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Tourette syndrome: A relentless drumbeat

- driven by misguided brain oscillations

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Abstract

Background: This annotation reviews recent evidence that points to the likely role of aberrant neural oscillations in the pathobiology of Tourette syndrome (TS). **Methods:** The available anatomic and electrophysiological findings in TS are reviewed in the context of an emerging picture of the crucial role that neural oscillations play in normal CNS function. **Results:** Neurons form behaviour-dependent oscillating networks of various sizes and frequencies that bias input selection and facilitate synaptic plasticity, mechanisms that cooperatively support temporal representation as well as the transfer and long-term consolidation of information. Coherent network activity is likely to modulate sensorimotor gating as well as focused motor actions. When these networks are dysrhythmic, there may be a loss of control of sensory information and motor action. The known electrophysiological effects of medications and surgical interventions used to treat TS likely have an ameliorative effect on these aberrant oscillations. Similarly, a strong case can be made that successful behavioural treatments involve the willful training of neurons in the prefrontal cortex to engage in tic suppression and the performance of competing motor responses to unwanted sensory urges such that these prefrontal regions become effective modulators of aberrant thalamocortical rhythms. **Conclusions:** A deeper understanding of neural oscillations may illuminate the complex, challenging, enigmatic, internal world that is TS for those afflicted.

Keywords: Tourette syndrome, Cognitive therapy, EEG, basal ganglia, thalamocortical dysrhythmia, habit reversal training

"*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, do not receive strict internal commands to trace with their eyes in midair the shape of each of Plato's regular solids, 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, 1999

Introduction

Tic disorders have been the subject of speculation for at least the past 300 years. Over the past 25 years, Tourette syndrome (TS) with its covert drumbeat of sensorimotor urges and its overt motor and vocal tics has come to be recognized as a model developmental disorder occupying the nexus of neurology, psychiatry, and psychology (Leckman, 2002). Its natural course, the identification of structural brain abnormalities involving the basal ganglia in neuroimaging studies (Peterson et al., 2003), the possibility of a post-infectious form of the disorder (Swedo et al., 1998), and the increasing appreciation of the interaction of genetic and environmental factors in disease expression have all contributed to making TS a model for understanding developmental psychopathology more broadly. The reality for patients is that TS can be a devastating condition, which alone, or in combination with other closely associated psychopathology, causes them and their families considerable suffering. For these

reasons, the search for a clearer understanding of disease aetiology and need for new approaches to treatment and prevention are vitally important.

Despite the overt nature of tics and decades of scientific scrutiny, our ignorance remains great. Notions of cause have ranged from "hereditary degeneration" to the "irritation of the motor neural systems by toxic substances, of a self-poisoning bacteriological origin" to "a constitutional inferiority of the subcortical structures… [that] renders the individual defenseless against overwhelming emotional and dynamic forces" (Kushner, 1999). Predictably, each of these aetiological explanations has prompted new treatments and new ways of relating to families. This annotation reviews recent evidence that points to the role of developmental and epigenetic processes that influence the functioning of the basal ganglia and related cortical and thalamic regions.

The hypothesis that TS is the result of aberrant neural oscillations is introduced (Table 1). Although the functional significance of oscillations remains to be elucidated in TS, advances in this area will likely shed light on the pathophysiology of a range of neuropsychiatric and movement disorders (Buzsáki, & Draguhn, 2004; Castellanos et al., 2005; Llinás, Ribary, Jeanmonod, Kronnberg & Mitra, 1999) and solve some of the puzzles of why certain cognitive-behavioural, pharmacological, and therapeutic surgical interventions are efficacious.

Insert Table 1 about here

Neural substrates of habit formation, motor control and tics

Habits are assembled routines that link sensory cues with motor actions. Understanding the neural substrates of habit formation and procedural learning may lead to a better understanding of TS (Leckman & Riddle, 2000). While no direct causal link between tics and habits has been established, a recent study of more than 50 children and adults with TS found that they had impaired habit learning relative to normal controls. Intriguingly, their acquisition rate of a procedural learning task correlated inversely with the severity of tic symptoms (Marsh et al., 2004). Similarly, Kéri, Szlobodnyik, Benedek, Janka, & Gadoros, (2002), found reduced probabilistic classification learning in children with TS. In addition to difficulties with procedural learning, patients with TS have consistently shown difficulties with fine motor control and visual motor integration (Schultz et al., 1998). Perhaps the most striking observation is the recent finding that poor performance with the dominant hand on the Purdue Pegboard test during childhood modestly predicts worse adulthood tic severity (Bloch et al., in press).

Investigators interested in procedural learning, habit formation and internally and externally guided motor control have focused their attention on multisynaptic neural circuits or loops that link the cerebral cortex with several subcortical regions (Graybiel & Canales, 2001; Middleton & Strick, 2003). These circuits direct information from the cerebral cortex to the basal ganglia, cerebellum and thalamus, and then back to specific regions of the cortex, thereby forming multiple cortical-subcortical loops (Figure 1).

Insert Figure 1 about here

A closer look at the striatum. Cortical neurons projecting to the striatum outnumber striatal medium spiny neurons by about a factor of ten (Zheng & Wilson, 2002). These 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 and relative striatal locations (Figure 1). The striosomal medium spiny projection neurons (SSs) are preferentially located in the ventromedial striatum and mainly receive convergent limbic and prelimbic inputs. In contrast, the medium spiny neurons in the matrix (MSs) are positioned in the dorsal lateral striatum and mainly receive convergent input from ipsilateral primary motor and sensory motor cortices and contralateral primary motor cortices. The response of particular medium spiny projection neurons in the striatum is partly dependent on perceptual cues that are judged salient, so rewarding and aversive stimuli can both serve as cues (Canales & Graybiel, 2000). GABAergic medium spiny neurons (SSs plus MSs, Figure 1) account for nearly 95 percent of all neurons in the striatum of rodents but somewhat less than 80 percent in humans and other primates (Holt, Graybiel, & Saper, 1997).

