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Review

Pharmacological animal models of Tourette syndrome

Maya Bronfeld, Michal Israelashvili, Izhar Bar-Gad*

Gonda Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat-Gan 52900, Israel

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ABSTRACT

Pharmacological animal models of Tourette syndrome (TS) are an important tool for studying the neural mechanisms underlying this disorder. Dysfunction of the cortico-basal ganglia (CBG) system has been widely implicated in TS but the exact nature of this dysfunction is unknown. Pharmacological treatments of TS have prompted multiple hypotheses regarding the involvement of different neuromodulators in the disorder. Pharmacological manipulations in animal models were used to investigate the relationships between these neuromodulators and different symptoms of TS, including motor (tics) and non-motor (sensorimotor gating deficits) phenomena. Models initially focused on the direct effects of pharmacology on behavior, and only recently have begun providing neurophysiological data reflecting the neuronal mechanism linking the two. Animal models support the notion of CBG dysfunction as the neural mechanism underlying TS, and suggest that it may be derived from either direct deficits of local striatal GABAergic networks or a dysfunction of the neuromodulator systems controlling them. These findings can provide the much- needed conceptual construct for the TS etiology and point to new therapeutic targets.

Contents

Abbreviations: 5-HT, serotonin/5-hydroxytryptamine; ACC, anterior cingulate cortex; ACh, acetylcholine; ADHD, attention deficit hyperactivity disorder; BG, basal ganglia; CBG, cortico-basal ganglia pathway; CNS, central nervous system; DA, dopamine; EMG, electromyography; FSI, fast spiking interneruon; GABA, gamma-aminobutyric acid; GPe/GPi, globus pallidus externus/internus; MSN, medium spiny neuron; NE, norepinephrine; NPY, neuropeptide Y; OCD/OCB, obsessive-compulsive disorder/behavior; PPI, pre-pulse inhibition; SMA, supplementary motor area; SMG, sensorimotor gating; SNc/SNr, substantia nigra pars compacta/reticulata; STN, subthalamic nucleus; TAN, tonically active neuron; TS, Tourette syndrome; VTA, ventral tegmental area.

* Corresponding author. Tel.: +972 3 5317141; fax: +972 3 5352184.
E-mail addresses: mayabr@gmail.com (M. Bronfeld), michalisrae@gmail.com (M. Israelashvili), izhar.bar-gad@biu.ac.il (I. Bar-Gad).

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1. Introduction

In 1885, the French physician Georges Gilles de la Tourette gave a detailed description of patients suffering from the hyperkinetic disorder which would later bear his name. His description of childhood-onset repetitive involuntary movements (termed motor tics) and vocalizations which followed a spontaneous course of waxing and waning remains remarkably relevant to this day (de la Tourette, 1885). While major advances have been made in the epidemiology and clinical presentation of the disorder (Bloch and Leckman, 2009; Freeman et al., 2000), treatment courses are still surprisingly limited and the etiology of the disorder remains largely unknown. Much of what we know about Tourette syndrome (TS) stems from epidemiological, genetic, clinical, pharmacological and imaging studies of TS patients. However, drawing conclusions from these studies is often hampered by the small size and highly heterogeneous nature of the research subjects who differ in multiple parameters such as age, gender, disease duration, comorbid conditions, medication history and other factors (Swerdlow and Sutherland, 2005). The use of animal models of the disorder provides an alternative platform for research that can control for most of these variables and extend the range of possible methods and manipulations used in the study of this disorder. Different types of animal models have been used in the study of TS, including ones based upon genetic, immunological, behavioral and pharmacological manipulations, and new animal models continue to emerge as new constructs regarding TS etiology and new research techniques continue to develop. In this review we focus on TS animal models that use pharmacological manipulations to model different aspects of the disorder. We review current knowledge and hypotheses regarding the involvement of different neuromodulator and neurotransmitter systems in TS and their related brain pathways, describe TS animal models based on pharmacological manipulations of these systems, discuss the advantages and disadvantages of these models and their implications for TS etiology, pathophysiology and future TS research.

