Tic Disorders: When Habit Forming Neural Systems Form Habits of Their Own?

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Key Words
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in vivo neuroimaging; obsessive-compulsive disorder; psychopharmacology; Tourette syndrome

Tourette syndrome (TS), obsessive-compulsive disorder (OCD) and related conditions are prevalent disorders affecting as many as 0.3-3% of the population. They are frequently chronic and can be associated with marked impairment and disability. Although clinical care has improved over the past decade, a significant number of patients fail to respond adequately or experience intolerable side effects. The etiology of these disorders is unknown. Compelling evidence suggests that the vulnerability to develop TS and OCD is mediated by both genetic and environmental factors, and that neural systems located in the basal ganglia and functionally related brain structures are involved in their pathogenesis.

Based on explicit models of pathogenesis for TS and OCD and building on work accomplished over the past two decades, an array of clinical, neuropsychological, genetic, neuroimaging, epidemiological neurobiological, and treatment studies have been completed or are underway at the Child Study Center at Yale University. A multi disciplinary team of investigators has joined forces to test specific hypotheses through the integration and translation of basic and clinical neuroscience research. All subjects have been studied using identical clinical, neuropsychological, genetic, neurobiological, and pharmacological techniques.

Current conceptualizations of TS have been shaped by advances in clinical phenomenology, genetics, systems neuroscience and the emerging understanding of the role of the basal ganglia in implicit learning and habit formation, neuroimmunology and psycho-pharmacology. An appreciation of the premonitory urges that precede tics and temporal dynamics of tics have provided useful viewpoints from which to regard the natural history of TS. While the long-term outcome of TS can be rela tively benign, the presence of comorbid conditions such as attention deficit/hyperactivity disorder (ADHD), OCD or a major affective disorder can have lasting untoward consequences. The identification of susceptibility genes in TS will doubtless be an important goal. While the characteristic repetitive movements can be regarded as an expression of the basal ganglia, the precise mechanism of the putative autoimmune reaction is still under investigation. Continued success in functional in vivo neuroimaging studies will lead to the targeting of specific brain circuits for more in depth study. Although ideal antithetic therapeutic agents are not available, recently completed clinical trials with alpha-adrenergic agents and atypical neuroleptics are encouraging.

Given these developments, 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 recent advances in the field of Tourette syndrome will lead to important therapeutic developments in the future.
From bad habit… take care my dear to guard against bad habits”. Samuel Johnson discussing his tic symptoms with a curious young woman (quoted by Murray, 1982)

“It’s part of my nature”. – Jim Eisenreich (1996)

Tic disorders have been the subject of speculation for at least the last three hundred years. Despite the overt nature of tics and more than thirty years of close 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 bacterial origin” to “a constitutional inferiority of the subcortical structures …[that] renders the individual defenseless against overwhelming emotional and dynamic forces”. Each of these etiological explanations has prompted new treatments. In this review, we will be gin by presenting a general model of disease pathogenesis before reviewing each of five areas (clinical phenomenology, genetics, environmental factors, neurobiological substrates, and treatment in greater detail area.

Models of pathogenesis

A schematic presentation of the general model of disease pathogenesis is presented in Fig. 1. In this model Tourette syndrome (TS) is seen as a disorder in which individuals are unable to inhibit premonitory sensory urges, leading to the emergence of small “pre-wired” bits of motor and phonic behavior. In ob-

![Fig. 1. Working model of pathogenesis. The pathogenesis for both Tourette’s syndrome (TS) and obsessive-compulsive disorder (OCD) involves the reciprocal interaction of genes and environment. The normal copies of these specific vulnerability genes are presumed to be turned on and off at specific points in development. Abnormal copies of these genes alter the course of development by changing the timing or degree of expression of specific gene products. A number of other risk and protective factors are also likely to be involved. Some of these factors may influence gene expression directly. In other cases, gene expression may be affected indirectly when aspects of the macroenvironment of the individual alter the microenvironment of neural systems through injury or by way of more subtle effects on signal transduction and second messenger systems. Conversely, these vulnerability genes influence directly their microenvironment by facilitating or repressing the production of specific proteins. This general model also pre sumes that these vulnerability genes acting in concert with specific environmental factors play a crucial role in the formation and/or activity of specific neural circuits that produce the neurobiological substrate for symp toms as associated with these disorders. Finally, this general model depicts the potentially “vicious cycle” that can sometimes be seen in which increasing tic and/or obsessive-compulsive (OC) symp toms create secondary problems of peer and/or family rejection that lead to a further exacerbation of the tic and OC symp toms.
sive-compulsive disorder (OCD), individuals are unable to inhibit specific, perhaps evolutionarily conserved “worries” leading to the emergence of in tense ego dystonic obsessions and compulsions. The pathogenesis for both conditions involves the reciprocal interaction of genes and environment. The normal copies of these specific vulnerability genes are presumed to be turned on and off at specific points in development. Abnormal copies of these genes alter the course of development by changing the timing or degree of expression of specific gene products. A number of other risks and protective factors are also likely to be involved. Some of these factors may influence gene expression directly. In other cases, gene expression may be affected in directly when aspects of the macroenvironment of the individual alter the microenvironment of neural systems through injury or by way of more subtle effects on signal transduction and second messenger systems. Conversely, these vulnerability genes influence directly their microenviron ment by facilitating or repressing the production of specific proteins. This general model also presumes that these vulnerability genes acting in concert with specific environmental factors play a crucial role in the formation and/or activity of specific neural circuits that provide the neurobiological substrate for symptoms associated with these disorders. Finally, this general model depicts the potentially “vicious cycle” that can some times be seen in which in creasing tic and/or obsessive-compulsive (OC) symptoms create secondary prob lems of peer and/or family rejection that lead to a further exacerbation of the tic and OC symptoms.

We next turn to a brief overview of the phenomenology and natural history of TS and OCD (sum marized in Table 1) as well as a brief consideration of attention deficit/hyperactivity disorder (ADHD) and other comorbid conditions.

