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Original Articles and Reviews

Neurobiological Substrates of Tourette's Disorder

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Abstract

Objective: This article reviews the available scientific literature concerning the neurobiological substrates of Tourette's disorder (TD).

Methods: The electronic databases of PubMed, ScienceDirect, and PsycINFO were searched for relevant studies using relevant search terms.

Results: Neuropathological as well as structural and functional neuroimaging studies of TD implicate not only the sensorimotor corticostriatal circuit, but also the limbic and associative circuits as well. Preliminary evidence also points to abnormalities in the frontoparietal network that is thought to maintain adaptive online control. Evidence supporting abnormalities in dopaminergic and noradrenergic neurotransmission remains strong, although the precise mechanisms remain the subject of speculation.

Conclusion: Structural and functional abnormalities in multiple parallel corticostriatal circuits may underlie the behavioral manifestations of TD and related neuropsychiatric disorders over the course of development. Further longitudinal research is needed to elucidate these neurobiological substrates.

> "*I finally apprehend the magnitude of the background noise that I have been experiencing for decades … the people around me do not share my tics* because *they do not hear the drumbeat. They do not feel the sensations without sources, do not have irresistible urges to pause in mid-sentence … and so on in endless, bewildering variety … Finally and most important, I feel convinced that this complex challenging enigmatic internal world is the obvious core of Tourette*." Hollenbeck, 2001

Introduction

Tourette's disorder (TD) is a neuropsychiatric disorder characterized by motor and vocal tics. Motor tics are sudden, repetitive, stereotyped movements such as eye blinking, facial twitching, and head or shoulder movements, whereas phonic tics include sounds produced by moving air through the nose, mouth, or throat (e.g., coughing and throat clearing) as well as repeating syllables, words, or phrases. TD typically has a prepubertal onset, and boys are more commonly affected than girls. Symptoms usually begin with transient bouts of simple motor tics. Tics can become more "complex" in nature and appear to be purposeful. Although individuals with TD have been described since antiquity, the systematic study of individuals with tic disorders dates only from the nineteenth century (Leckman and Cohen 1999).

By age 10 years, most children with TD are aware of sensory urges that precede some of their tics. Known as premonitory urges, these sensations are often localized to a specific body region where the tic is about to occur and are frequently experienced as nearly irresistible. The urges themselves can be a major source of preoccupation and impairment. A fleeting feeling of relief often follows performance of a tic or series of tics (Leckman et al. 1993; Woods et al. 2005). Tics increase during periods of stress, emotional excitement, and fatigue (Lin et al. 2007). Tics can be willfully suppressed for brief intervals and are highly suggestible. Tics typically diminish during periods of goal-directed behavior, especially those that involve both focused attention and fine motor control, as occur in musical and athletic performances. Tics typically follow a waxing and waning pattern of severity, intensity, and frequency (Leckman 2002). Tic severity usually peaks between 8 and 12 years of age, with many patients showing a marked reduction in severity by the end of adolescence (Leckman et al. 1998; Coffey et al. 2004; Bloch et al. 2006). Less than 20% of children with TD continue to experience a moderate level of impairment of global functioning by the age of 20 years (Bloch et al. 2006).

In both clinical and population-based samples, TD alone is the exception rather than the rule, because co-morbid conditions are

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prevalent. At most, only 10–20% of children with TD are free of a co-morbid disorder (Khalifa and von Knorring 2006; Mol Debes et al. 2008; Scahill et al. 2009). Attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) are among the most common co-morbidities in both clinical and epidemiological studies (Coffey et al. 2000; Khalifa and von Knorring 2006; Mol Debes et al. 2008; Scahill et al. 2009). The presence of these co-morbidities can add another layer of complexity, which may make it more difficult to develop a treatment plan that not only addresses the tics, but also the co-occurring disorders.

Neural Substrates of Habit Formation and Tics

Identifying the neural substrates implicated in TD is not only important to our understanding of this disorder, but is also relevant to the development of behavioral and pharmacological treatments. Tics are thought to result from dysfunctions in cortical and subcortical regions that are involved in habit formation, including the basal ganglia, thalamus, and frontal cortex (Graybiel 1998; Leckman and Riddle 2000; Leckman 2002; Leckman et al. 2006; Graybiel 2008). Similar to habits, tics are routines that link sensory cues with specific motor actions. The limbic, associative, and sensorimotor cortico-striatal-thalamo-cortical (CSTC) circuits are composed of multiple, partially overlapping, but largely ''parallel'' circuits that direct information from the cerebral cortex to subcortical structures, and then back again to specific regions of the cortex. Although multiple anatomically and functionally related cortical regions provide input, each circuit in turn refocuses its projections back to a discrete subset of the cortical regions. Advances in our understanding of TD have been led in part by investigators who have examined brain circuits that underlie habit formation (procedural learning), as well as internally and externally guided motor control (Middleton and Strick 2000; Graybiel 2008; Pennartz et al. 2009; Balleine and O'Doherty 2010; Haber and Knutson 2010). Aspects of our understanding of the neurons and circuits, which involve these CSTC circuits, are outlined below.

