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Tourette's Syndrome: When Habit-Forming Systems Form Habits of Their Own?

Review

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It's part of my nature.
—Jim Eisenreich (1996)

Tic disorders have been the subject of intense speculation for at least the last three hundred years. Despite the overt nature of tics and thirty years of scientific scrutiny, our ignorance remains profound. Notions of cause have ranged from "hereditary degeneration" to the "irritation of the motor neural systems by toxic substances, of a self-poisoning bacteriological origin" to "a constitutional inferiority of the subcortical structures …[that] renders the individual defenseless against overwhelming emotional and dynamic forces" (Kushner, 1999). Predictably, each of these etiological explanations has prompted new treatments and ways of relating to families.

While tics are common in childhood, full-blown Gilles de la Tourette's syndrome (TS) is not. Boys are more commonly affected than girls. The cardinal features of TS are motor and phonic tics that wax and wane in severity (Robertson et al., 1999). Tics are sudden habitual movements or utterances that typically mimic some fragment of normal behavior and that involve discrete muscle groups. As such, they can easily be confused with normal coordinated movements or vocalizations. Tics can also be mistaken for akathisia, tardive dyskinesia, or other hyperkinetic movement disorders (Kompoliti and Goetz, 1998). Once established, any given tic tends to persist for a time. Tics are often exacerbated by stress and fatigue. In contrast to other movement disorders, tics can occur during sleep but are usually much attenuated.

Motor and phonic tics occur in bouts over the course of a day and wax and wane in severity over the course of weeks to months. Less well known is the "self-similarity" of these temporal patterns across different time scales (Peterson and Leckman, 1998). It has recently been documented that the frequency distribution of intertic interval durations follows an inverse power law of temporal scaling. In addition, first return maps demonstrated "burst-like" behavior and short-term periodicity, proving that successive tic intervals are not random events. These findings provide suggestive, though not conclusive, evidence for the presence of fractal, and possibly chaotic, processes. Application of nonlinear dynamical methods may provide insight into the temporal features of tics that commonly are described clinically, such as short-term bouts or bursting and longer term waxing and waning. A deeper understanding of the multiplicative processes that govern these timing patterns may clarify both microscopic neural events occurring in millisecond time scales as well as macroscopic features of the natural history of tic disorders.

Motor tics typically begin between the ages of 3 and 8 with transient periods of intense eye blinking or some other facial tic. Vocal tics such as repetitive bouts of sniffing or throat clearing may begin as early as 3 years of age, but typically, they follow the onset of motor tics by several years. In uncomplicated cases, motor and vocal tic severity peaks early in the second decade with many patients showing a marked reduction in tic severity by the age of 19 or 20 (Leckman et al., 1998). However, the most severe cases are adults. Extreme forms of this illness involve forceful bouts of self-abusive motor tics such as hitting or biting and socially stigmatizing coprolalic utterances.

Many patients with tic disorders report the presence of associated sensory phenomena including "faint" premonitory urges that incessantly prompt the tics and feelings of momentary relief that follow the performance of a tic (Bliss, 1980). Many patients describe these sensations as being bodily feelings that are localized to discrete anatomical regions—like an urge to itch or a need to clear one's throat. Other antecedent sensory phenomena include a generalized inner tension that can be relieved only by the performance of a particular tic. Specific auditory or visual cues can also prompt tics in some patients. The range of these cues is enormous but highly selective for individual patients—a cough, a particular word, an alignment of angles, or specific shapes.

In addition to tics, many TS patients suffer from symptoms of obsessive-compulsive disorder and/or attention deficit hyperactivity disorder. When present, these coexisting conditions can add greatly to the morbidity associated TS (Leckman and Cohen, 1998).

Neural Substrates of Habit Formation and Tics

Habits are assembled routines that link sensory cues with motor action. They allow us to act without thinking—like riding a bicycle, driving a car, or delivering a well-rehearsed speech. As such, they are enormously adaptive and part of a common evolutionary heritage that we share with other vertebrates as we engage in goal-directed behavior. When we do things over and over again, we get better at it. There is less thinking about the action, and we can respond in a more nuanced manner to other environmental cues. How does brain manage these marvels? It appears likely that these events involve neural loops or spirals that connect the basal ganglia with the cortex and thalamus (Figure 1; Graybiel, 1998).