**Phenomenology and natural history**

TS is a chronic neuropsychiatric disorder of childhood on set that is characterized by tics that wax and wane in severity and an array of behavioral problems that include some forms of OCD. The range of symptoms in TS is enormous and includes motor and phonic tics, as well as obsessive and compulsions. Tics are sudden repetitive movements, gestures, or utterances that typi cally mimic some fragment of normal behavior, while obsessive and compulsions are intrusive, repetitive thoughts, images, or urges and related actions that are difficult to resist. Sensorimotor phe-

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**Table 1. Clinical phenotypes**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description of latent variable</th>
<th>Operational measures</th>
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<tbody>
<tr>
<td>TS</td>
<td>A chronic neuropsychiatric disorder of childhood onset characterized by tics that wax and wane in severity and an array of behavioral problems that include some forms of OCD and ADHD.</td>
<td>History and presenting tic symptoms based on information from multiple informants; ratings of symptom severity; treatment response; performance on neuropsychological battery; subtypes of TS will be distinguished on the basis of family study data from first degree relatives. Dimensional ratings of TS symptoms will also be used to phenotype individuals.</td>
</tr>
<tr>
<td>OCD</td>
<td>A chronic neuropsychiatric disorder characterized by the frequent and sudden intrusion into consciousness of unwanted worries or unpleasant images and/or urges to perform repeatedly seemingly senseless acts. Three putative forms of OCD will be studied in the proposed program of research: familial tic-related OCD, familial non-tic related OCD, and sporadic non-familial OCD.</td>
<td>History and presenting OC symptoms based on information from multiple informants; ratings of symptom severity; treatment response; performance on neuropsychological battery; subtypes of OCD will be distinguished on the basis of family study data from first degree relatives. Dimensional ratings of OCD symptoms will also be used to phenotype individuals.</td>
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TS = Tourette syndrome; OCD = obsessive-compulsive disorder; ADHD = attention deficit/hyperactivity disorder; OC = obsessive compulsive.
nom ena fre quently ac com pa ny tics \(^{10}\) and OC be hav ior. These ex pe ri en ces in clude pre mon i tory feel ings or urges that are re lieved with the per for mance of
tics, \(^{11,12}\) and a need to per form tics or com pul sions un til they are felt to be “just right”. \(^{13,14}\)

Motor and phonic tics oc cur in bouts over the course of a day and wax and wane in se ver i ty over the course of weeks to months. Less well known is the “self-similarity” of these tem po ral pat terns across dif fer ent time scales. It has re cently been doc u mented that the fre quency dis tri bu tion of inter-tic in ter val du ra tions fol low an in verse power law of tem po ral scal ing; spec tral anal y ses sim i lar ly dem on strated that the pow er den sit y of tic in ter val du ra tion scales in ver sely with fre quency. \(^{15}\) In ad di tion, first re turn maps dem on strated “burstlike” be hav ior and short-term pe ri od ic ity, pro ving that suc cessive tic in ter vals are not ran dom events. These find ings pro vide sug gester, though not con clus ive, ev i dence for the pres ence of frac tal, de ter ministic tic, and pos si bly cha otic pro cesses at work in tic time se ries. These an a lytic meth ods may pro vide in sight into the tem po ral fea tures of tics that com monly are de scribed clin i cally, such as short-term bouts or burst ing and lon ger term waxing and wan ing. A deeper un der stand ing of the mul ti pli ca tive pro cesses that gov ern these pat terns may clar ify both mi cro and macro scopic fea tures of the nat u ral his tory of tic dis or ders. These pro cesses may gov ern sub se quent ex acer ba tions in adult hood.

In what may be a fur ther dem on stra tion of fractal par tern ing, in vest i gators have doc u mented a char ac ter is tic pro gres sion of tic symp tom se ver i ty over the first two de cades of life. \(^{17,18}\) Mean (SD) tic on set at 5.6 (2.3) years of age was fol lowed by a pro gres sive par tern of tic wors en ing. On av er age, the most se vere pe ri od of tic se ver i ty oc cur red at 10.0 (2.4) years of age. In eight cases (22%), the fre quency and force ful ness of the tics reached a se ver e lev el dur ing the worst-ever pe ri od such that func tion ing in school was im pos si ble or in se ri ous jeop ardy. In al most ev ery case this pe ri od was fol lowed by a steady de cline in tic se ver i ty. By 18 years of age nearly half of the co hort was tic-free. The onset of pu berty was not as so ci ated with ei ther the timing or se ver i ty of tics.

In 14% (5/36) of these cases rel a tive max i mums other than the worse ever point was de scribed. Rather than see ing these as ex cep tional cases, it is prob a bly better to con si der the unimodal dis tri bu tion of rel a tive tic se ver i ty se ver i ty that are irresolv able at this level of tem po ral scal ing. View ed from this per spe ctive, the unimodal tic se ver i ty curves seen in this study may be a re -
tion of the same multi pli ca tive pro cesses that un der lie both the oc cur rence of tics in bouts (tem po ral scal ing at the level of sec onds) and their wax ing and wan ing pattern (tem po ral scal ing at the level of weeks to months). If true, this also im plies that sim i lar pro cesses may gov ern sub se quent ex acer ba tions in adult hood.

Dis cov ery of the events that con tribute to re cure nce or per sis tence of tics may ben e fit those in di vid u als, prob a bly con sis tently ob served de ficits oc cur on tasks re quiring the accu rate copy of geo met ric de signs, i.e., “vis ual-motor in te gra tion” or “vis ual-graphic” abil ity. \(^{19}\)

A sig nif i cant pro por tion of in di vid u als with TS have fo cused on a broad ar ray of func tions. Re view of the lit er a ture sug gester that the most con sis tently ob served de ficits oc cur on tasks re quir ing the accu rate copy of geo met ric de signs, i.e., “vis ual-motor in te gra tion” or “vis ual-graphic” abil ity. \(^{19}\)

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Once thought to be a rare con di tion, the preva lence of TS is cur rently es ti mated to be be tween 1 and 8 cases per thou sand boys, and be tween 0.1 and 4 cases per thou sand girls. \(^{23,24}\) There is some sug gester that the prevalence may even be higher. \(^{25,27}\) Com mu-
nity suggests that motor tics are frequently observed in the pediatric age group. Although the etiological relationship between these simple tics and TS has not been established, current evidence indicates that TS and chronic tic disorders are part of the same disease entity, with TS being a more severe form of tic disorder.29,31

Two putative subtypes of TS are considered in this review: familial TS vs. sporadic, non-familial TS. A majority of TS probands have a positive family history of chronic tics or TS.30 A familial form of OCD (so called “tic-related OCD”) also appears in these families.30,32,33 A form of ADHD may also be present in these families that appears to be of internal origin and that bears some relationship to obsessive-compulsive behaviors or with “pathological” doubt or doubting that lead to repetitive checking to prevent some catastrophe, e.g., reparing edly checking the stove to ensure that a fire does not start in a vent. Despite potential embarrassment, the performance of compulsive washing and checking is frequent and may be accompanied with a sense of urgency to act.

