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

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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” (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 overwhelm 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 (Koppoliti 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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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 focuses 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 substantia 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 stereotypes (Figure 1; Canales and Graybiel, 2000). These stereotypes 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 stereotypes 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-
nergic pathways likely play a key role in the consolida-

tion. In TS there is preliminary evidence that voluntary tic suppression involves activation of re-
gions of the prefrontal cortex and caudate nucleus and
bilateral deactivation of the putamen and globus pal-
lidus (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 substantia
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 moni-
tor individual tics as they occur in the magnet. These
studies should permit investigators to begin to define
the temporal sequence of activity within different por-
tions of these cortical-subcortical loops. In this regard,
it will be intriguing to study the involvement of the sup-
plementary motor area as electrical stimulation of the
SMA elicits a variety of bodily sensations that include
premonitory sensations or “urges” to perform a move-
ment or a sense of anticipation that a movement is about
to occur (Fried et al., 1991).

As with habits and stereotypies, ascending dopami-
nergic pathways likely play a key role in the consolida-
tion and performance of tics. First, dopamine D2 recep-
tor blocking agents are the mainstay of traditional
pharmacological approaches to the treatment of tics
(Riddle and Carlson, 2000). Second, studies of monozy-
gotic twins indicate that developmental shifts in the bal-
ance of tonic-phasic dopaminergic tone occur as a re-
sult of epigenetic differences, and the density of
dopamine D2 receptors may influence the severity of
TS (Wolf et al., 1996). Although future ligand-based func-
tional imaging studies in child and adolescent samples
complemented by neuropathological studies hold con-
siderable promise to elucidate these mechanisms, ethi-
cal concerns and logistic difficulties may limit these ave-
nuers of investigation, which in turn points to the need
to develop suitable animal models for TS and related
 disorders (Swedo 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 Genet-
ics, 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 ge-
nomic 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 chromo-
some 4q and another on chromosome 8p, are sugges-
tive of linkage. While it is disappointing that none of
the chromosomal regions (e.g., 3 [3p21.3], 9 [9q21.4], 9
[9pter], and 18 [18q22.3]) in which cytogenetic abnor-
malities 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 cytoge-
netic 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 ex-
pression 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 con-
cerning 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,
occuring 3–12 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 etiol-
ology. As in SC, antineuronal antibodies have been re-
ported to be elevated in the sera of some patients with
TS (Singer et al., 1998). It has been proposed that Pediat-
ric Autoimmune Neuropsychiatric Disorder Associated
with Streptococcal infection (PANDAS) represents a dis-
tinct 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 chil-
dren who met PANDAS criteria, GABHS infection was
likely to have preceded neuropsychiatric symptom on-
set for 44% of the children, whereas pharyngitis (no
culture obtained) preceded onset for another 28% of
the children.

Although the etiological significance of the antineu-
ronal antibodies and the association with prior GABHS
infections remains a topic of considerable debate (Kur-
lan, 1998), therapeutic interventions based on this mech-
anism 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 genet-
ic, neuroanatomic, and immunologic mechanisms
involved. This knowledge may provide a basis for the
rational design of therapeutic and preventative interven-
tions.
Table 1. Treatments for Tourette's Syndrome

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

At least one randomized, double-blind clinical trial has been reported. * positive results, † mixed or marginal results, ‡ 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


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