The motor, sensorimotor, association, and inhibitory neural circuits that course through the basal ganglia are

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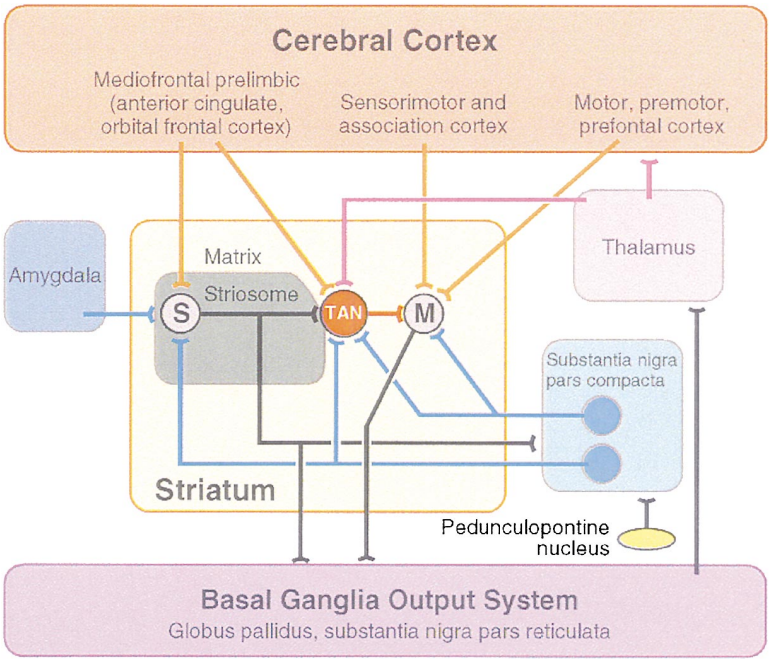

Figure 1. Cortical-Subcortical Circuits Implicated in Tics and Stereotypies

Schematic diagram illustrating the organization of the striatum and cortical-subcortical circuits (adapted from Aosaki et al., 1995). Animal models indicate that the medium spiny projection (MSP) neurons of the striatum exist within two closely intertwined compartments—striosomes (S) and the matrix (M). These two compartments differ with respect to their cortical inputs, with the striosomal MSP neurons receiving limbic and prelimbic inputs and the MSP neurons in the matrix receiving from ipsilateral primary motor and sensory motor cortices and contralateral primary motor cortices. An imbalance in the functional activity of the MSP neurons within these two compartments has been implicated in stereotypies (Canales and Graybiel, 2000). Similarly, changes in the responsiveness of tonically active neurons (TANs) located at the boundary between striosomes and matrix could selectively alter behaviors keyed to specific environmental perturbations. Dopaminergic projection neurons from the pars compacta of the substania nigra appear to tune this system to respond selectively to certain internal somatosensory or external perceptual cues.

commonly referred to by their successive processing components and are therefore called "cortical-striatal-thalamo-cortical" (CSTC) circuits. CSTC circuits are composed of multiple, partially overlapping, but largely "parallel" circuits that direct information from the cerebral cortex to the subcortex and then back again to specific regions of the cortex, thereby forming multiple cortical-subcortical loops. Although multiple anatomically and functionally related cortical regions provide input into a particular circuit, each circuit in turn refocuses its projections back onto only a discrete subset of the cortical regions initially contributing to that circuit's input. Within the basal ganglia and thalamus, each of the circuits appears to be microscopically segregated from others that course through the same macroscopic structure—hence the conceptualization of these overlapping pathways as being "parallel."

Although the number of anatomically and functionally discrete pathways is still the subject of controversy, the current consensus holds that CSTC circuitry has at least three components—those initiating from and projecting back to sensorimotor, orbitofrontal, or association cortices. Other functional components of CSTC circuitry likely exist and probably include those traditionally associated with the limbic system.

Based largely on work performed in Graybiel's laboratory, it appears that the response of particular medium spiny projection (MSP) neurons in the striatum is frequently dependent upon a selective set of perceptual cues and environmental conditions, suggesting that the coordinated striatal response is acquired through learning and experience. Inputs from ascending dopamine pathways originating in the substania nigra, pars compacta, play a crucial role in this learning process (Figure 1; Aosaki et al., 1994).