Recently, factor analysis has identified some of these cases to have verisimilar events or post-infectious autoimmune mechanisms.43-45 Advances in our understanding of the putative autoimmunity may provide evidence of identifying these patients more accurately. In our experience, these patients have an atypical natural history. For example, the TS often begins in childhood, OCD in adolescence, and ADHD in adulthood.30

The second category, “sporadic, non-familial TS,” at present is a rare pediatric entity. However, there is evidence linking some of these cases to adverse perinatal events or post-infectious autoimmune mechanisms.43-45 Advances in our understanding may provide evidence of identifying these patients more accurately. In our experience, these patients have an atypical natural history and pattern of treatment response.46

OCD (Table 1) is a chronic disorder defined as a disorder in which the individual repeatedly experiences the sudden intrusion of a conscious sense of unwanted worries or unpleasing images and perceptions to perform repeated activities or perform them in a certain manner. The intrusive mental images that besiege the consciousness of ten involve sexual or aggressive ideas that the individual regards as reprehensible.47 Compulsions are concerned either with fears of contamination that lead to hand washing or other grooming behaviors or with “pathological” doubt or doubt that lead to repetitive checking to prevent some catastrophe, e.g., repeatedly checking the stove to ensure that a fire does not start in a vent. Despite potential embarrassment, the performance of compulsive washing and checking is frequent and may be accompanied with a sense of urgency to act.48

Recent studies have suggested that this form of OCD is associated with a disturbance of the specific OCD symptoms and pattern of treatment response.

Childhood OCD has been recognized as being much more common (in the range of 2 to 5%) than previously believed.59-61 These figures are largely consistent with those of Karna et al.62 who reported that 3% of the adult population suffers from diagnosable OCD.63 Childhood onset OCD appears to have a worse prognosis than OCD that begins in adolescence or adulthood.64

In addition to the dimensional approach cited above, three putative forms of OCD will be studied in the proposed program of research: familial tic-related OCD, familial non-tic-related OCD, and sporadic, non-familial OCD. As noted above, a familial form of OCD (so called “tic-related OCD”) appears in TS families.30,32,33 In addition, approximately 30 to 40% of OCD families have a positive family history of OCD or subclinical OCD in the absence of any history of tics in the proband or other family members.33,65 Evidence exists to suggest that this condition (“familial, non-tic-related OCD”) is distinguishable by the absence of clinical features, neurobiology, and treatment response from tic-related OCD.13,14,30,35-40,56

The third OCD category, “sporadic, non-familial OCD,” at present is the residual category. As with sporadic cases of TS, there is evidence linking this form of OCD to a
post-streptococcal autoimmunemechanism.\textsuperscript{44,45,66}

Although not the principal focus of this review, the clinical phenotype and pathogenetic mechanisms that underlie ADHD also need to be considered. Briefly, ADHD is a chronic syndrome of childhood on set characterized by problems of inattention, distractibility, impulsivity and motoric hyperactivity. In order to be diagnosed with this condition, some of the symptoms that cause impairment must have been present before the age of 7 years. The symp toms of ADHD usually manifest themselves in loosely structured academic, social or occupation settings where there are many distractions as well as a clear need to be at times in order to succeed. In highly structured one-on-one situations the symptoms of ADHD may not be noticeable. Extensive studies of comorbidity among children and adults with ADHD have been undertaken.\textsuperscript{67-75} Comorbid chronic tic disorders and/or OCD are known to occur. But the more common comorbid conditions are conduct disorder, oppositional defiant disorder, major depression, anxiety disorders other than OCD, and learning disabilities. Some of these data suggest that some forms of ADHD, ADHD plus oppositional defiant disorder, and ADHD plus conduct disorder exist along a continuum of vertically transmitted familial factors.\textsuperscript{71} In the case of the other comorbid syndromes, the presence of evidence suggests that genetic vulnerability to ADHD segregation is dependent entirely from these other traits or conditions.

The prevalence of ADHD in community surveys of children and adolescents usually ranges from 2% to 9%.\textsuperscript{76-79} Most studies report that boys are 2 to 9 times more likely to manifest ADHD than are girls.

Although one of our goals has been to characterize ADHD specifically associated with TS and OCD,\textsuperscript{34} it is also abundantly clear that there are multiple and potentially overlapping phenotypes of ADHD, including: familial, non-tic related ADHD; ADHD associated with specific psychiatric comorbidity (par tic ularly ADHD comorbid with conduct disorder); familial, tic-related ADHD; and sporadic, non-familial ADHD. The current DSM-IV distinction between predominantly hyperactive-impulsive vs. predominantly inattentive forms of ADHD is supported by latent class and factor analyses.\textsuperscript{80,81} As with OCD and TS, such dimensional approaches may hold promise for unraveling this complex phenotype.