Cortical neurons projecting to the striatum outnumber striatal medium spiny neurons by about a factor of 10 (Zheng and Wilson 2002). As depicted in Fig. 1, convergent cortical efferent neurons project to the dendrites of medium spiny neurons within two structurally similar, but neurochemically distinct, compartments in the striatum—striosomes and matrix. These two compartments differ by their cortical inputs, with the striosomal medium spiny projection neurons mainly receiving convergent limbic and prelimbic inputs, and neurons in the matrix mainly receiving convergent input from ipsilateral primary motor and sensory motor cortices, as well as from contralateral primary motor cortices (Leckman 2002; Mink 2006). The response of particular medium spiny projection neurons in the striatum is partly dependent on perceptual cues that are judged salient, so that both rewarding and aversive stimuli can serve as cues (Canales and Graybiel 2000).

Several other less abundant striatal cell types probably have a key role in modulating tics and habit learning, including fast-spiking γ-aminobutyric acid-ergic (GABAergic) interneurons (FSINs) and cholinergic tonically active neurons (TANs) (Jog et al. 1999; Gonzalez-Burgos et al. 2005). The FSINs of the striatum receive direct cortical inputs predominantly from lateral cortical regions, including the primary motor and somatosensory cortex, and they are highly sensitive to cortical activity in these regions. They are also electrically coupled via gap junctions that connect adjacent cells. Although the precise nature of the interactions of these interneurons and adjacent medium spiny neurons is not yet fully elucidated (Pennartz et al. 2009), it does appear that the FSINs do fire in a coordinated fashion just prior to a decision being made in a striatal-dependent task (Gage et al. 2008). Once activated, these FSINs can inhibit many nearby striatal projection neurons synchronously via synapses on cell bodies and proximal dendrites (Koos and Tepper 1999). The characteristic electrophysiological properties of the FSINs (e.g., irregular bursting with stable intraburst frequencies) are similar to the temporal patterning of tics (Peterson and Leckman 1998).

TANs, in contrast, are sensitive to salient perceptual cues because they signal the networks within the corticobasal ganglia learning circuits when these cues arise. Specifically, they are responsive to dopaminergic inputs from the substantia nigra, and these signals probably participate in the calculation of perceived salience (reward value) of perceptual cues along with excitatory inputs from midline thalamic nuclei. Whereas the dopamine neurons' response reflects a mismatch between expectation and outcome, the TANs are invariant to reward predictability (Morris et al. 2004). In addition, TAN pairs are typically synchronized, compared to a minority of dopamine neuron pairs. It appears that the striatal cholinergic and dopaminergic systems carry distinct messages by different means, which can be integrated differently to shape the basal ganglia responses to reward-related events.

Neuropathology

Although neuropathological studies of postmortem TD brains are few in number, a recent stereological study indicates that they have a marked reduction in the number and density of GABAergic parvalbumin-positive cells in basal ganglia structures (Kalanithi et al. 2005). In the caudate nucleus, there was a greater than 50% reduction in the FSINs and a 30–40% reduction of these same cells in the putamen. This same study found a reduction of the GABAergic parvalbumin-positive projection neurons in the external segment globus pallidus (GPe) as well as a dramatic increase (>120%) in the number and proportion of GABAergic projection neurons of the internal segment of the globus pallidus (GPi). These alterations are consistent with a developmental defect in tangential migration from the ganglionic eminence (the developmental precursor of the basal ganglia) of some GABAergic neurons. A more recent postmortem study confirmed a 50–60% decrease of both GABAergic FSINs as well as a loss of the cholinergic TANs in the caudate nucleus and putamen (Kataoka et al. 2010). More specifically, these cholinergic interneurons were decreased in TD patients in the associative and sensorimotor regions, but not in the limbic regions of the striatum, such that the normal gradient in density of cholinergic cells (highest in associative regions, intermediate in sensorimotor regions, and lowest in limbic regions) was abolished. No significant difference was present in the densities of calretinin interneurons or the medium spiny neurons.

This work suggests the intriguing notion that a dysfunction of these interneurons in the associative and sensorimotor regions of the basal ganglia may underlie the emergence of tics and other forms of disinhibited behavior characterizing tic symptomatology. Future studies are needed to confirm and extend these findings, and might focus on developing a more complete understanding of how the different striatal interneurons are affected, and how alterations in FSINs and GPi projection neurons could lead to a form of thalamocortical dysrhythmia (Llinás et al. 2005; Leckman et al. 2006). Additional neuropathological studies that focus on specific neuromodulatory and neurotransmitter systems are discussed below.