1.1. Tourette syndrome

TS is a neuropsychiatric disorder characterized by multiple motor and vocal tics. Tics are defined as sudden, rapid, recurrent, non-rhythmic, stereotyped movements or vocalizations (American Psychiatric Association, 2000). The complexity of the abnormal movement or vocalization ranges from “simple” to “complex” tics. Simple tics manifest as brief isolated movements involving only one or a few closely related muscle groups or utterances of noises or simple sounds. Complex tics are more elaborate movements which involve the sequential or coordinated activation of several muscle groups or the production of complete words or phrases. TS onset occurs in early childhood, typically around the age of 6–7, and is estimated to affect ∼1% of all children. Tics appear multiple times a day, usually in bouts, against the backdrop of otherwise normal motor function. Tics usually wax and wane during the course of the disease, and patients may experience alternating periods of enhancement or reduction in the frequency and severity of tics. Despite the variable individual course of the disease, most patients experience a gradual reduction of symptoms during adolescence and complete (or near-complete) absence of tics by early adulthood (Bloch et al., 2006; Leckman et al., 1998). About 20% of patients continue to experience moderate to severe tics in adulthood (Bloch and Leckman, 2009), but no markers are currently known that reliably predict which patients will experience idiopathic remission and which ones will not.Tics of TS patients differ from other motor disorders by being partially predictable and controllable by the patient. TS patients typically report experiencing uncomfortable sensations preceding the tics, termed “sensory tics” or “premonitory urges” (Kwak et al., 2003; Leckman et al., 1993). Tics are reported by TS patients as being a means of alleviating the uncomfortable premonitory sensations, and their expression can be temporarily suppressed (Leckman et al., 1993). This sensory phenomenon has led researchers to hypothesize that TS is associated with a dysfunction of the sensorimotor gating (SMG) mechanism (reviewed in Swerdlow and Sutherland, 2005). SMG is a process by which irrelevant sensory, cognitive or motor information is suppressed, or “gated”, thereby allowing only relevant information to influence behavior. In TS, a breakdown of this process is thought to underlie the sensory perceptions experienced as premonitory urges and lead to the expression of tics. Although tics are the defining symptom of TS, almost all TS patients (∼90%) suffer from at least one other comorbid psychiatric condition (Freeman et al., 2000). The most common comorbid conditions are attention-deficit/hyper-activity disorder (ADHD) and obsessive compulsive disorder or behaviors (OCD/OCB) (Freeman et al., 2000).

The pharmacological treatment of tics is severely limited due to efficacy and safety issues of currently available drugs, to the point that it is only used in severe cases (milder tics can be managed by social and behavioral interventions). Even when pharmacological treatment is administered, its goal is usually to reduce tics to a level which lowers their related psychosocial disturbance rather than completely suppress them (Singer, 2010). The treatment of TS is further complicated by the presence of comorbid symptoms, whose treatment may conflict with the management of tics (Gadow et al., 1999; McDougle et al., 1993). The most effective pharmacological treatment of tics is antipsychotic drugs which act mainly as D2 dopamine receptor antagonists. Antipsychotics may achieve relatively high levels of tic suppression (up to 60–80% reduction of tic frequency and severity) in most patients, but their usefulness is significantly limited due to severe side effects, which include motor symptoms such as parkinsonism, dystonia or dyskinesia, cognitive impairment, mood disorders and weight gain (Scahill et al., 2006; Shapiro et al., 1989; Singer, 2010). The drugs that are currently considered as first-line treatment of tics are α2-Adrenergic agonists,

which primarily activate noradrenergic autoreceptors and reduce norepinephrine levels (Arnsten et al., 2007). These drugs generally have a lesser effect on tic expression than antipsychotics, but they are preferred for their milder side effects. Drugs that act as γ-Aminobutyric acid (GABA) agonists have also been reported to have a positive effect on the treatment of TS patients, but more rigorous study is needed to prove their potential benefits (Singer, 2010). Finally, cholinergic agents have been suggested as an augmenting agent for tic reduction, but their efficacy is still controversial (Sacco et al., 2004; Scahill et al., 2006). In the last decade, neurosurgery for the implantation of stimulating electrodes in deep brain structures has been investigated as therapy for severe treatment-refractory cases of TS (Hariz and Robertson, 2010).