Several other less abundant striatal cell types probably have a key role in habit learning and motor control, including cholinergic tonically active neurons (TANs) and fast-spiking GABAergic interneurons ([FSNs], Blazquez, Fujii, Kojima, & Graybiel, 2002; Gonzalez-Burgos, Krimer, Povysheva, Barrionuevo, & Lewis, 2005; Jog et al., 1999). The TANs are responsive to dopaminergic inputs from the substantia nigra, pars compacta (SNc) and these signals probably participate in calculation of the perceived salience (reward value) of perceptual cues along with excitatory inputs from midline

thalamic nuclei (Figure 1). While the dopamine neurons' response reflects a mismatch between expectation and outcome, the TANs are invariant to reward predictability (Morris, Arkadir, Nevet, Vaadia, & Bergman, 2004).

The FSNs of the striatum receive direct cortical inputs, including the primary motor and somatosensory cortex, and they are highly sensitive to cortical activity in these regions (Figure 1, McGeorge & Faull, 1989). They are also known to have a very extensive axonal collateral network and to be electrically coupled via gap junctions that connect adjacent dendrites. This property means that several of these cells can function as a unit and elicit synchrony throughout the dorsolateral striatum. Once activated, these FSNs inhibit many matrisomal striatal projection neurons via synapses on cell bodies and proximal dendrites (Kita, Kosaka, & Heizmann, 1990; Koos & Tepper, 1999). These synaptic locations indicate that these FSNs can powerfully inhibit the MSs and elicit widespread rebound synchronous excitation. We also note that the characteristic electrophysiological properties of the striatal FSNs—e.g. irregular bursting with stable intra burst frequencies—are reminiscent of temporal patterning of tics (Peterson & Leckman, 1998).

Oscillatory brain activity and habit formation. Although we have relatively little understanding of how patterns of neuronal activity are transmitted and transformed, they are likely to be fundamentally important with regard to the emergence of goal directed behaviour and the formation of habits. As with respiration and the sleep-wake-cycle, goal directed behaviour and expression of habits are likely to depend upon the oscillatory activity of groups of neurons (Table 1, Steriade, & Timofeev, 2003). These

oscillations are phylogenetically preserved and appear to be an essential feature of neural function (Buzsáki & Draguhn, 2004).Their synchronization with phase-locking and frequency stabilization can be seen as a resonance phenomenon of the brain. Selectively distributed oscillatory systems of the brain exist as resonant communication networks through large populations of neurons, which work in parallel and are interwoven with sensory, motor, cognitive and emotional functions (Basar et al., 2001). These oscillating neural networks can bias input selection and induce synaptic plasticity and thus serve to consolidate learning, habit formation and long term memory (Buzsáki & Draguhn, 2004). For example, there is spontaneous, anatomically restricted thalamocortical oscillatory electrical activity near 40 Hz (gamma band). This activity is related to motor and cognitive processing in response to sensory information (Yordanova et al., 2002). The speed and spatial distribution of these high frequency oscillations is likely to support the representations that form the content of our subjective conscious experience (Llinás, 2001). This band of oscillatory electrical activity has also been implicated in the fMRI BOLD response in the human cerebral cortex (Mukamel et al., 2005; Niessing et al., 2005). Since these oscillations increase in power with the synchrony of cortical synaptic events, it appears likely that there is a close correlation between the extent of hemodynamic responses and neuronal synchronization. Networks of cortical FSN GABAergic interneurons (functionally similar to those present in the striatum) appear to play a major role in generating and maintaining high frequency gamma oscillations in the cortex by eliciting rebound synchrony in cortical pyramidal cells (Hasenstaub et al., 2005).

Oscillatory activity has long been recognized in the electroencephalogram (EEG), in which synchrony between thalamus and cortex can be observed in different frequencies. These oscillations span five orders of magnitude in frequency and are usually sub-divided into types on the basis of their characteristic frequencies: delta (< 2 Hz), theta (~2-7 Hz), alpha (~8-12 Hz), beta (~15-30 Hz) and, gamma (30-80 Hz).

Recent evidence suggests that normally occurring rhythmic oscillatory activity within basal ganglia circuits plays a key role in the emergence and performance of voluntary actions and habits. For example, Courtemanche, Fujii and Graybiel (2003) observed synchronized oscillatory activity in the range of 15-30 Hz (beta band) within the striatum of awake squirrel monkeys. They suggest that broadly synchronous oscillatory activity interfaces with specific spatio-temporal patterns of task related activity. These oscillations in the basal ganglia also appear to be linked with electric activity from regions of the prefrontal and mesiofrontal cortices during the repetitive performances of learned behaviours (Fujii & Graybiel, 2005).

A similar band of synchronous activity in the range of 15-25 Hz has also been reported in task related recordings from rodents (Berke, Okatan, Skurski, & Eichenbaum, 2004). Intriguingly, this rodent study also reported synchronous activity in the striatum during task performance at two other frequencies, 7-9 Hz and 45-55 Hz. The 7-9 Hz rhythm was observed primarily in the ventral medial striatal regions and was entrained with the theta rhythm of the hippocampus. Similar theta rhythm oscillations have been documented in the amygdala regions suggesting that activity in limbic regions may also influence the activity of neurons in the ventral striatum (Páre & Gaudreau, 1996).