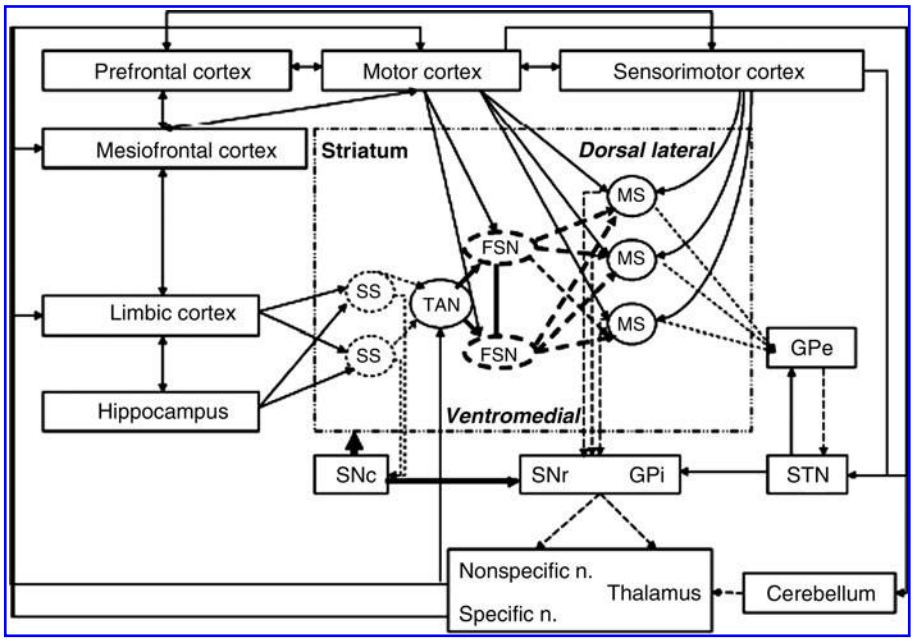

FIG. 1. Schematic diagram of the major connections of the basal ganglia associated with Tourette's syndrome. In the sensorimotor and motor circuits excitatory glutamatergic cortical neurons converge on the matrisomal (MS) γ-aminobutyric acid (GABA)–containing medium spiny neurons in the dorsal lateral striatum. These circuits are likely to be critically involved in the initiation and completion of tics. These cortical projections are organized somatotopically (with specific regions devoted to specific body regions). These MSs then project to the internal segment of the globus pallidus (GPi) and the pars reticulata of the substantia nigra (SNr), either directly or indirectly via both the external segment of the globus pallidus (GPe) and the subthalamus nucleus (STN). Inhibitory GABAergic projection neurons in the GPi and SNr, in turn, project to the specific or nonspecific (intralaminar) thalamic nuclei as well as brainstem nuclei. This loop is then completed by excitatory glutamatergic thalamocortical projection neurons to cortical neurons in the supplementary motor area. Both the specific and nonspecific thalamic excitatory glutamatergic nuclei project to both inhibitory fast spiking cortical GABAergic interneurons, as well as glutamatergic pyramidal projection neurons in the cortex (not shown). The 'cognitive' cortico-striato-thalamo-cortical (CSTC) circuit (not depicted in this figure) consists of cortical neurons in the prefrontal cortex that project to the head of the caudate nucleus. These signals are then relayed through the GP to the excitatory glutamatergic thalamocortical projection neurons. This circuit is likely to play a key mediating role in the therapeutic efficacy of habit reversal training. In addition to the motor, sensorimotor, oculomotor, and cognitive association circuits, limbic loops have also been characterized. The limbic system mediates emotional states, threat appraisal and motivation. It consists of cortical projections from limbic, pre- and perilimbic regions such as the hippocampus and amygdala to striosomial (SSs) medium spiny neurons in the ventral medial striatum. These inhibitory GABAergic cells in turn project to dopaminergic cells in the pars compacts of the substantia nigra (SNc) as well as to cholinergic neurons identified as tonically active neurons (TANs). The TANs receive input from both dopaminergic cells in the SNc and excitatory glutamatergic cortical neurons, synapse on fast-spiking neurons (FSNs) in the striatum. The FSNs appear to play a key role modulating the activity of the MSs (described above, see text). Excitatory glutamatergic projections are depicted as black solid arrows. They arise from cortical and thalamic sites. The STN also has excitatory glutamatergic projections. Inhibitory GABAergic projections are depicted as dashed arrows. They arise from medium spiny neurons in the striatum (both MSs and SSs) as well as the GPe and the basal ganglia output neurons in the SNr and GPi. The fast-spiking interneurons of the thalamus and cortex are also GABAergic, as are the FSNs in the striatum. FSNs can form gap junctions with other FSNs so that multiple cells can fire in unison (depicted as the solid line between the two FSNs). The location of their synapses on the cell bodies and proximal dendrites of the MSs also means that they can be very powerful inhibitors of the activity of MSs. The GABAergic interneurons in the cortex and thalamus as well as the FSNs, and some of the GABAergic cells in the SNr, GPi and GPe contain parvalbumin and share a common origin early in brain development. Dopaminergic projections (single large arrow) from the SNc are diffuse and can affect each cell type depicted in the striatum (not shown). The cholinergic projections from the schematic TANs are also depicted as solid lines. (Reprinted, with permission, from Leckman et al. 2006.)

Neuromodulatory and Neurotransmitter Systems

The CSTC circuits contain a wide spectrum of classic neurotransmitters, neuromodulators, and neuropeptides. The functional status of a number of these systems in TD has been evaluated in both neuropathological studies and pharmacological interventions. Although a disorder of dopaminergic neurotransmission has been considered most likely, other transmitters and neuromodulators have also been implicated (Singer and Minzer 2003). Emerging data in this arena will have the greatest potential impact for the development of novel pharmacologic agents.