Ensemble recordings, in which the activity of multiple MSP neurons are recorded simultaneously, have begun to clarify the role of the striatum and related brain circuits in the learning and production of habitual or "automatic" behavioral responses. Recently, Graybiel and colleagues have recorded from ensembles of electrodes in the sensorimotor areas of rat striatum during cued learning tasks. Their results demonstrated large-scale changes in recruitment and firing patterns of these neurons (Jog et al., 1999). Of special interest was the tendency of the number of units firing at the start and end of goal-directed activity to increase asymptotically during successive stages of learning.

Animal studies have also indicated that the balance of activity of MSP neurons located in the striosomes versus the matrix of the striatum may crucially determine an individual's vulnerability to dopamine-mediated stereotypies (Figure 1; Canales and Graybiel, 2000). These stereotypies include a range of repetitive tic-like head and paw movements, as well as repetitive sniffing.

If habits are coordinated ensembles of thought and action, then conceptually tics or stereotypies may be best seen as those prewired bits of behavior that are available to be assembled into habits. Like habits, tic action sequences often arise from a heightened and selective sensitivity to environmental cues from within the body or from the outside world. These perceptual cues include faint premonitory feelings or urges that are relieved with the performance of tics and a need to perform tics or compulsions until they are felt to be "just right." Although the neural mechanisms that conspire to produce tics have yet to be elucidated, preliminary evidence suggests that they involve the same structures that underlie habit formation. The basal ganglia and their open-ended neural loops and their cortico-cortical connections have long been a focus of TS research. Advances in neuroimaging and neurophysiological tech-

niques have made it possible to examine these circuits in living subjects. In TS there is preliminary evidence that voluntary tic suppression involves activation of regions of the prefrontal cortex and caudate nucleus and bilateral deactivation of the putamen and globus pallidus (Peterson et al., 1998). If confirmed, these findings are consistent with the well-known finding that chemical or electrical stimulation of inputs into the putamen can provoke motor and vocal responses that resemble tics. They also suggest that prefrontal cortex-basal ganglia circuits participate in shaping of the inhibitory influence of the output neurons in the internal segment of the globus pallidus and the pars reticulata of the substania nigra.

Most functional magnetic resonance imaging (fMRI) studies to date have employed a block design in which the activation/deactivation signal reflects a presumed continuous mental state. More recently, event-related fMRI techniques have been developed that will greatly enhance the temporal resolution of these studies. Work in progress suggests that it should be possible to monitor individual tics as they occur in the magnet. These studies should permit investigators to begin to define the temporal sequence of activity within different portions of these cortical-subcortical loops. In this regard, it will be intriguing to study the involvement of the supplementary motor area as electrical stimulation of the SMA elicits a variety of bodily sensations that include premonitory sensations or "urges" to perform a movement or a sense of anticipation that a movement is about to occur (Fried et al., 1991).

As with habits and stereotypies, ascending dopaminergic pathways likely play a key role in the consolidation and performance of tics. First, dopamine D2 receptor blocking agents are the mainstay of traditional pharmacological approaches to the treatment of tics (Riddle and Carlson, 2000). Second, studies of monozygotic twins indicate that developmental shifts in the balance of tonic-phasic dopaminergic tone occur as a result of epigenetic differences, and the density of dopamine D2 receptors may influence the severity of TS (Wolf et al., 1996). Although future ligand-based functional imaging studies in child and adolescent samples complemented by neuropathological studies hold considerable promise to elucidate these mechanisms, ethical concerns and logistic difficulties may limit these avenues of investigation, which in turn points to the need to develop suitable animal models for TS and related disorders (Swerdlow and Young, 1999).

Susceptibility: Genetics and Autoimmunity

TS is a familial disorder (Pauls et al., 1991; Walkup et al., 1996). An international consortium of researchers is making incremental progress in the genetics of TS (The Tourette Syndrome International Consortium for Genetics, 1999). Building on the results of a genome-wide scan of affected sibling pairs, this group of investigators is actively completing high-density maps of several genomic regions in an effort to refine and extend their preliminary results in a new sample of sibling pairs as well as in well-characterized high-density families. This sib-pair approach is suited for diseases with an unclear mode of inheritance and has been used successfully in studies of other complex disorders, such as diabetes mellitus. Specifically in TS, two areas, one on chromosome 4q and another on chromosome 8p, are suggestive of linkage. While it is disappointing that none of the chromosomal regions (e.g., 3 [3p21.3], 8 [8q21.4], 9 [9pter], and 18 [18q22.3]) in which cytogenetic abnormalities have been found to cosegregate with TS showed any convincing evidence for linkage, it is still possible that TS susceptibility genes may be found in one or more of these regions using molecular cytogenetic techniques. Furthermore, none of the regions in which associations had been reported with candidate genes such as DRD2 [11q22] and DRD4 [11p15] were supported by the results of this study. Future progress is anticipated. Clarity about the nature and normal expression of even a few of the TS susceptibility genes is likely to provide a major step forward in understanding TS pathogenesis.