Genetic factors

Genetic factors play an important role in the transmission and expression of these disorders. Twin and family studies support the view that TS is a genetically mediated disorder.\textsuperscript{32,34,82-85} Although the initial segregation analyses were compatible with a single major autosomal gene, subsequent linkage studies have failed to detect a genomic region linked to the TS phenotype in large multigenerational families.\textsuperscript{86,87} An international consortium of researchers is making incremental progress in the genetics of TS.\textsuperscript{88} Building on the results of a genome-wide scan of affected sibpairs, 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 families. This sibling 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 evidence of linkage. While it is disappointing that none of the chromosomal regions (e.g., 3p21.3, 8q21.4, 9p13, and 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. Further, 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. We hypothesize that a small number of genetic loci will eventually be identified and that these regions have the potential to provide a major step forward in understanding this complex phenotype.
Table 2. Genetic factors

<table>
<thead>
<tr>
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<th>Operational measures</th>
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<tbody>
<tr>
<td>G&lt;sub&gt;TS&lt;/sub&gt;</td>
<td>Genes of major and minor effect that underlie the vulnerability to develop familial TS and tic-related forms of OCD and ADHD.</td>
<td>Positive family history of TS or chronic motor or vocal tic disorder in first degree family members; candidate genes involved with the development and activity of central dopamine pathways and the CSTC circuits implicated in TS.</td>
</tr>
<tr>
<td>G&lt;sub&gt;OCD&lt;/sub&gt;</td>
<td>Genes of major and minor effect that underlie the vulnerability to develop familial, non-tic-related forms of OCD.</td>
<td>Positive family history of OCD in the absence of TS or chronic motor or vocal tic disorder in first degree family members; candidate genes involved with the development and activity of the CSTC circuits implicated in OCD.</td>
</tr>
<tr>
<td>G&lt;sub&gt;OTHER&lt;/sub&gt;</td>
<td>Other genes that can modify the expression and clinical severity of TS, OCD, and/or ADHD including the genetic factors associated with comorbid conditions including: ADHD, depression, bipolar disorder, conduct disorder, anxiety disorders, learning disabilities, Sydenham’s chorea, and related autoimmune conditions.</td>
<td>Positive family history for comorbid psychiatric conditions and genes linked to these comorbid disorders; positive family history for possibly related autoimmune disorders, including rheumatic fever, in first degree family members; candidate genes implicated in ADHD; candidate genes relevant to the immunological processing of streptococcal antigens.</td>
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TS = Tourette syndrome; OCD = obsessive-compulsive disorder; ADHD = attention deficit/hyperactivity disorder; CSTC = cortico-striato-thalamo-cortical.

Fig. 2. Working model of Tourette syndrome (TS) pathogenesis. Unique features of this model include the role of the TS specific genes (G<sub>TS</sub>) and their putative interrelationship with the environmental factors that are active early in central nervous system (CNS) development (RP<sub>PN</sub>). A crucial question remains: do the TS genes in any way set the stage for any of the perinatal risk factors or are they separate and independent mechanisms? Heuristically, we entertain the view that some of the specific TS genes are themselves involved in the development of the cortico-striato-thalamo-cortical (CSTC) circuits. GABA = gamma-aminobutyric acid; 5-HT = 5-hydroxytryptamine; OCD = obsessive-compulsive disorder; ADHD = attention deficit/hyperactivity disorder.
Twin and family studies also suggest that genetic factors are likely to play an important role in the transmission and expression of OCD. A small number of candidate genes have been evaluated in OCD with negative or contradictory results. However, segregation analyses, as well as classical genetic linkage studies have not yet been performed. We hypothesize that there is a specific set of genes that confer vulnerability to familial, non-tic-related OCD (Table 2 and Fig. 3).

Although not the principal focus of this review, genetic factors are likely to contribute to an individual's vulnerability to ADHD. Briefly, twin, family-genetic, and adoption studies provide consistent evidence that supports a role for genetic factors in the transmission and expression of ADHD. Segregation analyses are consistent with the effect of a single major gene, but the differences in fit among the genetic models was small suggesting an indeterminant result. Two studies have reported an association between an allelic variant at the dopamine transporter (DAT1) locus and the transmission of ADHD. Less consistent results have suggested that functional variants at the dopamine DRD4 loci may also confer an increased risk. As with OCD, classical genetic linkage studies and affected sib-pair methods have not yet been performed in ADHD. We hypothesize that the vulnerability to develop ADHD and/or other comorbid conditions will be associated with a third set of genes (Table 2 and Figs. 2, 3). This set of genes may partially overlap with those in cluded

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**Fig. 3.** Working model of obsessive-compulsive disorder (OCD) pathogenesis. Unique features of this model include the role of OCD specific genes (GOCD) in the development and functional activity of the orbitofrontal (OF) cortico-striato-thalamo-cortical (CSTC) circuit. Although the most striking functional changes have been documented in the head of the caudate nucleus, we are particularly interested in the role of the OF and the limbic (LI) cortices and the amygdala in activating the caudate. GABA = gamma-aminobutyric acid; 5-HT = 5-hydroxytryptamine; ADHD = attention deficit/hyperactivity disorder.
in the G\textsubscript{TS} and G\textsubscript{OCD} classes. Alternatively, the presence of these genetic vulnerabilities in individuals susceptible to TS or OCD may influence their clinical presentation and course.

Vulnerability genes associated with a range of other important comorbid conditions including depression, bipolar disorder, other anxiety disorders, conduct disorder, and learning disabilities included in the G\textsubscript{OTHER} are also included in this category. Although the available evidence suggests that these disorders do not co-segregate with TS or OCD in family studies, their presence has the potential to alter the severity and course of these disorders.

The last set of genes included in this G\textsubscript{OTHER} category are those that may influence some aspects of the body's immunological system which could include some viral aids more susceptible to the conditions such as Sydenham's chorea or related post-streptococcal autoimmune phenomena.

**Risk and protective factors**

The prevailing models of TS and OCD pathogenesis emphasize the importance of the interaction between genes and epigenetic or environmental factors over the course of central nervous system (CNS) development. In contrast to the relatively slow progression in identifying specific vulnerability genes, efforts to identify risk and protective factors that may affect the expression of TS and OCD have been more successful.

Events during the perinatal period (Tables 3 and Figs. 2, 3) have been consistent in plied in both TS and OCD.\textsuperscript{83,114-117} We hypothesize that perinatal risk and protective factors in influence the development of TS and OCD have been more successful.