Dopaminergic systems

Dopamine has an important influence on frontal–subcortical neurotransmission. Inputs from ascending dopamine pathways originating in the pars compacta of the substania nigra play a crucial role in coordinating the output from the striatum (Aosaki et al. 1994; Haber et al. 2006). Within frontal regions, dopaminergic fibers arising from the ventral tegmental area (VTA) modulate pyramidal cell excitability directly as well as indirectly via synapses on interneurons (Smiley et al. 1994; Mrzljak et al. 1996). "Dopamine" hypotheses for TD posit an excess of nigrostriatal

dopaminergic activity, whether through supersensitive dopamine receptors, dopamine hyperinnervation, or abnormal presynaptic terminal function. These hypotheses are consistent with multiple lines of empirical evidence from clinical trials as well as emerging data from animal models of habit formation. First, data implicating central dopaminergic mechanisms include the results of double-blind clinical trials in which haloperidol, pimozide, tiapride, and other neuroleptics that preferentially block dopaminergic D2 receptors have been found to be effective in the temporary suppression of tics for a majority of patients (Scahill et al. 2006). Second, tic suppression has also been reported following administration of agents such as tetrabenazine, which inhibits the uptake of dopamine into synaptic vesicles and so diminishes the amount of dopamine released at synapses (Kenney et al. 2007). Third, increased tics have been reported following withdrawal of neuroleptics or following exposure to agents that increase central dopaminergic activity such as L-dopa and central nervous system (CNS) stimulants, including cocaine (Anderson et al. 1998). In contrast, the dopamine agonists pergolide and ropinirole improve tics when given at much lower doses than those prescribed to treat Parkinson's disease (Gilbert et al. 2003; Anca et al. 2004). The mechanism of action is speculated to involve presynaptic rather than postsynaptic striatal or cortical dopamine receptors.

In vivo neuroimaging studies have documented increases of dopamine transporter (DAT) binding in the neostriatum and increases of dopamine storage and dopamine release in the ventral striatum (Nikolaus et al. 2009). For example, dopamine release measured as amphetamine-induced decrease of D2 receptor binding was found to be higher in the putamen and in the right ventral striatum of patients with TD but not in the caudate (Singer et al. 2002; Wong et al. 2008). The increase of DA release in TD patients exceeded the increase of DA release in healthy individuals by more than 90%. Other positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies have provided limited or equivocal support for dopaminergic hyperinervation of the striatum (Malison et al. 1995; Müller-Vahl et al. 2000; Albin et al. 2003; Serra-Mestres et al. 2004; Cheon et al. 2004; Albin et al. 2009; Nikolaus et al. 2009). The potential role of dopaminergic systems in frontal regions has also been evaluated with conflicting results both in postmortem and *in vivo* imaging studies involving a small number of subjects (Gilbert et al. 2006; Yoon et al. 2007; Nikolaus et al. 2009).

Noradrenergic system

Noradrenergic projections from the locus coeruleus project widely to the prefrontal and other cortical regions. Noradrenergic pathways are also likely to indirectly influence central dopaminergic pathways via projections to areas near the VTA (Grenhoff and Svensson 1989). Speculation that noradrenergic mechanisms might be relevant to the pathobiology of TD was based initially on the beneficial effects of α2-adrenergic agonists, including clonidine, in TD patients (Cohen et al. 1979). In open and double-blind trials, both clonidine and another related α2-adrenergic agonist, guanfacine, have been reported to reduce tic severity and improve ADHD symptoms (Scahill et al. 2001; The Tourette's Syndrome Study Group 2002). This effect was recently confirmed in a systematicic meta-analysis (Bloch et al. 2009).

Clonidine has been traditionally viewed as a selective α2-adrenoceptor agonist active at presynaptic sites. Its primary mode of action may be its ability to reduce the firing rate and the release of norepinephrine from central noradrenergic neurons. Evidence of heterogeneity among the α2-class of adrenoceptors and their distinctive distribution within relevant brain regions, however, adds further complexity to this hypothesis. Specifically, differential effects in cortical regions mediated by specific receptor subtypes may account for the differential responsiveness of particular behavioral features of this disorder to treatment with clonidine versus guanfacine (Arnsten et al. 2007). It is also of interest that the relative density of the 2A subtype of the α-adrenergic receptors was increased in the prefrontal cortex (Brodmann areas 10 and 11) in a small number of neuropathological specimens from TD subjects (Yoon et al. 2007).

The involvement of the noradrenergic pathways may be one of the mechanisms by which stressors may influence tic severity. For example, a series of adult TD patients were found to have elevated levels of cerebrospinal fluid (CSF) norepinephrine (Leckman et al. 1995) and to have excreted high levels of urinary norepinephrine in response to the stress associated with a lumbar puncture (Chappell et al. 1994). These elevated levels of CSF norepinephrine may also contribute to the elevation in CSF corticotropin-releasing factor and peripheral cortisol levels seen in some TD patients (Chappell et al. 1996; Corbett et al. 2008).