1.2. Neuromodulatory systems associated with TS

A wide spectrum of neurotransmitter, neuromodulator and neuropeptide systems has been implicated in the etiology of TS. Models and hypotheses regarding the involvement of different neuropharmacological systems in TS are based on findings utilizing variable methods, including responses to specific medications, neurochemical assays on biological samples from TS patients (e.g., cerebrospinal fluid, blood or urine) or postmortem brain tissue, imaging studies and pharmacological animal models. In this section we review the major neuropharmacological systems that have been implicated in TS, focusing on the neuromodulatory systems for which TS-related pharmacological animal models have been suggested.

1.2.1. The dopaminergic system

Dopamine (DA) is produced by neurons residing in multiple brain areas, with primary attention paid to the neurons of the mesencephalon; the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). Dopaminergic projections innervate many brain regions including the striatum and other basal ganglia nuclei, different frontal cortical areas, and parts of the limbic system. The three main dopaminergic pathways are the nigrostriatal pathway (SNc→dorsal striatum), the mesolimbic pathway (VTA→nucleus accumbens) and the mesocortical pathway (VTA→frontal cortex). Five different DA receptor subtypes have been identified, and are classified into two subfamilies: D1-type receptors (including the D1 and D5 subtypes) and D2-type receptors (including the D2, D3 and D4 subtypes) (Sibley and Monsma, 1992). D1 receptors are located post-synaptically, whereas D2 receptors can be found both pre- and post-synaptically, and they act as autoreceptors on dopaminergic neurons (Beaulieu and Gainetdinov, 2011). Over the years, DA has been associated with motor control, goal directed behaviors, learning and memory (Schultz, 1997; Schultz, 2007; Wise, 2004). DA has also been extensively studied in relation to its role in the reward system, where it was shown to reflect changes or errors in the prediction of future rewarding events. These findings are the basis for adaptive optimizing control theories that attribute a key role to DA in guiding behavior based on previous experience (Schultz et al., 1997). Dysfunctions of the dopaminergic system have been associated with a range of neurological and psychiatric disorders. The dopaminergic system is extensively studied in relation to Parkinson's disease, in which the death of the dopaminergic neurons in the SNc are posited to lead to its main clinical symptoms. A DA dysfunction has also been implicated in schizophrenia (Seeman, 1987) and ADHD (Solanto, 2002), primarily due to the well-established therapeutic effects of drugs modulating the DA system in the treatment of these disorders.

Evidence for a link between dopaminergic dysfunction and TS pathophysiology stem from a variety of studies. Interest in the DA system initially arose following reports of the successful treatment of TS patients with antipsychotic drugs such as pimozide and haloperidol that act primarily as D2 receptor antagonists (Shapiro and Shapiro, 1968). These clinical findings led to the development of the 'DA hypothesis' of TS, which suggests a causal relationship between DA abnormality and TS symptoms. This hypothesis states that excessive dopaminergic activity leads to TS pathophysiology, either due to the super-sensitivity of DA receptors, DA hyper-innervation or increased postsynaptic receptor density (Singer et al., 1981). Based on the tonic-phasic DA hypothesis of schizophrenia (Grace, 1991), Singer suggested that increased activity of the DA transporter leading to reduced tonic levels of DA could increase the levels of phasically-released DA, possibly due to understimulation of the D2 autoreceptors (Singer et al., 2002). The DA hypothesis was supported by imaging studies in TS patients which found increased D2 receptor densities (Wolf et al., 1996; Wong et al., 1997), increased levels of the DA transporter (Cheon et al., 2004) and increased DA release (Albin et al., 2003; Steeves et al., 2010; Wong et al., 2008). However, other studies of these same dopaminergic substrates have yielded conflicting results, and have failed to find differences between TS patients and normal controls (George et al., 1994; Stamenkovic et al., 2001; Turjanski et al., 1994). In light of these discrepancies, the role of DA in TS is still being investigated using a variety of methods; the contribution of pharmacological animal models to this area of investigation is described in Section 2.4.