In contrast to the range oscillations observed during goal directed behaviour, during periods of rest the predominant activity is relatively slow. For example, Berke and colleagues (2004) also observed the episodic entrainment of dorsal lateral striatal MSs to slow (~8 Hz), high-voltage spindle oscillations ("spike wave discharges") over wide regions of the frontal and somatosensory cortices while the animals were “at rest.” Several investigators have that the FSNs fire earlier than the main neuronal population of the dorsal lateral striatum, both during slow and fast gamma-band activity, suggesting that the FSNs were instrumental in orchestrating the oscillatory activity of the MSs in the dorsal lateral striatum (Figure 1) (Berke et al.,2004; Mallet, Le Moine, Charpier, & Gonon, 2005).

In sum, these observations suggest that depending on the state of the animal (sleeping; awake, but at rest; or involved in a specific goal-directed task), different regions of the basal ganglia oscillate in synchrony with specific cortical and thalamic regions. They also suggest that oscillations involving the basal ganglia can influence thalamocortical oscillatory activity.

Connectivity modeling of the subthalamic nucleus (STN) and the output structures of basal ganglia (primarily the globus pallidus, pars interna [GPi], and the pars reticulata of the substantia nigra [SNr]) indicates that slow oscillations observed at rest may also arise as a property of neuronal networks within the basal ganglia (Ruskin, Bergstrom, Tierney, & Walters, 2003). Two types of slow oscillations have been described. Oscillations at 0.3-2 Hz were observed in basal ganglia recordings of both local field potential and single-unit activity in anesthetized rodents. In addition, ultraslow, multisecond oscillations (2-60 sec and longer) were also frequently seen in recordings

from awake, immobilized and partially restrained rats. These ultraslow oscillations appear to be particularly sensitive to increases in dopaminergic stimulation, resulting in a greater degree of coherence both within and between various output nuclei of the basal ganglia (Ruskin et al., 1999; Ruskin et al., 2003). Dopamine agonists also decreased the oscillation period in both the GPi and the SNr as well as increasing the oscillation amplitude in the GPi, but not the SNr. Recently, Foffani, Bianchi, Baselli, & Priori (2005) were able to show, using recordings from deep brain stimulation electrodes implanted in patients with Parkinson's disease, that frequency modulation beta rhythms within the STN are significantly associated with movement preparation, execution and recovery, and that these frequency modulations are regulated by the dopamine levels in the system.

In addition to cortical and subcortical oscillations, oscillations of the olivo-cerebellar system are likely to also play a pivotal role in the temporal control of movement execution including tics (Kazantsev, Nekorkin, Makarenko, & Llinás, 2004; Llinás, 2001). Recently, Courtemanche and Lamarre (2005) have documented the presence of 10-25 Hz synchronous oscillations electrically linking the cerebellum with primary motor cortex and primary somatosensory cortex during task performance.

Hypotheses

The prevailing theory concerning the pathophysiology of TS is that there is an increased activity of the inhibitory direct pathway connecting the basal ganglia striatal input to its output in the GPi and decreased activity in the indirect pathway via the external globus pallidum (GPe) and STN. The net effect of this imbalance between the pathways is to

reduce the firing rate of inhibitory neurons in GPi that project to important premotor structures, such as the thalamus. Disinhibition of premotor centers provides the anatomical basis for the emergence of tics (Albin, Young, & Penney, 1989; Rothenberger, 1991). A prediction of this model of TS and other hyperkinetic movement disorders such as dystonia and chorea is that these disorders are associated with low firing rates in GPi output neurons. However, recent observations indicate that the GPi activity seen in dystonia and tic disorders is similar to that in Parkinson's disease (Hutchison, Lang, Dostrovsky, & Lozano, 2003; Marsden & Obeso, 1994; Zhaung, Li, & Hallett, 2004a; Zhaung, Hallett, Zhang, & Li, 2004a), thus challenging the prevailing wisdom. Similarly, the therapeutic inactivation of GPi, either by high-frequency stimulation or ablative surgery, improves tics and dyskinesias as well as parkinsonism (Houeto et al., 2005; Marsden & Obeso, 1994; Zhaung et al., 2004a).

These contradictions taken together with the evident functional importance of *oscillatory processes* have led us to hypothesize that firing rate models may not be enough to explain the complexity brain functioning and that one or more of these oscillatory processes are aberrant in TS and related disorders.

***Hypothesis 1*: Loss of basal ganglia control.** In TS, we hypothesize, first, that “at rest” clusters of MSs associated with tics in the dorsal lateral striatum become disengaged from their usual episodic strong entrainment to synchronized oscillatory activity. This disengagement may mediate in part the relentless drumbeat of sensory information that besieges the conscious mind of the individual with TS. We propose that this vulnerability to autonomous disengagement may be due to a number of factors

including a relative loss of FSNs in the striatum leading to an increased effect of cortical sensory inputs to the MSs.

***Hypothesis 2*: Thalamocortical dysrhythmia.** Next, we hypothesize that the normal patterns of discharge from the basal ganglia output nuclei are finely modulated oscillations, and that these oscillations are disrupted similarly to what is seen in patients with dystonia. The irregular bursting of the GPi projection neurons would transiently hyperpolarize selected thalamocortical neurons, causing them to transiently increase the amplitude of their high-frequency membrane potential oscillations (20-80 Hz) which in turn would lead to the ectopic activation of selected cortical pyramidal neurons, leading to the overt and/or subliminal perception of premonitory urges and the performance of tics.

***Hypothesis 3*: Frontal lobe compensation.** We hypothesize that compensatory systems originating in the prefrontal cortex (PFC) adaptively modulate the misguided striatal and thalamocortical oscillations that are characteristic of TS. Repeated activation of these frontal systems can lead not only to tic suppression, but also to a willful alteration of the character of the movements involved.