Finally, the past decade has seen the reemergence of an area of research that is examining the hypothesis that postinfectious autoimmune mechanisms contribute to the pathogenesis of some TS cases. Speculation concerning a postinfectious (or at least a postrheumatic fever) etiology for tic disorder symptoms dates from the late 1800s. It is well established that group A β hemolytic streptococci (GABHS) can trigger immune-mediated disease in genetically predisposed individuals. Acute rheumatic fever (RF) is a delayed sequela of GABHS, occurring $\sim$3 weeks following an inadequately treated upper respiratory tract infection. RF is characterized by inflammatory lesions involving the joints, heart, and/or central nervous system (Sydenham's chorea [SC]).

SC and TS share common anatomic areas—the basal ganglia of the brain and the related cortical and thalamic sites. Furthermore, some SC patients display motor and vocal tics as well as obsessive-compulsive and ADHD symptoms, suggesting the possibility that at least in some instances these disorders share a common etiology. As in SC, antineuronal antibodies have been reported to be elevated in the sera of some patients with TS (Singer et al., 1998). It has been proposed that Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection (PANDAS) represents a distinct clinical entity and includes SC and some cases of TS and OCD. Further suggestive evidence comes from Swedo and colleagues (1998), who reported that in children who met PANDAS criteria, GABHS infection was likely to have preceded neuropsychiatric symptom onset for 44% of the children, whereas pharyngitis (no culture obtained) preceded onset for another 28% of the children.

Although the etiological significance of the antineuronal antibodies and the association with prior GABHS infections remains a topic of considerable debate (Kurlan, 1998), therapeutic interventions based on this mechanism show promise (Perlmutter et al., 1999). Further, if specific immunological alterations are associated with onset or acute clinical exacerbations, then the nature of these alterations should provide insight as to the genetic, neuroanatomic, and immunologic mechanisms involved. This knowledge may provide a basis for the rational design of therapeutic and preventative interventions.

Table 1. Treatments for Tourette's Syndrome

Intervention	Advantages	Disadvantages
Educational interventions (home, school)	Better informed families, teachers and peers; diminished stigma, high patient acceptance	Few disadvantages, potential for re-enforcing the patient's identity as a "Tourette sufferer" to the exclusion of other self-perceptions; little empirical data demonstrating improved symptoms or social adjustment
Cognitive-behavioral therapy (habit reversal)	Few side effects	Contingent responses are difficult for children to maintain, requirement for a well trained specialist
Traditional pharmacological approaches		
Dopamine D2 blockade: *haloperidol*,[a] *pimozide*,[a] *tiapride*,[a] *fluphenazine, sulpiride*	Proven short term anti-tic efficacy	Limited patient acceptance due to side effects and potential for tardive dyskinesa
Atypical neuroleptics: *risperidone*,[a] *ziprasidone*,[a] *olanzapine, clozapine*[c]	Promising early trials for two agents	Improved patient acceptance, variable response, potential for marked weight gain especially in the pediatric age group
Alpha-2 adrenergic agonists: *clonidine*,[b] *guanfacine*[a]	High patient acceptance, relatively few side effects	Potential for sedation, modest benefit, disputed efficacy in clinical trials
GABAergic agents: *clonazepam*	Promising open trials	Potential for disinhibition, limited effectiveness
Newer agents		
Dopamine depleting agents: *tetrabenazine*	Promising open data in a small number of subjects	Potential for sedation, parkinsonism, and depression, not available in the US
Dopamine (auto?) receptor agonists: *apomorphine (nonspecific), pergolide* (D2 class D3, D2, D4),[a] *tiapexole* (D2)[c]	Promising open data in a small number of subjects, pergolide well tolerated	Limited data on effectiveness
Cholinergic agents: *nicotine patches, Botulinum toxin, mecamylamine*	Promising open data in a small number of subjects	Limited data on effectiveness; nicotine requires continued treatment with neuroleptics plus addictive potential; botulinum requires injections and is not appropriate for all tics
Antiandrogens: *flutamide*[b]	Mixed picture with a small number of patients doing well in the short term	Limited data on effectiveness, loss of effect with continued treatment, potential for serious side effects
Opioid agonists/antagonists: *propoxyphene*,[c] *tramadol, naltrexone*[b]	Promising open data in a small number of subjects	Limited data on effectiveness, addictive potential for the agonists
Cannabinols *Delta-9-tetrahydrocannabinol*	Promising open data in a small number of subjects	Limited data on effectiveness, addictive potential
Immunomodulatory/antimicrobial treatments		
Plasma exchange,[a] intravenous IgG[a]	Potential for etiologically based approach; promising open data in a select group of subjects	Invasive medical procedure with the potential for high-risk side effects
Antibiotic prophylaxis: *penicillin V*[c]	Potential for etiologically based approach, promising open data in a small number of subjects	Potential for increasing antibiotic resistance among some microorganisms
Circuit-based approaches		
Neurosurgical procedures: *ablation versus high frequency stimulation of thalamic nuclei*	Promising open data in a small number of subjects	Invasive medical procedure with the potential for high-risk side effects; best procedures remain to be established
Transcranial magnetic stimulation	Noninvasive procedure	Limited open data in a small number of subjects, best stimulation parameters for TMS remain to be established