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A second set of environmental risk and protective factors (Table 3) concerns the perinatal role of "acquired nature" (infections, trauma, toxins, and drugs). For example, during the epidemic of encephalitis lethargica (1916-1926), tics, OC, and attentional problems were common place. Recent attention has focused on the role of post-streptococcal autoimmunity in the development of Sydenham's chorea (SC), OCD, TS, and ADHD.\textsuperscript{43-45,66,118-120}

Finally, the past decade has seen the reemergence of an area of research that is ex amining the hypothesis that post-infectious autoimmune mechanisms contribute to the pathogenesis of some TS cases. Speculation concerning the post-infectious (or at least the post-rheumatic fever) etiology of tic disorders or other symptom dates from the late 1800s. It is well established that group A beta-hemolytic streptococci (GABHS) can trigger immune-mediated disease in genetically predisposed individuals. Acute rheumatic fever (RF) is a delayed sequela of GABHS, occurring approximately three weeks following an inadequately treated post-streptococcal infection. RF is characterized with inflammatory joints, heart and/or central nervous system (CNS). SC and TS share common anatomic areas - the basal ganglia of the brain and the related cortical and thalamic sites. Further, some SC patients display motor and vocal tics, OC, and ADHD symp toms suggest that the possibility of some cases of TS and OCD. Further suggestions evidence comes from Swedo et al.\textsuperscript{44} who reported that in children 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 on set for another 28% of the children.

Although the etiological significance of the anti-neuronal antibodies and the association with prior GABHS infections remains a topic of considerable debate,\textsuperscript{29} therapeutic interventions based on this mechanism show promise.\textsuperscript{121} Further, if specific immunological alterations are associated with on set or acute clinical exacerbations, then the nature of these alterations should provide insight as to the genetic, neuroanatomic, and immune mechanism involved. This knowledge may provide a basis for rational design of therapeutic and preventive interventions.
We hypothesize that infectious agents and autoimmune phenomena can influence the development and function of specific brain circuits in vulnerable individuals and that these effects result in a range of phenotypic outcomes with regard to tics and OC symptoms. The measurement of streptococcal-related antibodies found in serum should allow us to examine the role of these environmental factors in greater detail. Further, by characterizing the protein epitopes recognized by these circulating antibodies and through the creation of animal models, we may be able to gain fundamental insights into the immunological mechanisms involved.

A third crucially important set of risk factors (Table 3 and Figs. 2, 3) concerns an individual’s level of adaptive functioning as well as the presence of comorbid medical and psychiatric disorders (particularly depression, bipolar disorder, other anxiety disorders, conduct disorders, and learning disabilities).123-125 The effects of supportive family, peer and social supports; history of stressful events including limited peer and family acceptance, punitive parenting styles, and marital discord.

**Table 3. Environmental risk and protective factors**

<table>
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<th>Symbol</th>
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<th>Operational measures</th>
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<tbody>
<tr>
<td>RP&lt;sub&gt;PN&lt;/sub&gt;</td>
<td>Early perinatal factors that influence the development and age-related activity of CSTC circuits and related structures implicated in TS and OCD.</td>
<td>History of events and exposures occurring during the perinatal period. Prospectively collected data concerning obstetrical complications with a focus on events associated with hypoxia and ischemia.</td>
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<tr>
<td>RP&lt;sub&gt;EG&lt;/sub&gt;</td>
<td>Other microenvironmental factors that may influence the activity of CSTC circuits as well as the severity and course of TS and OCD.</td>
<td>History of exposures to infectious agents, trauma and/or medications that may contribute to a worsening of TS and OCD; serum titers for streptococcal related antigens.</td>
</tr>
<tr>
<td>RP&lt;sub&gt;AC&lt;/sub&gt;</td>
<td>Level of adaptive functioning and the presence of comorbid conditions that may influence the course and outcome of TS and OCD.</td>
<td>Level of adaptive behavior; presence of comorbid medical, neurological and/or psychiatric disorders (particularly depression, bipolar disorder, other anxiety disorders, conduct disorders, and learning disabilities).</td>
</tr>
<tr>
<td>RP&lt;sub&gt;SS&lt;/sub&gt;</td>
<td>Stressful and/or supportive external events, interpersonal and social factors that may influence the course and outcome of TS and OCD.</td>
<td>Socioeconomic status; familial, peer and social supports; history of stressful events including limited peer and family acceptance, punitive parenting styles, and marital discord.</td>
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</table>

PN = perinatal; CSTC = cortico-striato-thalamo-cortical; TS = Tourette syndrome; OCD = obsessive-compulsive disorder; EG = epigenetic; AC = adaptive/comorbid; SS = stress/support.

Neurobiological substrates

Based on available neuroanatomical and neurobiological data, there is convincing evidence for the involvement of specific cortico-striato-thalamo-cortical (CSTC) circuits in the expression of TS and related disorders (Ta ble 4 and Fig. 4).6,126-129 These circuits contain multiple, interconnected units that are distributed according to highly ordered repetitive patterns. These hierarchicalatomic arrangements are well suited to convey cortical information in a highly specific manner throughout the basal ganglia and to modulate precisely the neuronal activity of several functional brain systems which are intimately related to the control (initiation and monitoring vs. inhibition) of different aspects of psychomotor behavior.130-132 These modulatory corticostriatal projections are viewed as sculpting in di vi dual com ponents of motor and cog-
native action sequences. As ceding “value” or salience circuits can then facilitate the assembly of representations of motor and cognitive action sequences.

The formation of habits is a key function of these CSTC circuits. Habits are as sembled routines that link sensory or emotive cues with motor action. They allow us to act with our thinking—like riding a bicycle or driving a car. In the midst of performing a habitual act there is less conscious awareness of the action sequences needed. The neurobiological substrates of habits has been explored by Graybiel who has followed the lead of Miller in asserting that when we do something over and over, our brains compress the relevant information into “chunks” and that it is the coordination of these chunks that permit the formation of habitual action sequences.