Histaminergic system

Based on the finding of a rare variant in a non-consanguineous two-generation pedigree in which nine individuals were affected with TD (Ercan-Sencicek et al. 2010), there may be a major role for histaminergic neurotransmission in the pathobiology of this condition. Histamine is a transmitter in the nervous system and a signaling molecule in the gut, the skin, and the immune system. Histaminergic neurons in mammalian brain are found only in the tuberomamillary nucleus of the hypothalamus, and they project throughout the CNS (Haas et al. 2008). They are active solely during waking, and they are thought to maintain wakefulness and attention. The finding of a relative loss of function of the L-histidine decarboxylase (HDC) has the potential to lead to the development of animal models and eventually the development of novel therapeutics for TD.

Serotonergic system

Ascending serotonergic projections from the dorsal raphe have been repeatedly invoked as playing a role in the pathophysiology of both TD and OCD. The most compelling evidence relates to OCD and is based largely on the well-established efficacy of potent serotonin reuptake inhibitors (SRIs), such as clomipramine and fluvoxamine, in the treatment of OCD. However, it is clear that the SRIs are less effective in treating tics (Scahill et al. 1997) and tic-related OCD compared to other forms of OCD (Bloch et al. 2006). Preliminary postmortem brain studies in TD have suggested that serotonin and the related compounds tryptophan and 5-hydroxy-indoleacetic acid may be globally decreased in the basal ganglia and other areas receiving projections from the dorsal raphe (Anderson et al. 1998). More recently Yoon et al. (2007) reported no differences in the relative density of serotonin (5HT-1A) receptors in postmortem brain tissue from frontal and occipital regions in TD subjects. Finally, Nikolaus et al. (2009) in a detailed review of the *in vivo* neuroimaging literature found little evidence in support of abnormalities in the serotoninergic neurotransmission in TD. However, the number of studies and subjects has been relatively small.

Excitatory amino acid systems

The excitatory neurotransmitter glutamate is released upon depolarization by the corticostraital, corticosubthalamic, sub-

thalamic, and thalamocortical projection neurons (Fig. 1). As such, these excitatory neurons are key players in the functional anatomy of the basal ganglia and the CSTC loops. Very limited data are available to assess the role of glutamatergic neurotransmission in TD (DeVito et al. 2005; Anderson et al. 1998). Although no compelling neuroanatomical alterations have been seen in this class of neurons, it is clear that the relative balance of activity between glutamatergic projection neurons and GABAergic cells is likely to be a key factor in the emergence of tic behaviors (Leckman et al. 2006; Singer et al. 2010). Future magnetic resonance spectroscopy studies that are capable of measuring these crucially important neurotransmitters in specific brain regions will likely help to answer this question (Jissendi Tchofo and Balériaux 2009).

Inhibitory amino acid systems

As presented in Fig. 1, neurons containing inhibitory amino acid neurotransmitters, particularly GABA, also form major portions of CSTC loops. These include GABAergic medium spiny projection neurons of the striatum that project to the internal segment of the GP and the pars reticulata of the substantia nigra within the ''direct pathway.'' GABAergic neurons are also present in the ''indirect pathway'' that relays information from the striatum to the external segment of the GP and from there to the internal segment of the GP. An imbalance between the output from the striosomal versus the matriosomal striatal compartment has been hypothesized in TD (Canales and Graybiel 2000; Leckman 2002). This imbalance may well be mediated, in part, by the reduction in both the GABAergic FSINs in the caudate and putamen (Kalanithi et al. 2005; Kataoka et al. 2010). In contrast, from a pharmacological perspective, there are fairly little data to support the value of GABAergic interventions. For example, while benzodiazepines, which enhance the inhibitory effect of GABA, have some efficacy in tic suppression (Gonce and Barbeau 1977), the GABAergic muscle relaxant baclofen in one small double-blind placebo-controlled crossover study was no better than placebo in reducing tic severity in children (Singer et al. 2001).

Cholinergic system

As noted above, the cholinergic TANs are few in number but found throughout the striatum. They are likely to be critically involved in the coordination of striatal response through interactions with central dopaminergic and GABAergic neurons (Aosaki et al. 1994; Graybiel 2008). Specifically, cholinergic TANs are thought to be present at the striosomal boundaries and likely mediate the functional interface between the striatal compartments. In addition, cholinergic projections from the basal forebrain are found throughout the cortex and within key structures of the basal ganglia and mesencephalon, including the internal segment of the GP, the pars reticulata of the substantia nigra, and the locus coeruleus. In recent postmortem studies, these TANs interneurons were reduced in number in the associative and sensorimotor regions of the striatum, but not in the limbic region (Kataoka et al. 2010). From a pharmacologic perspective, nicotine administered as a transdermal patch or chewing gum, has been evaluated in open-label studies and one controlled study (Scahill et al. 2006). In one study, mecamylamine, a nicotinic receptor antagonist, was no better than placebo in reducing tics (Shytle et al. 2002). These studies provide unconvincing evidence that nicotine can provide an adjunctive benefit for tic suppression when added to ongoing treatment with an antipsychotic (Silver et al. 2001). Thus, the practical application of manipulating nicotinic receptor function does not appear useful at present.