1.2.2. The serotonergic system

Serotonin (5-hydroxytryptamine [5-HT]) is produced by neurons located in several clusters, mostly at the brainstem raphe nuclei (Dahlstroem and Fuxe, 1964). Like other neuromodulators, serotonergic neurons innervate virtually all regions of the central nervous system (CNS) (Butcher and Woolf, 1982; Parent et al., 1981). Multiple classes and subtypes of serotonergic receptors have been identified so far, belonging to the 5-HT_{1-7} receptor families (Barnes and Sharp, 1999). 5-HT has multiple and complex effects on behavior, including the regulation of mood, eating, sleep and cognitive function (Buhot, 1997; Lucki, 1998; Monti and Jantos, 2008; Sirvio et al., 1994). Serotonergic involvement has also been implicated in multiple psychiatric disorders, including depression, eating disorders, OCD, and others (Lucki, 1998).

A possible role for 5-HT in TS was initially based on the high comorbidity rates between TS and other disorders involving serotonergic dysfunction, most notably OCD (Zohar et al., 2000). However, biochemical measurements of CNS serotonergic function in TS patients have generated conflicting results. Although some studies report decreased levels of 5-HT, its precursors or metabolites in urine, blood or cerebrospinal fluid samples of TS patients compared to healthy controls (Bornstein and Baker, 1992a,b; Comings, 1990), other studies found small or no differences (Bornstein and Baker, 1990; Leckman et al., 1995; Singer et al., 1982). *In-vivo* imaging studies have found reduced binding of the serotonergic transporter in TS patients, but they have also indicated that binding levels may be affected by pre-existing pharmacological treatments or the degree of comorbid OCD/OCB symptoms (Heinz et al., 1998; Muller-Vahl et al., 2005; Wong et al., 2008). Some studies have focused on the unique role of the 5-HT_{2A} receptor subtype in TS. Interest in this receptor increased following the discovery of the high affinity of some atypical antipsychotic drugs, which are effective tic-reducing agents, to the 5-HT_{2A} receptor (Leysen et al., 1993). Haugbol and colleagues have reported increased binding of the 5-HT_{2A} receptor in multiple brain regions of TS patients (Haugbol et al., 2007), but other groups have failed to replicate this finding (Wong et al., 2008). Notably, in addition to the potential direct effect of 5-HT on TS symptoms, the existing data has led to the hypothesis of the involvement of 5-HT in TS through its interactions

with the dopaminergic system Steeves and Fox (2008). Overall, the extent to which serotonergic dysfunction is involved in TS and the mechanisms governing its involvement are still unclear.

1.2.3. The noradrenergic system

Norepinephrine (NE) is a neuromodulator regulating the activity of both the central and the peripheral nervous systems. NE-producing neurons are located in the brain stem, mainly in the locus coeruleus, and send widespread projections innervating virtually all CNS regions (Foote et al., 1983). The NE system interacts with other neuromodulatory systems, primarily the dopaminergic system, at multiple levels. At the molecular level, DA is the precursor for NE synthesis (Hartman, 1973), and drugs that influence DA levels may also affect levels of NE (Dayan and Finberg, 2003). At the system level, NE-producing neurons are reciprocally connected with DA-, acetylcholine (ACh)- and 5-HT- producing neurons (reviewed in: Briand et al., 2007; Foote et al., 1983). Thus, both naturally occurring changes and pharmacologically induced manipulations of NE signaling may lead to complex changes in other modulatory pathways.