Evidence in support of Hypothesis 1. Preliminary anatomical, neurosurgical, and psychopharmacological evidence from TS patients as well as data from animal models provide support for our first hypothesis. The quantitative anatomical examination of the brains of three individuals severely affected with TS revealed altered numbers of FSNs

in the striatum, among other abnormalities (Kalanithi et al., 2005). The number of FSNs (identified by their immunoreactivity for the calcium-binding protein parvalbumin [PV]) was reduced by 54 percent in the striatum and by 39 percent in the caudate and putamen (Figure 1). In accordance with our first hypothesis, the loss of these FSNs cells would allow clusters of MSs within the somatotopic areas associated with tics to become disengaged from the high-voltage spindle oscillations and to become relatively autonomous, giving rise to tics.

Physiological studies demonstrate that the cerebral cortex use FSNs to exert powerful feed-forward inhibition upon MSs (Mallet et al., 2005), suggesting that this inhibitory system with its ensuing oscillatory activity may be used to suppress and filter out of consciousness unattended patterns of activity. Hence, we also predict that with the disruption of the basal ganglia oscillation that many TS patients would be easily distracted and would have difficulty performing the saccade tasks similar to those described by Courtemanche et al. (2003). This, indeed, appears to be the case as documented by Nomura, Fukuda, Terao, Hikosaka, & Segawa (2003) and their study of saccades in more than 100 children and adolescents with TS.

A decreased inhibitory influence of FSNs over MSs could allow the cortical sensorimotor inputs to more easily activate MSs, eliciting the premonitory urges experienced by individuals with TS (Leckman et al., 1993; Banaschewski, Woerner & Rothenberger, 2003). This speculation is consistent with the hypothesis that sensory inputs guide the basal ganglia in action selection and that such sensory inputs can switch selected regions of the cortex-basal ganglia circuitry from an “idling state” characterized by the high voltage spindles to an active state characterized by gamma

band synchrony (Brown & Marsden, 1998). It would also seem likely that because the FSNs play a key role in the flexible entrainment of a variety of oscillatory patterns in the basal ganglia, inappropriate tic-related oscillations(in the gamma band) involving the sensorimotor cortex and the basal ganglia, would be more readily established when fewer inhibitory FSNs are present. Over time, tics may lead to fixed patterns of synchronous oscillations within the gamma band (possibly because of aberrant patterns of synaptic plasticity?). These tic-specific patterns would be likely to interfere with normal functioning of these circuits, e.g., procedural memory tasks, and it has been documented that individuals with TS have deficits in this arena of cognitive function (Kéri et al., 2002; Marsh et al., 2004).

Premonitory sensory phenomena are quite often subjectively located in peripheral muscle groups, indicating that there exists some subliminal sensory registration, which may serve as feedback to the brain. Such thalamocortical circuit activity may increase slowly in amplitude and finally give rise to a tic-specific fixed action pattern of thalamocortical oscillatory activity that becomes increasingly difficult to inhibit once a certain intensity has been reached. It seems likely that the premonitory urges arise at the thalamic level (perhaps as a result of faulty GPi activity), and it is probable that other circuits active during central-peripheral feedback processes may play a role in tic occurrence (Rothenberger, 1991).

In addition to these neuropathological findings, neurosurgical procedures used to treat refractory cases of TS also support our first hypothesis. It has been recently reported that deep brain stimulation (or the lesioning) of the intralaminar nuclei of the thalamus may work by re-establishing more normal, tic-suppressing oscillatory patterns

via its effect on TANs and the indirect stimulation of the FSNs in the striatum (Figure 1, Temel & Visser-Vandewalle, 2004).

Although ideal anti-tic treatments are not presently available, there is a large body of data that indicates that agents that potently block postsynaptic D_2 receptors can be helpful in achieving a reduction in the severity of tics in some cases. Pimozide, haloperidol, sulpiride, and tiapride are the most frequently used typical neuroleptics, whereas risperidone and ziprasidone are two atypical neuroleptics with proven tic-suppressant efficacy (Scahill et al., 2004). Remarkably, intrastriatal injections of dopamine D_2 receptor antagonists (but not D_1 receptor antagonists) *greatly increase* the incidence of the cortical high-voltage spindles (Buzsáki, Smith, Berger, Fisher, & Cage, 1990; Semba & Komisaruk, 1984). The beneficial effects of alpha adrenergic agonists on tics are more controversial (Scahill et al., 2004), but these agents have also been reported to *increase* the incidence of the anti-kinetic cortical high-voltage spindles (Riekkinen, Lammintausta, Ekonsalo, & Sirvio, 1992).

Finally, the functional significance of the loss of these neurons is manifest in an animal model of idiopathic paroxysmal dystonia in which there is a 30 percent to 50 percent loss of the FSN 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 TS. In addition, these motor symptoms show an age-dependent reduction in severity that is similar to the natural history of TS (Gernert, Bennay, Fedrowitz, Rehders, & Richter, 2002). Hence, maturational effects of basal ganglia and frontal lobes leading to better entrainment of the FSN inhibitory

system in cortex and striatum might explain to a certain extent the reduction of tics in late adolescence.

Evidence in support of Hypothesis 2. Circumstantial evidence derived from intra-operative recordings from patients with severe dystonia and patients with refractory TS, postmortem brain studies, and animal models of hyperkinetic movement disorders provide limited support for our second hypothesis. Single unit intra-operative recordings have been performed in both dystonic and severe tic disorder patients with similar results – the clear presence of altered neuronal slow activity including grouped discharges in the GPi that were in turn correlated with the EMG signals at the frequency of the abnormal movements in the range of 0.12 to 0.84 Hz (Vitek et al., 1999; Zhuang et al., 2004a; 2004b). Remarkably, abolishing this activity through electrolytic lesions in the GPi resulted in an immediate improvement of tics (Zhuang et al., 2004a) as well as severe dystonia (Lozano et al., 1997; Vitek et al., 1998). Similar benefits have been reported following bilateral deep brain stimulation of the GPi in a single TS patient (Houeto et al., 2005).