Structural and Functional Neuroimaging Studies

Volumetric magnetic resonance imaging (MRI) studies of basal ganglia in individuals with TD are consistent with the postmortem findings, in that there appears to be an approximate 5% reduction in caudate volume (Peterson et al. 2003; Kalanithi et al. 2005). This decrease in the volume of the caudate was observed in both the child and adult age groups. More recently, Bloch and colleagues (2005) found an inverse correlation between caudate volume in childhood and tic severity in early adulthood. Other volumetric changes reported in this group of more than 150 children and adults with TD include an approximate 5% increase in the volumes of the hippocampus, amygdala, and thalamus (Peterson et al. 2007). Larger regional prefrontal volumes in children with TD have also been documented (Peterson et al. 2001; Hong 2002).

Cortical thickness has also been measured using MRI images of affected children and adolescents with TD age- and sex-matched controls (Sowell et al. 2008). Cortical thinning was most evident in regions of the sensory and motor homunculi. Thinning in this cortical regional directly correlated with worst-ever tic severity. Cortical thinning was also evident in the right dorsal lateral cortex as well as in the entorhinal and orbital frontal regions. Cortical thinning in these regions may influence an individual's inhibitory control and could contribute to a loss of sensorimotor gating and increased vulnerability to OCD and depression.

More recently, Fahim et al. (2009) studied 16 fraternal twin pairs concordant for TD from the same population isolate and found that a number of limbic regions showed the highest degree of heritability of cortical thickness. These limbic regions included the left and right anterior cingulate and the left posterior cingulate cortices. Using a slightly lower threshold for heritability, the left medial frontal/motor cortical region (BA6) and the right insula were also identified. The cortical thickness of the right insula was also inversely correlated with current tic severity. In addition children with TD appear to have smaller corpus callosum (CC) areas, as well as reduced white matter connectivity, as measured by the Fractional Anisotropy (FA) index from diffusion tensor images (Plessen et al. 2004; Plessen et al. 2006).

In sum, the volumetric MRI studies of the basal ganglia are consistent with the available preliminary postmortem studies using unbiased stereology and indicate that TD is associated with volumetric alterations in each of the major CSTC circuits (limbic, associative, and sensory motor). A number of other cortical regions have also been implicated, mostly in limbic and prefrontal regions. These results are consistent with recent studies in primates that emphasize that projections from different reward-processing and cognitive cortical areas occupy both separate and converging territories within the corticostriatal circuits (Haber et al. 2006).

Thus far, there have been relatively few published studies of TD using functional magnetic resonance imaging (fMRI). In adults with TS, Peterson et al. (1998) compared brain activity during blocks of time in which tics were suppressed voluntarily or not suppressed. During tic suppression, prefrontal cortical and right caudate nucleus activity was increased while thalamic and basal ganglia areas were deactivated. Positive correlations between increased activity in the frontal cortex and the right caudate nucleus, and between increased activity in the right caudate nucleus and decreased activity in the GP and thalamus, were robust. These findings are consistent with the known presence of excitatory

projections from the frontal cortex to the caudate nucleus and the known inhibitory projections from the caudate nucleus to the GP (Fig. 1). In addition, significant inverse correlations of the severity of symptoms with activity in all subregions of the basal ganglia suggest insufficient activity upstream in the pathway at the right caudate nucleus in the initial prefrontal-striatal or the subsequent striatopallidal projections. Although this study and other PET and SPECT studies cannot further specify which of these projections is more likely to be the culprit, the functional consequence of each alternative is the same—insufficient activity in the inhibitory striatopallidal neurons projecting to the rest of the basal ganglia and eventually to the thalamus and the cortex (Gerard and Peterson 2003).

Subsequently, Bohlhalter and colleagues (2006) studied the neural correlates of tics and associated urges using an event-related fMRI protocol. On the basis of synchronized video/audio recordings, fMRI activities were analyzed 2 seconds before a tic and at tic onset. A brain network of limbic areas, including the anterior cingulate and insular cortex, supplementary motor area (SMA), and parietal operculum, was found to be activated prior to tic onset. This was followed at tic onset by activity in sensorimotor areas, including cerebellum and superior parietal lobule bilaterally.

Most recently, Hampson et al. (2009) used a novel method to compare brain activation patterns during tics and intentional movements. First, the part of motor cortex specific to each patient's tic movement was identified. The brain areas activating prior to, during, and after tics were identified by temporally cross-correlating the time course of that region of motor cortex with activity patterns throughout the rest of the brain. The spatiotemporal pattern of coactivation with the motor cortex during tics was then contrasted with that seen in healthy control subjects during matched, intentional movements. Nearly identical patterns of cross-correlation to the motor cortex throughout the brain were observed in the two groups. However, the SMA showed a significantly broader profile of cross-correlation to the motor cortex during tics than during intentional movements, highlighting the potential importance of the SMA in tic generation.

