (Barr et al., 1999; Tourette Syndrome Association International Consortium for Genetics, 2007; Adamczyk et al., 2010) and reduced levels of glutamate in globus pallidus interna, globus pallidus externa, and substantia nigra pars reticulata in a small number of post-mortem brains (Anderson et al., 1992). Altered cholinergic neurotransmission has been implicated by the postmortem finding of decreased numbers of cholinergic interneurons in the striatum of TS patients (Kataoka et al., 2010). Although there is little direct evidence, it has been hypothesized that an alteration of GABAergic projections from the striatum or an impairment of cortical inhibition could cause TS. Last, since multiple neurotransmitters interact with adenosine 3',5'-monophosphate (cAMP), a postreceptor defect could explain an involvement with multiple transmitter systems. In a small number of post-mortem brain samples, the amount of cAMP was reduced in several brain regions (Singer et al., 1991), but a further study showed no abnormality of phosphatidylinositol second messenger generating systems (Singer et al., 1995). In summary, further investigations are required to identify the underlying biochemical defect in this complex disorder.

Limitations and Future Directions

After decades of extensive research, the pathophysiology underlying TS remains poorly understood. Interpretation of studies is often limited by small sample sizes, incomplete characterization of the subjects, varying ages and clinical severity, concurrent use of pharmacotherapy, and diverse statistical methodologies. Table 1 summarizes the studies discussed in this review, commenting on their methodologies and limitations. Even in the studies containing relatively large numbers of patients, there is often little discussion of how variation in TS symptomatology and related comorbidities relates to the findings. It is certainly possible that simple tics, complex tics, and tic disorders asso-

ciated with different comorbidities result from distinctly different underlying pathologies, yet few studies analyze or control for this. Many studies peripherally address the comorbid conditions of ADHD and OCD, but again there have been few studies to adequately and systematically explore the differences between these disorders. Questions also remain regarding the meaning of the neuroanatomical changes observed in TS patients. Although they may be representative of the underlying pathophysiology, they may also be indicative of compensatory changes that have occurred as a result of tics. It would be interesting to study unaffected but at-risk individuals, such as siblings of TS patients, to see whether there are neuroanatomic alterations that exist before the development of tics. As has been suggested in a few studies, developmental or maturational changes are likely important in the pathophysiology, but longitudinal studies exploring changes over time are sparse.

Tourette syndrome provides clinicians, clinician-scientists, and basic researchers with abundant possibilities for future research. On the clinical level, it is essential to further characterize variations in phenotype, understand the relationship between tics and associated comorbidities, clarify factors that modify tic behavior, and continue the search for new and improved behavioral and pharmacologic therapies. Advanced techniques for evaluating the human genome need to be applied to large cohorts with well defined clinical characteristics. The role of the epigenetic modulation requires further attention, both in terms of its ability to potentially modify genetic actions as well as to influence clinical behavior. Clarifying the precise neuroanatomical location and underlying biochemical mechanism would be a major scientific advance not only for TS, but for multiple other neuropsychiatric disorders such as OCD and ADHD. Knowledge of a specific biological alteration will enable the direct pursuit of new ways to treat affected individuals and, dare one say, a possible cure. A highly recommended

source for additional information on TS is the Tourette Syndrome Association, 42-40 Bell Boulevard, Bayside, NY 11361-2820; telephone 718-224-2999; www.tsa-usa.org.

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