The synchronous ultra-slow activity in the multi-second range (2-60 sec and longer) that is found in the GP of experimental animals (Ruskin et al., 2003) may also be dysregulated in TS. These oscillations are very sensitive to the presence of dopamine agonists and substantial evidence exists for a heightened dopaminergic innervation of the basal ganglia in some individuals with TS (Albin et al., 2003; Cheon et al., 2004; Heinz et al., 1998; Malison et al., 1995; Singer, Hahn, & Moran, 1991; Singer et al., 2002; Stamenkovic et al., 2001; Wolf et al., 1996). Remarkably, chronic

administration of apomorphine in rats for one year is associated with multiweek oscillations in the frequency of stereotypies (Csernansky, Csernansky, King, & Hollister, 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 (Leckman et al., 1998; Peterson & Leckman, 1998). These multisecond oscillations have also recently been implicated by Castellanos, Sonuga-Barke, Scheres, Di Martino, Hyde, & Walters (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.

In addition, recent preliminary postmortem studies of the brains from individuals with severe TS provide further indirect evidence that the electrical activity in the pallidum may be aberrant. The most extraordinary finding from the same postmortem study discussed above (Kalanithi et al., 2005) was the *120 percent increase* in the PV-positive GABAergic projection neurons in the GPi (coexisting with the decrease of striatal interneurons, see above) in the three patients with extremely severe TS. The functional consequences of this increase are as yet unclear, but it would not be surprising if this increase led to the “irregular neuronal activity with grouped discharges” described by Zhuang et al. (2004b). We predict that this abnormally slow and irregular discharge pattern from the GPi would transiently hyperpolarize their target thalamocortical neurons causing them to reset the phase and transiently increase the amplitude of high-frequency membrane potential oscillations (20-80 Hz) (Figure 1, Pedroarena & Llinás, 1997) which in turn would lead to the aberrant activation of a

selected pattern of cortical pyramidal neurons and the overt perception of premonitory urges and tics.

In addition to the striatum and the GPi, Kalanithi et al. (2005) also found that the number of neurons in the GPe was significantly reduced by approximately 45 percent in the three postmortem brain specimens. Since the GPe inhibitory neurons directly project to the GPi, this reduction could likely contribute to the abnormal electrical activity in GPi noted above.

In the *dt*^{sz} hamsters, whose phenotype closely resembles severe TS and is characterized by a loss of striatal FSNs, there is an age-dependent shift toward grouped-irregular and burst-like firing in the EPN but not in the SNr (Gernert et al., 2002). Unfortunately, whether these animals show an increase in PV-positive neurons in the EPN has not been determined. We also note that these same animals show a marked increase in their symptoms following systemic or striatal injections of amphetamine or dopamine D_2 agonists and a moderate decrease in symptoms (~33 percent) following the systemic administration of the D_2 antagonist raclopride (Rehders, Loscher, & Richter, 2000). These findings are not too dissimilar to those seen in TS patients treated with D_2 antagonists (Scahill et al., 2004). These animals also show an increase in D_2 receptor binding in the shell of the nucleus accumbens (Nobrega, Richter, Tozman, Jiwa, & Loscher, 1996), a finding that may be consistent with the observations of Wolf and colleagues (1996).

Evidence in support of Hypothesis 3.

Surface EEG recordings, functional and structural neuroimaging studies, as well as the recent success of Habit Reversal Training in the treatment of mild to moderate tics all provide circumstantial support for our third hypothesis. Serrien and co-workers (2005) recently identified sensorimotor-frontal neuronal activity apparently involved in the acute suppression of involuntary tics, as evidenced by increased EEG coherence in the alpha frequency band (8-12 Hz) range during suppression of voluntary movements in individuals with TS compared with healthy subjects during a Go-NoGo task. Unfortunately, the specificity of this oscillatory system is unclear, since it was the only one investigated. Earlier Rothenberger (1990, 1995) found a frontal shift of *Bereitschaftspotential*, a movement-related cognitive potential indicative of motor preparation, when tic patients performed a voluntary movement, which was normalized after intake of D_2 receptor blockers. Both of these clinical studies point to a dynamic circuit involved in normal inhibition of movement that is increased in activity in TS and which can be further activated acutely in the voluntary suppression of tics.

Tic suppression has also been studied using functional MRI (Peterson et al., 1998). This study revealed a consistent pattern of activations (right frontal cortex, right caudate nucleus and regions of the cingulate and temporal cortices) and deactivations bilaterally in subcortical areas (putamen, GP, and thalamus). Remarkably, increased activity in the right frontal cortex was associated with increased activity in the right caudate nucleus, and increased activity in the right caudate nucleus in turn was associated with greater decreases in activity of the GP, the putamen, and the thalamus during tic suppression (Figure 1). The decreased activities of the GP and the putamen were correlated, and both positively predicted thalamic activity. Equally impressive is the

fact that the levels of activation (right caudate) or deactivation (putamen, GP, and thalamus) during periods of tic suppression were correlated with the individual's current level of tic severity outside the magnet.

The brain regions that are activated during tic suppression are virtually identical to those that have been described as belonging to a distributed neural circuit that participates in the inhibition of unwanted impulses (Goldman-Rakic, 1987). This circuit consists of the prefrontal, parietal, temporal, and cingulate cortices, which are thought to modulate the activity in the basal ganglia and thalamus. Precisely how this circuit inhibits inappropriate responses allowing the desired behavioural responses in the motor cortex to occur is not entirely clear. We suggest that this regulation depends upon the integration and cross talk of the prefrontal circuits with the sensorimotor circuits in the basal ganglia and thalamus leading to an enhanced parallel synchronization of different oscillatory systems in motor cortex and basal ganglia depending on the task. This is more difficult in children with tics, since they show a general motor circuit inhibitory deficit, which in adults is confined to the very circuit related to the observable tics (Moll, Heinrich, Gevensleben, & Rothenberger, 2005).