Stern and colleagues (2000) found that increased activity in a set of neocortical, paralimbic, and subcortical regions (including SMA, premotor, anterior cingulate, dorsolateral-rostral prefrontal, primary motor cortices, Broca's area, insula, claustrum, putamen, and caudate) were highly correlated with tic behavior. Perhaps not surprisingly, in the 1 patient with prominent coprolalia, the vocal tics were associated with increased activity in prerolandic and postrolandic language regions, insula, caudate, thalamus, and cerebellum. Some of these areas are known to be involved in the motor movements of the mouth and speech production. Investigators have also examined how coupling between brain regions may be disturbed in TD. An fluorodeoxyglucose (FDG)-PET study reported differences in connectivity in TD patients and controls, particularly to the ventral striatum, as well as a reversal in coupling between the limbic and motor CSTC loops (Jeffries et al. 2002). That is, the motor and limbic circuits tended to be negatively correlated in healthy subjects and positively correlated in TD patients.

More recently, Church et al. (2009), using resting state fMRI, examined the development of two of the brain's task control networks—a frontoparietal network likely involved in more rapid, adaptive online control and a cingulo-opercular network apparently important for set maintenance. They found that adolescents with TD had immature patterns of connectivity, particularly the frontoparietal network that is thought to maintain adaptive online control. In addition, to the immature patterns of connection, anomalous connections were also documented in regions involved in the frontoparietal network, possibly resulting in deficient inhibition of unwanted behaviors, such as tics.

Neurophysiology

Noninvasive *in vivo* neurophysiological research in TD has led to several areas of significant progress with regard to the experimental therapeutic use of deep brain stimulation and repetitive transcranial magnetic stimulation (rTMS) (Leckman et al. 2006). For example, several groups of investigators have reported that TD patients have deficits in sensory gating across a number of sensory modalities (Castellanos et al. 1996; Swerdlow et al. 2001). Prepulse inhibition (PPI) abnormalities have been observed across a variety of neuropsychiatric conditions, including schizophrenia, OCD, Huntington's disease, nocturnal enuresis, ADHD, and Asperger's syndrome, in addition to TD. With respect to TS, these deficits in inhibitory gating are consistent with the idea that there is some diminished ability to appropriately manage or ''gate'' sensory inputs to motor programs, which are released as tics (Swerdlow et al. 2000; Swerdlow et al. 2006). It is also of interest that in animal studies PPI is regulated by both norepinephrine and dopamine substrates that are neurochemically separable (Swerdlow et al. 2006). In a recent study, Zebardast et al. (2009) observed that healthy controls displayed greater PPI than subjects with either active, current tic symptoms or a history of remitted tic symptoms. The comparable deficits in PPI among remitted and active TD subjects suggest that sensory gating deficits remain even when tics subside. Large regional overlap in brain activity between two TD populations and their differential activation compared to controls suggest these regions may be trait markers for TD and thus responsible for sensory gating deficits in this population. Striatal and cerebellar regions showing differences between the two TD populations may represent state markers of TD. Correlation analysis indicated that change in response in these regions to PPI was significantly related to tic severity. These may be regions of compensatory importance in TD remission.

Second, investigators have hypothesized that the normal patterns of discharge from the basal ganglia output nuclei are disrupted so that the firing of the GPi projection neurons transiently hyperpolarize selected thalamocortical neurons, causing them to transiently increase the amplitude of their high-frequency membrane potential oscillations (20–80 Hz). This, in turn, results in the ectopic activation of selected cortical pyramidal neurons, ultimately leading to the overt and/or subliminal perception of premonitory urges and the performance of tics (Llinás et al. 1999; Llinás et al. 2005; Leckman et al. 2006). Circumstantial evidence from intraoperative recordings of patients with refractory TD provides limited support for this hypothesis (Zhuang et al. 2004a; Zhuang et al. 2004b). Remarkably, abolishing this activity through electrolytic lesions in the GPi resulted in an immediate improvement of tics. The synchronous ultraslow activity in the multisecond range (2–60 seconds and longer) that is found in the GP of experimental animals may also be disregulated in TD (Ruskin et al. 2003). These oscillations are very sensitive to the presence of dopamine agonists, and evidence exists for a heightened dopaminergic innervation of the basal ganglia in some individuals with TD (Nikolaus et al. 2009). Remarkably, chronic administration of apomorphine in rats for 1 year is associated with multiweek oscillations in the frequency of stereotypies (Csernansky et al. 1986). These temporal patterns bear a resemblance to the occurrence of tics in bouts over seconds to minutes, as well as the waxing and waning of tic symptoms over weeks to

months (Peterson and Leckman 1998; Leckman 2002). Recently, these multisecond oscillations have also been implicated by Castellanos et al. (2005) in the variability of neuropsychological performance of children with ADHD. Future research is needed to determine whether these apparent similarities are based on a common set of processes.