Fig. 4. Corticostriatal-thalamocortical circuits. Excitatory projections are depicted as solid lines, while inhibitory projections are represented as dashed lines. Numerous cortical regions send projections to the striatum (caudate and putamen) where the inputs from as many as 10,000 cortical neurons converge on a single medium-spiny (MS) neuron. Striatal neurons in turn project to the external or internal segment of the globus pallidus (GPe or GPi), or the pars reticulata of the substantia nigra (SNr). The latter two sites are way stations of the “direct” pathway while projections to the GPe form part of the “indirect” pathway. The coordination of striatal MS neurons is associated with specific emotive-cognitive-action sequences. As ceding dopaminergic projections to the SNr can influence the coordination of these circuits and sculpt these coordinated discharge patterns. Diffuse cortical inputs may also converge on the subthalamic nuclei (STN). The STN also receives inputs from the GPe and in turn projects to the Gpi and the SNr where STN inputs may serve to reset emotive-cognitive-action sequences. For a detailed overview see Table 4, the text, and Petersen et al. (1998).
selective sensitivity to environmental cues from within the body or from the outside world. These per cessional cues include faint premonitory feelings or urges that are relieved with the performance of tics (Fig. 2), and a need to perform tics or compulsions until they are felt in effect to be "just right." Although the neural mechanisms that underlie tic performance are not fully understood, the concept suggests that they involve the same structures that underlie tic behavior.

Structurally within each of the CSTC circuits, the medium spiny neurons of the striatum are divided into two developmentally and neurochemically distinct compartments – striosomes and matrixes. Among other differences, the medium spiny neurons within the striosomes tend to receive their cortical afferents from limbic regions in contrast to matrixes whose input comes in part from the motor and sensorimotor cortices. From here, information leaves the basal ganglia pellis directly through the internal segment of the globus pallidus (GPi) and its brainstem counterparts, the substantia nigra pars reticulata (SNr) are believed to send information to the thalamus and cortex. Some striatal projections (arising mostly from striosomes) directly to the basal ganglia output neurons in the GPi and the SNr. This is called the "direct path way" by some authors.

In contrast to striatal projections, the more arising from matrixes) to the external segments of the globus pallidus (GPe), give rise to projections directed primarily to the reticular thalamic nucleus, subthalamic nucleus, and GPi. This is known as the "indirect path way." Be it the direct or indirect pathways, the basal ganglia output neurons (both GPi and GPe) project to the thalamus, thereby activating thalamic target neurons, which in turn reduce GABAergic transmission to the thalamus, thereby acutely affecting thalamic target neurons. Acute thalamic nucleus is essential for the initiation of movement. Thus, in increased striatal acuity it can be regarded as disinhibiting thalamic nuclei and corticothalamic neurons, since it acutely reduces the two GABAergic synaptic contacts leading to, and out of, the GPi/SNr. In increased striatal acuity in projecting to GPe will simultaneously disinhibit reticulotegmental thalamic neurons, but be cause these reticular nuclei in turn inhibit other thalamic nuclei, in increased striatal acuity of GPe will be malleable in hibiting those same thalamic neurons. GPe in high treshold of the GPe will pro duce a functionally similar thalamic inhibition. Therefore, increased striatal acuity can either either in the hibit or disinhibit the same thalamic nuclei and corticothalamic neurons, depending upon whether the GPe or GPi, respectively, is the target of striatal activity.

The subthalamic nucleus (STN) is an important element of CSTC circuitry. Although STN projects to all basal ganglia elements, excitatory projections to both pallidal segments and SNr are par ticul arly large. In diatonic subthalamic axons, which project to both GPi and GPe, arborize extensively throughout their rostrocaudal extent and appear to influence uniformly large subpopulations of neurons in both pallidal segments. Intracellular recordings suggest that STN modulates the thalamic nucleus, thereby modulating pallidal responsiveness and sensitiv ity to incoming striatal signals. Several CSTC circuits need to be considered. The sensorimotor circuitry CSTC circuit cludes: projections from the SM, pri mary motor, and supplementary motor cortex to portions of the thalamus and the head of the caudate nucleus. As many as 380,000 cortical axons converge and innervate the den dritic tree of a single medium spiny striatal output neuron. These striatal cells in turn project to portions of the GPi and SNr. These pallidal and nigral output neurons of the basal ganglia then project to ven tral and midbrain nuclei in the thalamus in turn project to cortex. Based on the observed relationship between the development and functional connectivity of this circuitry.
and its cortical commissural connections are critically involved in the functional pathobiology of TS.

A second CSTC circuit, labeled “orbitofrontal” (OF) by Alexander et al., in cludes: projections from the orbitofrontal cortex, cingulate, and temporal cortices to the head of the caudate nucleus. These striatal neurons then project to portions of the ventral anterior and medial dorsal nuclei in the thalamus that in turn project back to cortex. We, and others, hypothesize that the development and functional activity of this circuit and its cortical commissural connections are critically involved in the pathobiology of OCD.

We presume that the SM and OF circuits are to some degree functionally related to the remaining other “association” (AS) circuits described by Parent & Hazrati. These AS circuits in clude: projections from various association cortices in the frontal, temporal, and parietal lobes to the ventral striatum (most of the head, body, and tail of the caudate; and portions of the putamen). These striatal neurons then project to portions of the Gpi and the SNr. These output neurons then project to portions of the parvicellular areas of the ventral anterior and medial dorsal nuclei in the thalamus that in turn project to cortex. We, and others, hypothesize that the development and functional activity of these circuits and their commissural connections are critically involved in the remaining other “association” (AS) circuits described by Parent & Hazrati.

A fourth CSTC circuit, labeled “limbic” (LI) by Parent & Hazrati, includes: projections from anterior cingulate, hippocampal, entorhinal, and temporal cortices and amygdala to the ventral striatum (ventral most putamen and caudate nuclei, nucleus accumbens, and portions of the olfactory tubercle). These ventral striatal neurons then project to the ventral pallidum and to portions of the Gpi and the SNr. These output neurons then project to portions of the parvicellular areas of the ventral tegmental area (VTA) that in turn project back to various corticostriatal, pallidal, and thalamic circuits.

The role of the basal ganglia in drawing disturbances is particularly intriguing because neuroimaging, neuropathological and phenomenological studies implicate the basal ganglia and functionally laden LI information. There is clear evidence for its involvement in OCD and other anxiety disorders and it may well provide part of the neurobiological substrates for TS and ADHD as well.
related cortical and thalamic structures in the pathobiology of TS. A specific role for the right caudate in the pathobiology is suggested by an MRI study of 10 pairs of monozygotic twins concordant for tics. The size of the right caudate nucleus was significantly reduced in the more severely affected twin. Abnormalities of the right caudate, therefore, could have a primary role in both the tic behavior and the impaired visuo-motor integration skills seen in TS. In recent follow-up study of these twins, Wolf et al. reported greater D2 dopamine receptor binding in the head of the caudate bilaterally using single-photon emission computed tomography in the more severely affected co-twin. Intrapair binding differences accounted for nearly all of the variance in the core sponging within pair differences in symptom severity. These finding s are consistent with our findings of a central role in the pathobiology of TS, OCD, and ADHD.