Persistence of tic symptoms into adulthood may reflect a failure of this circuitry to operate properly because of anatomical limitations. For example, two groups of investigators have independently documented that smaller caudate volumes are a trait marker for TS (Hyde, Aaronson, Randolph, & Weinberger, 1995; Peterson et al., 2003). We note in passing that the animal model that most closely resembles severe TS also has a 13 percent reduction in striatal volume (Gernert et al., 2000). It appears that the smaller an individual's caudate is in childhood, the more likely they are to have

persistent tics into adulthood (Bloch et al., 2005). The nature of this volume reduction is being studied in postmortem tissue using unbiased stereological methods. Whether there are other findings besides the 50 percent reduction in the number of PV-positive FSNs awaits future investigations. One would also speculate that frontal abnormalities such as those seen in ADHD might limit an individual's ability to mobilize this inhibitory system (Booth et al., 2005; Filipek et al., 1997; Frederickson et al., 2002). In the individuals that are able to compensate, one might also expect to see prefrontal hypertrophy in an effort to regulate tic symptoms (Peterson et al., 2001) as well as other adaptive changes in other structures including the corpus callosum (von Plessen et al., 2004).

We also posit that it is via this distributed neural circuit that treatments such as Habit Reversal work in some cases of TS (Wilhelm et al., 2003). The presence of premonitory sensations distinguishes TS from other movement disorders such as Parkinson's disease, Huntington's chorea, and hemiballismus. Acutely aware of their premonitory urges, many adult patients report (or can be taught) that they can inhibit tics or change the tic through a variety of behavioural strategies like *competing motor responses* (alternative actions that are by their nature incompatible with the performance of a specific tic) made in response to the premonitory urges.

In agreement with Woods et al. (2003), we regard the competing response as a voluntary act that requires attention. We further contend that the PFC, applying a competing response contingent on actual tic occurrence over time uncouples the discriminative stimulus (i.e., the premonitory urge) from the performance of the tic. How this willful act affects this outcome is unclear and raises metaphysical questions beyond

the scope of this annotation (Nagel, 1974; Schwartz & Begley, 2002; Schwartz, Stapp, & Beauregard, 2005). By increasing the input from prefrontal areas it may be possible to alter the functional association of premonitory urge and tic expression and diminish the power of the urge to initiate the vicious cycle of tics and urges via the various nigral, pallidal, and cerebellar channels. Lastly, relaxation training is conducted to reduce the amplitude of peripheral-central sensorimotor feedback and probably diminishes limbic afferent inputs to the striatum to decrease dopaminergic tone from the SNc. We predict that if surface EEG recordings (analyzed with recent three dimensional localization algorithms) or functional MRI studies of tic suppression were completed before and after successful Habit Reversal Treatment we would see both a further increase in frontomesial EEG coherence in the alpha frequency band (8-12 Hz) after training, as well as a larger area of neural activation both in the right prefrontal area and in the right caudate nucleus, similar to what is seen after neurofeedback training in ADHD (Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004). Further, reduction of tics in patients with TS plus ADHD while taking either methylphenidate (a dopamine agonist) or atomoxetine (a norepinephrine agonist) might be explained by an increase of dopamine in frontal cortex by both substances (Banaschewski, Roessner, Dittmann, Santosh, & Rothenberger, 2004).

Are these hypotheses testable?

We posit that tics are governed by a multiplicity of factors that influence oscillatory patterns within basal ganglia networks, particularly those that interface with frontal, limbic, and cerebellar circuits. This model has generated three hypotheses that are

consistent with the available scientific literature and that contain many testable elements.

First, studies using magneto-encephalography (MEG) and dense array EEG offer considerable promise particularly when applying these techniques before, during and after various cognitive-behavioural, pharmacological and neurosurgical treatments. One key prediction from our first hypothesis is that,at baseline, the number of high voltage spindles (or the beta band oscillations) will be reduced in the basal ganglia of individuals with TS, and that when present, smaller regions of the frontal and somatosensory cortices will participate in these oscillations. We predict that the number of high voltage spindles will increase following successful treatment with both dopamine D2 antagonists and alpha 2 adrenergic agonists.

Our second hypothesis can also be directly tested using MEG and dense array EEG recordings (Jeanmonod et al., 2003). Compared to age matched controls we would expect to see evidence of thalamocortical dysrhythmia as evidenced by an increase of MEG power at the theta-delta interface and an associated increase of coherence both within this domain and between it and the beta-range (Llinás et al., 2005). We also predict that individuals whose tics remit in adulthood will show less thalamocortical dysrhythmia than adults with active TS. Similarly, recordings of neural oscillations before, during and after neurosurgical interventions for adults with severe, persistent, refractory, self injurious tics will likely lead to a better understanding of these phenomena.

Our third hypothesis is best tested in the context of Habit Reversal Training. We predict that successful Habit Reversal Training will lead to enhanced alpha coherence

between prefrontal, mesiofrontal, sensorimotor and motor cortical regions as measured using MEG and dense array EEG. We also anticipate that charting the developmental time course of measures of alpha coherence, and the volume and myelinization status of various cortical regions, particularly the dorsal lateral and mesial prefrontal regions, may advance our understanding of the neurobiological determinants of the natural history of TS.