A third advance has been the investigation of motor system excitability by means of single- and paired-pulse TMS. Studies to date in groups of patients with TD have indicated that the cortical silent period (a period of decreased excitability following stimulation) is shortened in TD. This intracortical excitability is frequently seen in children with a tic disorder and co-morbid ADHD (Ziemann et al. 1997; Moll et al. 1999). This heightened level of cortical excitability may be related to the possible reduction in the number of GABAergic interneurons in the cortex (Kalanithi et al. 2005). This may even fit with recent genetic findings in sequence variants involved in the genes that regulate axonal–dendritic development (Abelson et al. 2005).

Fourth, Serrien and co-workers (2005) recently identified similar sensorimotor-frontal connections involved in the acute suppression of involuntary tics as evidenced by increased electroencephalograph (EEG) coherence in the alpha frequency band (8–12 Hz) range during suppression of voluntary movements in individuals with TD compared with healthy subjects during a Go–NoGo task.

Fifth, although initial studies with rTMS targeting motor and premotor sites have had no success in treating TD (Munchau et al. 2002; Orth et al. 2005), two open-label studies which targeted the SMA demonstrated that low-frequency rTMS produced a clinical significant improvement in a small number ($n = 7$) of TD patients (Mantovani et al. 2006; Mantovani et al. 2007).

Finally, the preliminary findings that ablation (or high-frequency stimulation using deep brain stimulation) in regions of the GPi and/or the midline thalamic nuclei can ameliorate tics in severe, persistent cases of TD powerfully support the view that these brain regions are critical elements in the neurobiological circuitry underlying TD (Vandewalle et al. 1999; Zhuang et al. 2004a; Zhuang et al. 2004b; Servello et al. 2008; Welter et al. 2008). In the future, electrophysiological studies may also illuminate the neural basis of behavioral treatments, such as habit reversal training (HRT) (Leckman et al. 2006) and rTMS (Mantovani et al. 2006; Mantovani et al. 2007). The rTMS treatment focuses on disrupting those neural circuits that perpetuate the tics by using low-frequency magnetic stimulation to subdue the overactive motor cortical areas implicated in tic generation. HRT is a behavioral approach focused on helping people with TD become aware of the premonitory urges that precede tics and subsequently developing a competing response that physically prevents completing the tic. With repeated practice, the tic, as well as the premonitory urge, is expected to diminish. An understanding of the neural circuits involved in the pathogenesis of TD will allow treatment providers to better tailor behavioral treatments to more effectively target the tic etiology, not just the tic symptoms. This is important because effective behavioral interventions would be preferable for many individuals with TD.

Animal Models

Future progress in elucidating the pathogenesis and treatment of TD could be greatly accelerated with the development of animal models. At present, animal models of idiopathic paroxysmal dystonia and the introduction of mutant genes into murine models offer the greatest promise (Leckman et al. 2006). If the loss of GABAergic FSINs and the cholinergic TANs is confirmed, then it should be possible to replicate this loss in animal models by producing genetically altered mice in which these interneurons can be selectively altered or eliminated. Observing the behavioral consequences of such a disruption will help us understand the role of these interneurons and how their reduced numbers influence the TD phenotype or cause the disorder itself.

An animal model has already been developed for idiopathic paroxysmal dystonia (dt^{sz} hamsters), in which there is documented a 30–50% loss of this interneuron population (Gernert et al. 2000). Remarkably, the phenotype of these animals includes facial contortions, hyperextension of limbs, and other dystonic postures associated with co-contractions in opposing muscle groups (Loscher et al. 1989), all features seen in severe cases of TD. In addition, these motor symptoms show an age-dependent reduction in severity that is similar to the natural history of TD (Gernert et al. 2002). Finally, Hamann et al. (2007) reported that the spontaneous age-dependent remission of paroxysmal dystonia in older dt^{sz} hamsters (age >90 days) was found to coincide with a normalization of the density of striatal FSINs. Understanding how these cells can be replenished or how their cellular identity can be altered over the course of development could be a major scientific advance in not only the understanding of TD but also in the treatment of the disorder.

Alternatively, the establishment of animal models based on rare genetic variants, such as SLITRK-1, provides a complementary approach (Abelson et al. 2005; Stillman et al. 2009). Finally, animal models using pathogenic stimuli, such as through the passive transfer of autoantibodies in the recently described mouse model of PANDAS also show promise (Yaddanapudi et al. 2009).

Conclusions and Future Prospects

Current conceptualizations of TD 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 postmortem brain studies, systems neuroscience, and functional *in vivo* neuroimaging has set the stage for a major advance in our understanding of TD. 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? In this regard, it will be particularly important to sort out what findings are specific to TD and which are associated with other developmental neuropsychiatric disorders (e.g., ADHD, OCD). Will it be possible to track treatment response using neuroimaging or neurophysiological techniques? The use of higher magnetic fields (3.0 T) in magnetic resonance spectroscopy should allow the detection and quantification of glutamate, glutamine, and GABA peaks in discrete brain regions. This scientific advance should greatly facilitate efforts to develop new pharmacological treatments. And will specific circuit-based therapies using deep-brain stimulation and rTMS emerge as useful interventions to treat refractory cases? As the research continues, one day we will hopefully be able to answer all these questions and more.

Disclosures

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