The intrinsic neurotransmitters and neuromodulators (Table 4 and Figs. 2, 3) in involved in these circuits include: excitatory amino acids, such as glutamate, in the cortico-striatal projections and the thalamo-cortical projections; and inhibitory amino acids, such as GABA in the striato-pallidal and pallido-thalamic projections. The arrangement of projections in these CSTC loops (cortico-striatal, excitatory; striato-pallidal, inhibitory; pallido-thalamic, inhibitory; and thalamo-cortical, excitatory) suggests that cortical sites could be disinhibited by a number of mechanisms including abnormalities in the corticostriatal loop, the thalamo-cortical projections, and the thalamo-pallidal loop.

The extrinsic neurotransmitters and neuromodulators (Table 4 and Figs. 2, 3) in involved in these circuits include: the classical excitatory neurotransmitter glutamate and inhibitory neurotransmitter GABA. These findings are consistent with our hypothesis that TS, OCD, and ADHD can be usefully viewed as syndromes of obsessive-compulsive disorder. GABA = gamma-aminobutyric acid; DA = dopamine; 5-HT = 5-hydroxytryptamine; NE = norepinephrine.
“disinhibition” that directly involve these particular CSTC circuits and their cortical connections.\(^6,126,164\) As part of this conceptualization, TS is seen as a disorder in which individuals are unable to inhibit premonitory sensory urges, leading to the emergence of small “pre-wired” bits of motor and phonic behavior. In OCD, individuals are unable to inhibit specific, perhaps evolutionarily conserved “worries” leading to the emergence of intense ego-dystonic obsessions and compulsions.

Some of the extrinsic neurotransmitter and neuromodulator systems (Table 4 and Figs. 2, 3) that regulate the activity of these CSTC circuits include dopamine, serotonin, and norepinephrine. Dopamine projections from midbrain sites innervate cortical projection neurons and the medium spiny projection neurons in the striatum among others.\(^133,165\) Although controversial, age-dependent changes in central dopaminergic pathways may also be characteristic of many children with TS.\(^166\) Developmental shifts in the balance of tonic-phasic dopaminergic tone are likely and may influence the natural history of TS.\(^167,168\) Although future ligand-based functional imaging studies in child and adolescent samples complemented by neuropsychological studies hold considerable promise to elucidate these mechanisms, ethical concerns and logistical difficulties may limit these avenues of investigation which in turn points to the need to develop suitable animal models for TS and related disorders. Further, animal studies have in diated that the balance of activity of medium spiny neurons located in the striosomes vs. the matrix of the striatum may crucially determine an individual’s vulnerability to dopamine-mediated stereotypes.\(^169\) These stereotypes in clude a range of repetitive tic-like head and paw move ments, as well as repetitive sniffing. Serotoninergic projections from midbrain, pontine and medullary sites innervate cortical, striatal, pallidal, and thalamic structures. Norepinephrine projections arise from pontine and medullary tegmental regions and project through out the neural axis including the entire neo cortex. Each of these systems is stress sen sitive. We hy pothesize that the development of this module of anxiety and functional activity of these modulatory systems critical in fluence the severity of the behavioral dysfunction seen in TS (motor and phonic tics and other more complex disinhibited behaviors) and OCD (obsessions and compulsions).\(^35,170\)

Other neuromodulatory systems also need to be considered in these models of pathogenesis (Table 4 and Figs. 2, 3). For example, given the high prevalence of TS, ADHD and some forms of childhood OCD in males, it is likely that gonadal steroids acting via sexually dimorphic brain systems, in cluding the hypothalamus and other limbic structures, modulate the activity of these CSTC circuits and are important determinants of the natural history of these disorders.\(^171,172\)

**Heuristic models of pathogenesis**

In the spirit of offering a more integrated view of the pathogenetic mechanisms and their involvement in particular outcomes, we present a schematic model of the pathogenesis of TS and OCD (Figs. 2, 3). We recognize the hazards in such reductionistic formulations: the categories are not necessarily mutually exclusive, nor are they necessarily internally homogeneous.

**Anti-tic therapeutics**

Multimodal therapy for TS is usually in diated, 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 co-existing 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. In deed, for some medication, it is much easier to continue treatment than to discontinue 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 (Table 5).
Table 5. Anti-tic therapeutics: current approaches and promising leads