In addition to studies of patients with TS across the lifespan, much work remains to be done, including a replication and extension of the ongoing postmortem studies, to include cortical, thalamic, as well as cerebellar brain regions. In addition, the causative mechanisms underlying the changes in the number of PV-positive FSNs in the striatum and GABaergic projection neurons in the globus pallidus have not been identified and warrant further study. One lead worthy of pursuit is that many of these PV-positive FSNs originate in the medial ganglionic eminence during embryonic CNS development. Could genetic vulnerabilities and/or adverse events arising at a specific point in development lead to the altered distribution of these PV-positive neurons and an increased risk for developing TS? If a developmental process is responsible, we would also predict that PV-positive interneurons in various cortical regions might be diminished as they are also born in the median ganglionic eminence (Anderson, Marin, Horn, Jennings, & Rubenstein, 2001). Indeed, a relative reduction in this population of interneurons could account for the shortening of the cortical silent period following transcranial stimulation in adults and children with TS (Moll et al., 1999, 2005; Ziemann, Paulus, & Rothenberger, 1997). One possible environmental culprit might be perinatal hypoxia, as the FSNs appear to be particularly sensitive to ischemic insults (Larsson,

Lindvall, & Kokaia, 2001). Transient episodes of hypoxic stress or fetal distress during the perinatal period are not uncommon in the histories of individuals with severe and/or persistent TS (Leckman et al., 1990; Burd, Severud, Klug, & Kerbeshian, 1999; Eapen, Fox-Hiley, Banerjee, & Robertson, 2004; Kano, Leckman & Pauls, 2002). Early hypoxic stress may also have some impact on the subcortical dopamine systems that may result in an increased dopaminergic innervation of the striatum (Boksa & El-Khodor, 2003). However, despite these early abnormalities in basal ganglia systems in the preschool and primary school years, there is often sufficient developmental adaptive capacity to normalize these systems later in development from 6 to 16 years (Rothenberger, Woerner, & Blanz, 1987). The mechanisms that underlie the adaptive capacity are currently unclear. Two processes that could play a role are an increased myelinization of prefrontal regions and compensatory increased postnatal generation of inhibitory interneurons (Dayer, Cleaver, Abouantoun, & Cameron, 2005), which could both contribute to increased functional capacity of these frontal regions . This speculation is also consistent with the observation by Peterson et al. (2001) that adult patients with persistent TS have smaller dorsal lateral prefrontal cortices than do controls and that on average children with TS have larger dorsal lateral prefrontal cortices than do age matched healthy subjects, suggesting that increased myelinization or inhibitory neuron number may underlie frontal compensation leading to tic improvement during the second decade of life.

Third, further characterization of promising animal models as well as the development of new animal models will be a crucial step forward. The *dt*^{sz} hamster mutant appears to show the greatest promise, with its similar age-dependent

phenotype, the comparable loss of striatal FSNs, and responsiveness to D2 antagonists (Gernert et al., 2000; 2002; Nobrega et al., 1996; Rehders, Loscher, & Richer, 2000). Determination of the recessive gene(s) that are responsible for this phenotype is an important goal. It will also be important to document whether or not there are any changes in the occurrence or distribution of the high voltage spindles in these animals. Anatomical studies of the number of PV-positive neurons in the output structures of the basal ganglia are also indicated. It may also be of interest to model in mice the genetic susceptibility that underlies an increased risk of developing greater losses in inhibitory interneurons after perinatal adverse events, as well as those genes that may promote an increased recovery during childhood and adolescence. Finally, we are enormously hopeful that animal models which incorporate the genetic abnormalities reported in four TS probands will demonstrate at least in part the pathophysiological features discussed here (Abelson et al., 2005).

Lastly, the exploration of the aberrant oscillations of TS may provide deeper insights into the functional significance of these oscillations in the anticipation and performance of “normal” actions, thoughts and emotions as well as into the brain’s interface with the subjective realities of conscious experience over the course of development (Llinás, 2001).

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Acknowledgements

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Table 1: Definitions†

Term	Definition
Magnetoencephalography (MEG)	Every current generates a magnetic field. ***MEG*** measures the intercellular currents of the neurons in the brain, spontaneously or in response to a given sensory stimulus or task performance.
Neural Oscillations	***Oscillation*** is the periodic variation, typically in time, of some measure as seen, for example, in a swinging pendulum. In the case of neural oscillations it is the periodic variation seen in the firing of neurons measured by electrical current or using a MEG device. Even single neurons are endowed with complex dynamics, including their intrinsic abilities to oscillate at multiple frequencies which suggest that precise timing of their activity within neuronal networks could represent information.
Synchrony	Integration of neural information requires ***synchrony*** of the convergent inputs. Synchrony is defined by the temporal window within which an earlier electrical event is retained and integrated by the neurons with a subsequent event. Although synchronous neurons can be generated by

	common inputs, or by inhibitory modulation, oscillation-based synchrony is the most energy-efficient means for temporal coordination of nerve cells. Neurons are thought to function as "coincidence detectors". Some investigators have suggested that the subjective experiences of perception, memory, and consciousness could result from synchronized networks. The synchronous activity of oscillating networks is now viewed as the critical "middle ground" linking single-neuron activity to behaviour.
Coherence & phase	***Coherence*** is a constant phase difference in two or more waves over time. Two waves are said to be in phase if their crests and troughs meet at the same place at the same time, and the waves are out of phase if the crests of one meet the troughs of another. The waves are incoherent if the crests and troughs meet randomly. Long-term behaviour of neural systems can be predicted from short-term observations of their ***phase*** angle. The phase angle is the number of degrees (between 0^o and 360^o) between a point on the wave and a reference point. Oscillations generated by neurons can

	separate the information transfer phase from the receiving phase. Two different populations of neurons can robustly oscillate synchronously with great stability. These features of brain oscillators make their time course predictable and their phase easy to reset.
Thalamocortical dysrhythmia	***Thalamocortical dysrhythmia*** is characterized by increased low-frequency theta rhythmicity in conjunction with a widespread and marked increase of coherence among high- and low-frequency oscillations. This coherent theta activity is due to the generation of bursts by thalamic cells brought about by hyperpolarization (by either excess inhibition or disfacilitation). The emergence of tic symptoms is likely to be the result of ectopic gamma-band activation (the "edge effect"). This effect is thought to be due to an inhibitory asymmetry between high- and low-frequency thalamocortical modules at the cortical level.