At least one randomized, double-blind clinical trial has been reported. [a] positive results, [b] mixed or marginal results, [c] negative results. See Riddle and Carlson (2000) and Leckman et al. (2000) for details.

Anti-Tic Therapeutics

Multimodal therapy for TS is usually indicated, although the efficacy of this approach has not been empirically documented. This approach includes educational and supportive interventions appropriate for any chronic disease. Many cases of TS can be successfully managed

without medication. When patients present with coexisting ADHD, OCD, and/or depression, it is often better to treat these "co-morbid" conditions first, as successful treatment of these disorders will often diminish tic severity.

Ideal anti-tic treatments are not currently available. None of the agents or techniques can be used effectively just when tics are at their worst. Most of the available pharmacological agents require long-term treatment, and many have potentially serious side effects. Indeed, for some medications, it is much easier to commence treatment than to continue or stop it. For example, haloperidol in the short term is effective in more than 80% of cases, but fewer than 12% stay on the drug because of unwanted effects on cognitive skills, mood, and motivation. The advantages and disadvantages of various treatments are summarized in Table 1.

Animal Models

Future progress in elucidating the pathogenesis and treatment on Tourette's could be greatly accelerated with the development of animal models. At present, stimulant and stress-induced stereotypies continue to offer the greatest promise (Figure 1; Leckman et al., 1986). If tics, like stereotypies, vary according to the balance of activity MSP neurons in the striosome and matrix compartments of the striatum (Figure 1; Canales and Graybiel, 2000), then it should be possible to examine the clinical impact of genetic and/or developmental insults that affect the relative number and sensitivity of MSP neurons in the two striatal compartments. For example, perinatal ischemic and hypoxic insults involving parenchymal lesions increase the risk of tic disorders 8-fold (Whitaker et al., 1997). Do they also increase an animal's susceptibility to develop stereotypies in response to psychomotor stimulants? If so, is there evidence of a differential injury to MSP neurons in the matrix?

Further, this model may provide a meaningful integration of knowledge about tics drawn from a number of perspectives, including the stress responsiveness of tics (limbic activation), the presence of premonitory sensory urges (as sensory motor and primary motor cortical inputs converge on the fewer MSPs in the matrix), the reduction of tics when an individual is engaged in acts that require selective attention and guided motor action (heightened activity within the matrix compartment), and the need to "even-up" sensory and motor stimuli in a bilaterally symmetrical fashion (convergence of information from both ipsi- and contralateral primary motor neurons on MSP within the matrix). The timing of tics and the course of tic disorders may be reflected in the collective burst firing of dopaminergic neurons.

From a developmental perspective, it is clear that many of the GABAergic interneurons of the cerebral cortex migrate tangentially from the same embryonic regions in the ganglionic eminence that also give rise to the GABAergic MSP neurons of the striatum (Ware et al., 1999). Could adverse events occurring at a specific point in development account for both the striatal imbalance and the intracortical deficits inhibition seen in some patients with Tourette's syndrome (Ziemann et al., 1997)?