<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, relaxation therapies</td>
<td>Few side effects</td>
<td>Contingent responses are difficult for children to maintain, requirement for a well trained specialist</td>
</tr>
<tr>
<td>Traditional pharmacological approaches</td>
<td>Proven short term anti-tic efficacy</td>
<td>Limited patient acceptance due to side effects and potential for tardive dyskinesa</td>
</tr>
<tr>
<td>Dopamine D2 blockade:</td>
<td>Proven short term anti-tic efficacy</td>
<td>Improved patient acceptance, variable response, potential for marked weight gain especially in the pediatric age group</td>
</tr>
<tr>
<td>Haloperidol†, pimozide†, tiapride†, fluphenazine, sulpiride</td>
<td>Proven short term anti-tic efficacy</td>
<td>Improved patient acceptance, variable response, potential for marked weight gain especially in the pediatric age group</td>
</tr>
<tr>
<td>Atypical neuroleptics:</td>
<td>Proven short term anti-tic efficacy</td>
<td>Improved patient acceptance, variable response, potential for marked weight gain especially in the pediatric age group</td>
</tr>
<tr>
<td>Risperdone†, ziprasidone†, olanzapine, clozapine†</td>
<td>Proven short term anti-tic efficacy</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:</td>
<td>Promising open trials</td>
<td>Potential for disinhibition, limited effectiveness</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Promising open trials</td>
<td>Potential for disinhibition, limited effectiveness</td>
</tr>
<tr>
<td>Newer Agents</td>
<td>Promising open data in a small number of subjects</td>
<td>Potential for sedation, parkinsonism, and depression, not available in the US. Limited data on effectiveness</td>
</tr>
<tr>
<td>Dopamine depleting agents:</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>Tetraabenazine</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>Dopamine receptor agonists:</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>apomorphine (nonspecific), pergolide (D2 class D3, D2, D4), tiapexole (D2)§</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>Cholinergic agents:</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>nicotine patches, Botulinum toxin, mecamylamine</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>Antiandrogens:</td>
<td>Promising open data in a small number of subjects</td>
<td>Limited data on effectiveness, additive potential for the agonists</td>
</tr>
<tr>
<td>flutamide‡</td>
<td>Promising open data in a small number of subjects</td>
<td>Limited data on effectiveness, additive potential for the agonists</td>
</tr>
<tr>
<td>Opioid agonists/antagonists:</td>
<td>Promising open data in a small number of subjects</td>
<td>Limited data on effectiveness, additive potential for the agonists</td>
</tr>
<tr>
<td>propoxyphene§, tramadol, naltrexone§</td>
<td>Promising open data in a small number of subjects</td>
<td>Limited data on effectiveness, additive potential for the agonists</td>
</tr>
<tr>
<td>Cannabinols:</td>
<td>Promising open data in a small number of subjects</td>
<td>Limited data on effectiveness, additive potential for the agonists</td>
</tr>
<tr>
<td>Delta-9-tetrahydrocannabinol</td>
<td>Potential for etiologically based approach. Promising open data in a select group of subjects</td>
<td>Potential for sedation, parkinsonism, and depression, not available in the US. Limited data on effectiveness</td>
</tr>
<tr>
<td>Immunomodulatory/antimicrobial treatments:</td>
<td>Potential for etiologically based approach. Promising open data in a select group of subjects</td>
<td>Potential for sedation, parkinsonism, and depression, not available in the US. Limited data on effectiveness</td>
</tr>
<tr>
<td>Plasma exchange†, intravenous IgG§</td>
<td>Potential for etiologically based approach. Promising open data in a select group of subjects</td>
<td>Potential for sedation, parkinsonism, and depression, not available in the US. Limited data on effectiveness</td>
</tr>
<tr>
<td>Antibiotic prophylaxis:</td>
<td>Potential for etiologically based approach. Promising open data in a select group of subjects</td>
<td>Potential for sedation, parkinsonism, and depression, not available in the US. Limited data on effectiveness</td>
</tr>
<tr>
<td>penicillin V§</td>
<td>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>Promising open data in a small number of subjects</td>
<td>Invasive medical procedure with the potential for high risk side effects</td>
</tr>
<tr>
<td>Neurosurgical procedures:</td>
<td>Promising open data in a small number of subjects</td>
<td>Invasive medical procedure with the potential for high risk side effects</td>
</tr>
<tr>
<td>ablation vs. high frequency deep brain stimulation of thalamic nuclei</td>
<td>Invasive medical procedure with the potential for high risk side effects. Best procedures remain to be established</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>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>Noninvasive procedure</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>
</tbody>
</table>

*See Leckman et al. (2001) for details.
At least one randomized, double-blind clinical trial has been reported: †positive results, ‡mixed or marginal results, §negative results.
Animal models

Future progress in elucidating the pathogenesis and treatment of TS could be greatly accelerated with the development of animal models. At present, stimulant, stress and autoantibody in duced stereotypies con tinue to of fer the great est pro mise.173-175 If tics, like stereotypies, vary according to the balance of activity of medium spiny neu rons in the striosome and matrix com part ments of the striatum (Fig. 4, Ca na les and Graybeil169), then it should be pos si ble to ex am ine the clin i cal im pact of ge netic and or de vel op men tal in sults that af fect the relative number and sensitivity of MSP neu rons in the two striatal com part ments. For ex am ple, perinatal ischemic and hypoxic in sults in volving parenchymal le sions in crease the risk of tic dis or ders eight-fold.42 Do they also in crease an an i mal’s sus cep ti bil ity to de velop stereo typies in re sponse to psy cho motor stim u lants? If so, is there ev i dence of a dif fer en tial in jury to me dium spiny neu rons in the ma trix?

Fur ther, this model may pro vide a mean ing ful in te gra tion of knowl edge about tics drawn from a num ber of per spec tives in clud ing the re sponse to psy cho motor stim u lants? If so, is there ev i dence of a dif fer en tial in jury to me dium spiny neu rons in the ma trix?

Finally, it is tempt ing to spec u late that in SC and in post-infectious forms of TS the func tional ac tiv ity of the me dium spiny neu rons of the ma trix is dif fer en tially impaired as a result of the au toimmune re sponse. In deed, one plau si ble hy poth e sis is that the antineural an ti bod ies found in a sub set of TS pa tients may mod u late syn ap tic trans mis sion and al ter the bal ance be tween the striosomal and matrix com part ments of the striatum.

Conclusions

Advances in the clini cal pheno men ology of TS have mar vel ously kept pace with ad vances in sys tems neuro sci ence and the emerg ing un der stand ing of the role of the basal gan glia in re sponding to cues from the internal environment of the body and external world as pre sented by our sen sory ap par atus. In deed, re cent prog ress in neuroanatomy, sys tems neuro sci ence, and func tional in vivo neuroimaging has set the stage for a major advance in our un der stand ing of these dis or ders. Suc cess in this area will lead to the tar get ing of spe cific cir cuits for more in ten sive study. Di ag nos tic and prog nos tic ad vances can also be ap prec iated, e.g., which cir cuits are in volved and to what de gree? How does that de gree of in volve ment af fect the pa tient’s symp tomat ic course and out come?

Given this po ten tial, TS can be con sid ered a model dis or der to study the dy namic in ter play of neuro biologi cal sys tems dur ing de vel op ment. It is likely that the re search par a digms uti lized in these stud ies and many of the em pi rical find ings re sult ing from them, will be rel e vant to other dis or ders of child hood on set and to our un der stand ing of nor mal de vel opment.

Acknowledgements

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