†Several of the definitions offered in this table are paraphrases of definitions offered by: Buzsáki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science*. *304,* 1926-1929; and Llinás, R., Urbano, F.J., Leznik, E., Ramirez, R.R.,

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Figure 1. Schematic diagram of the major connections of the basal ganglia associated with Tourette syndrome. In the sensorimotor and motor circuits excitatory glutamatergic cortical neurons converge on matrisomal (MS) gamma aminobutyric acid (GABA) containing medium spiny neurons in the dorsal lateral striatum. These cortical projections are somatotopically organized (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 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. Both the specific and non-specific 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).

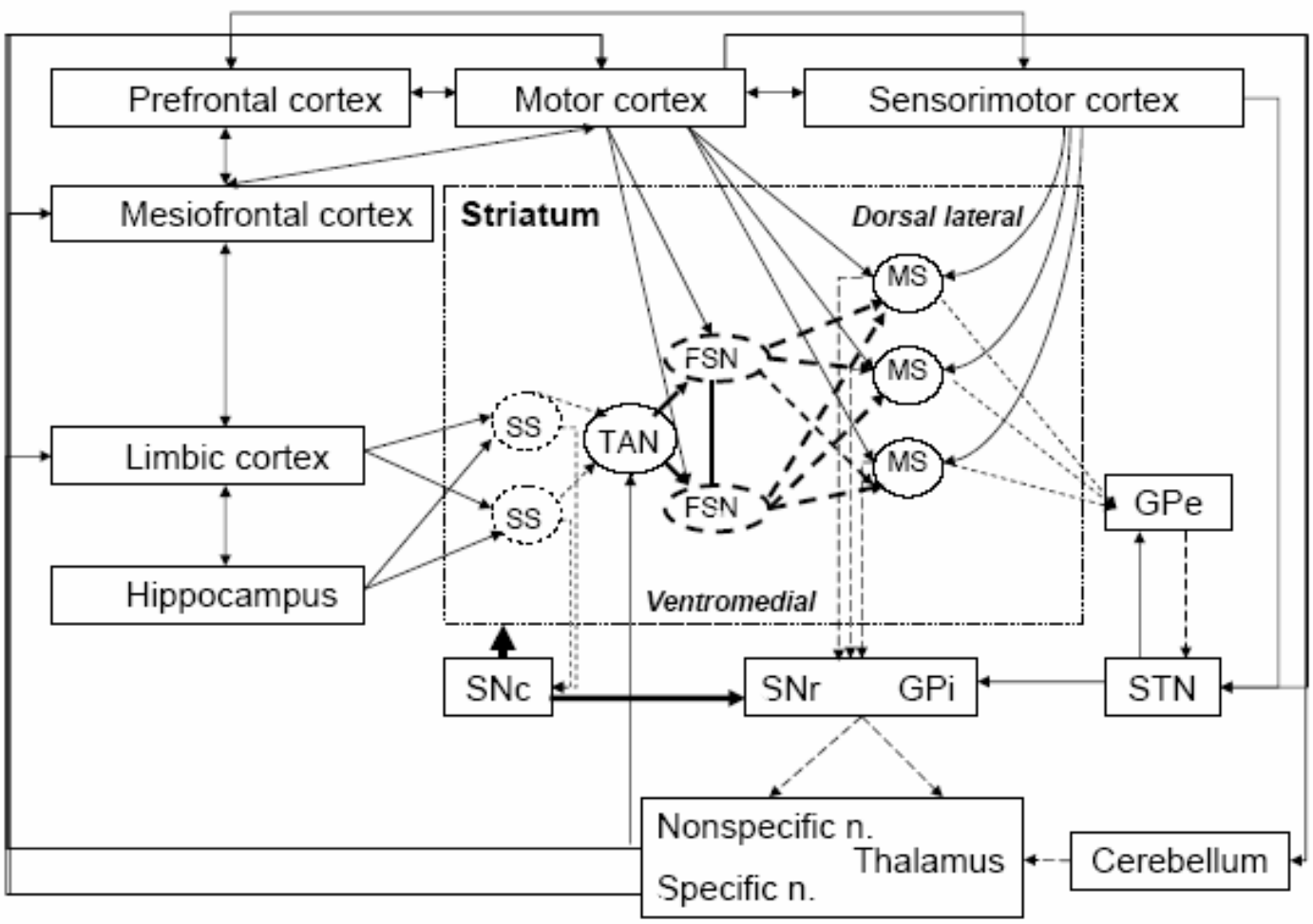
The “cognitive” cortico-striato-thalamo-cortical (CSTC) circuit (not depicted in this figure) consists cortical neurons in the prefrontal cortex that project to the head of the caudate nucleus. These signals are then relayed through the globus pallidus to the excitatory glutamatergic thalamocortical 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 peri-limbic 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 tonically active cholinergic neurons identified as tonically active neurons (TANs). The TANs, in addition to both dopaminergic cells in the SNc and excitatory glutamatergic 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 (designated by dashed circles). 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 TAN neurons are also depicted as solid lines.

Figure 1:


Prefrontal cortex
Motor cortex
Sensorimotor cortex
Mesiofrontal cortex
Striatum
Dorsal lateral
MS
MS
MS
FSN
FSN
SS
SS
TAN
Limbic cortex
Hippocampus
Ventromedial
GPe
SNc
SNr
GPi
STN
Nonspecific n.
Thalamus
Specific n.
Cerebellum