Finally, it is tempting to speculate that in SC and in postinfectious forms of Tourette's the functional activity of the MSP neurons of the matrix is differentially impaired as a result of the autoimmune response. Indeed, one plausible hypothesis is that the antineural antibodies found in a subset of TS patients may modulate synaptic transmission and alter the balance between the striosomal and matrisomal compartments of the striatum.

Conclusion

Current conceptualizations of TS have been shaped by advances in systems neuroscience and the emerging understanding of the role of the basal ganglia in implicit learning and habit formation. Although the evidence that the same mechanisms are involved in both habit formation and tics is circumstantial, recent progress in neuroanatomy, systems neuroscience, and functional in vivo neuroimaging has set the stage for a major advance in our understanding of TS. Continued success in these areas will lead to the targeting of specific brain circuits for more intensive study. Diagnostic, treatment, and prognostic advances can also be anticipated, e.g., which circuits are involved and to what degree? How does that degree of involvement affect the patient's symptomatic course and outcome? Will it be possible to track treatment response using neuroimaging techniques? And will specific circuit-based therapies using deep-brain stimulation emerge to treat refractory cases (Vandewalle et al., 1999)?

The identification of susceptibility genes in TS will doubtless point in new therapeutic directions for treatment, as will the characterization of the putative autoimmune mechanisms active in the PANDAS subgroup of patients. Given this potential, TS can be considered a model disorder to study the dynamic interplay of genetic vulnerabilities, epigenetic events, and neurobiological systems active during early brain development. It is likely that the research paradigms utilized in these studies and many of the empirical findings resulting from them will be relevant to other disorders of childhood onset and to our understanding of normal development.

References

Aosaki, T., Graybiel, A.M., and Kimura, M. (1994). Effect of the nigrostriatal dopamine system on acquired neural responses in the striatum of behaving monkeys. Science *265*, 412–415.

Aosaki, T., Graybiel, A.M., and Kimura, M. (1995). Temporal and spatial characteristics of tonically active neurons of the primate's striatum. J. Neurophysiol. *73*, 1234–1252.

Bliss, J. (1980). Sensory experiences of Gilles de la Tourette syndrome. Arch. Gen. Psychiatry *37*, 1343–1347.

Canales, J.J., and Graybiel, A.M. (2000). A measure of striatal function predicts motor stereotypy. Nat. Neurosci. *3*, 377–383.

Fried, I., Katz, A., McCarthy, G., Sass, K.J., Williamson, P., Spencer, S.S., and Spencer, D.D. (1991). Functional organization of human supplementary motor cortex studied by electrical stimulation. J. Neurosci. *11*, 3656–3666.

Graybiel, A.M. (1998). The basal ganglia and chunking of action repertoires. Neurobiol. Learn. Mem. *70*, 119–136.

Jog, M.S., Kubota, Y., Connolly, C.I., Hillegaart, V., and Graybiel, A.M. (1999). Building neural representations of habits. Science *286*, 1745–1749.

Kompoliti, K., and Goetz, C.G. (1998). Hyperkinetic movement disor-

ders misdiagnosed as tics in Gilles de la Tourette syndrome. Mov. Disord. *13*, 477–480.

Kurlan, R. (1998). Tourette's syndrome and 'PANDAS': will the relation bear out? Neurology *50*, 1530–1534.

Kushner, H.I. (1999). A Cursing Brain? The Histories of Tourette Syndrome (Cambridge, MA: Harvard University Press).

Leckman, J.F., and Cohen, D.J. (1998). Tourette's Syndrome: Tics, Obsessions, Compulsions—Developmental Psychopathology and Clinical Care (New York: John Wiley and Sons).

Leckman, J.F., Cohen, D.J., Price, R.A., Riddle, M.A., Minderaa, R.B., Anderson, G.M., and Pauls, D.L. (1986). The pathogenesis of Gilles de la Tourette's syndrome: a review of data and hypothesis. In Movement Disorders, N.S. Shah and A.B. Shah, eds. (New York: Plenum Press), pp. 257–272.

Leckman, J.F., Zhang, H., Vitale, A., Lahnin, F., Lynch, K., Bondi, C., Kim, Y.-S., and Peterson, B.S. (1998). Course of tic severity in Tourette syndrome: the first two decades. Pediatrics *102*, 14–19.

Leckman, J.F., Cohen, D.J., Goetz, C.G., and Jankovic, J. (2000). Tourette syndrome—pieces of the puzzle. In Tourette Syndrome, D.J. Cohen, C.G. Goetz, and J. Jankovic, eds. (Philadephia, PA: Lippincott, Williams & Williams), in press.

Pauls, D.L., Raymond, C.L., Stevenson, J.M., and Leckman, J.F. (1991). A family study of Gilles de la Tourette syndrome. Am. J. Hum. Genet. *48*, 154–163.

Perlmutter, S.J., Leitman, S.F., Garvey, M.A., Hamburger, S., Feldman, E., Leonard, H.L., and Swedo, S.E. (1999). Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet *354*, 1153–1158.

Peterson, B.S., and Leckman, J.F. (1998). The temporal dynamics of tics in Gilles de la Tourette syndrome. Biol. Psychiatry *44*, 1337–1348.

Peterson, B.S., Skudlarski, P., Anderson, A.W., Zhang, H., Gatenby, J.C., Lacadie, C.M., Leckman, J.F., and Gore, J.C. (1998). A functional magnetic resonance imaging study of tic suppression in Tourette syndrome. Arch. Gen. Psychiatry *55*, 326–333.

Riddle, M.A., and Carlson, J. (2000). In Tourette Syndrome, D.J. Cohen, C.G. Goetz, and J. Jankovic, eds. (Philadephia, PA: Lippincott, Williams & Williams), in press.

Robertson, M.M., Banerjee, S., Kurlan, R., Cohen, D.J., Leckman, J.F., McMahon, W., Pauls, D.L., Sandor, P., and van de Wetering, B.J. (1999). The Tourette syndrome diagnostic confidence index: development and clinical associations. Neurology *53*, 2108–2112.

Singer, H.S., Giuliano, J.D., Hansen, B.H., Hallett, J.J., Laurino, J.P., Benson, M., and Kiessling, L.S. (1998). Antibodies against human putamen in children with Tourette syndrome. Neurology *50*, 1618–1624.

Swedo, S.E., Leonard, H.L., Garvey, M., Mittleman, B., Allen, A.J., Perlmutter, S., Lougee, L., Dow, S., Zamkoff, J., and Dubbert, B.K. (1998). Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am. J. Psychiatry *155*, 264–271.

Swerdlow, N.R., and Young, A.B. (1999). CNS Spectrums *4*, 65–74.

The Tourette Syndrome International Consortium for Genetics. (1999). A complete genome screen in sib pairs affected by Gilles de la Tourette syndrome. Am. J. Hum. Genet. *65*, 1428–1436.

Vandewalle, V., van der Linden, C., Groenewegen, H.J., and Caemaert, J. (1999). Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. Lancet *353*, 724.

Walkup, J.T., LaBuda, M.C., Singer, H.S., Brown, J., Riddle, M.A., and Hurko, O. (1996). Family study and segregation analysis of Tourette syndrome: evidence for a mixed model of inheritance. Am. J. Hum. Genet. *59*, 684–693.

Ware, M.L., Tavazoie, S.F., Reid, C.B., and Walsh, C.A. (1999). Coexistence of widespread clones and large radial clones in early embryonic ferret cortex. Cereb. Cortex *9*, 636–645.

Whitaker, A.H., Van Rossem, R., Feldman, J.F., Schonfeld, I.S., Pinto-Martin, J.A., Tore, C., Shaffer, D., and Paneth, N. (1997). Psychiatric outcomes in low-birth-weight children at age 6 years: relation to neonatal cranial ultrasound abnormalities. Arch. Gen. Psychiatry *54*, 847–856.

Wolf, S.S., Jones, D.W., Knable, M.B., Gorey, J.G., Lee, K.S., Hyde, T.M., Coppola, R., and Weinberger, D.R. (1996). Tourette syndrome: prediction of phenotypic variation in monozygotic twins by caudate nucleus D2 receptor binding. Science *273*, 1225–1227.

Ziemann, U., Paulus, W., and Rothenberger, A. (1997). Decreased motor inhibition in Tourette's disorder: evidence from transcranial magnetic stimulation. Am. J. Psychiatry *154*, 277–284.