The behavioral roles of NE include a generally increasing effect on overall levels of arousal (Berridge, 2008), and modulation of a variety of cognitive processes, including working memory, attention and behavioral inhibition (Sara, 2009). Accordingly, dysfunction of the NE system has been implicated in depression, anxiety, attention deficit and other stress-related disorders (Anand and Charney, 2000; Arnsten et al., 2007; Southwick et al., 1999; Sullivan et al., 1999). The involvement of NE in TS mainly derives from the beneficial effects of drugs which activate the presynatic α2-adrenergic autoreceptors (Aoki et al., 1994) in the treatment of TS patients (e.g., Leckman et al., 1991). The primary mode of action of these drugs is a reduction of NE levels (Szabo et al., 2001), suggesting that TS might be associated with a hyper-adrenergic dysfunction. However, estimations of NE levels in TS patients have so far yielded conflicting results, with different studies reporting increased (Leckman et al., 1995), decreased (Baker et al., 1990) or normal levels (Singer et al., 1990). Notably, the study of the role of NE in TS may be confounded by the involvement of NE in TS comorbid symptoms, such as ADHD (Arnsten et al., 2007), and in the regulation of overall levels of anxiety and arousal, which are known to affect tic expression (Conelea and Woods, 2008).

1.3. Neuroanatomical pathways associated with TS

Multiple brain regions and pathways have been implicated in TS. In this review we focus on the most extensively studied pathway in the context of the disorder: the cortico-basal ganglia (CBG) loop. Abnormalities in this pathway are currently hypothesized to be the major underlying cause of TS (Albin et al., 2003; Kalanithi et al., 2005; Kataoka et al., 2010; Peterson et al., 2003; Wang et al., 2011).

1.3.1. The basal ganglia

The basal ganglia (BG) are a group of interconnected sub-cortical nuclei that are involved in motor, associative and limbic functions (Alexander et al., 1986). They receive information from most areas of the cerebral cortex and the thalamus, and project back to frontal cortical areas through the thalamus, thus forming the CBG loop. The BG are comprised of the striatum (subdivided into the putamen, the caudate and the nucleus accumbens), the subthalamic nucleus (STN), the substantia nigra pars compacta (SNc) and pars reticulata (SNr), and the two segments of the globus pallidus [externus (GPe), and internus (GPi)]. Excitatory (glutamatergic) projections from multiple cortical areas are sent to the input nuclei of the BG: the striatum and the STN. The striatum receives additional

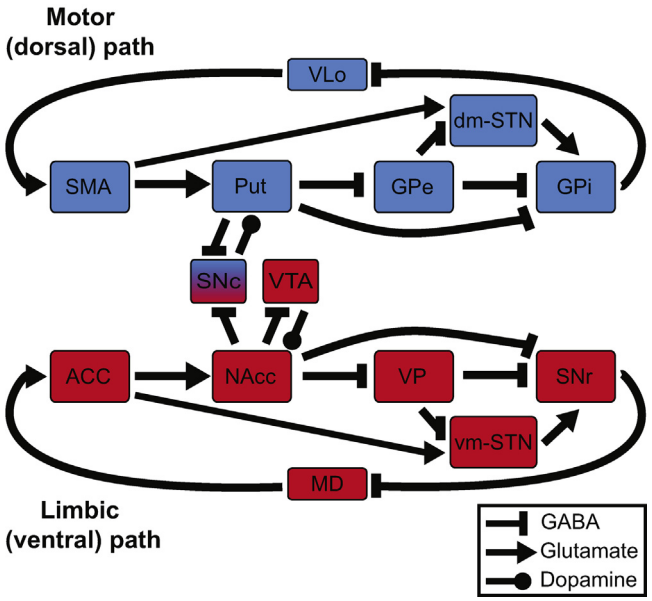

Fig. 1. Cortico-basal ganglia functional loops. Simplified diagram depicting the main nuclei and connections comprising multiple cortico-basal ganglia functional loops. The predominant loops associated with TS are the motor/dorsal (blue) and limbic/ventral (red) pathways. (Based on Alexander et al., 1986; Haber et al., 2000). Abbreviations: ACC = anterior cingulate cortex; dm-STN = dorsomedial subthalamic nucleus; GPe = Globus pallidus externus; GPi = Globus pallidus internus; MD = mediodorsal nucleus of the thalamus; NAcc = nucleus accumbens; Put = putamen; SMA = supplementary motor area; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; VLo = ventro-lateral nucleus of the thalamus – oral part; vm-STN = ventro-medial subthalamic nucleus; VP= ventral pallidum; VTA = ventral tegmental area.

information from the thalamus and from midbrain dopaminergic neurons by its reciprocal connections with the SNc and the VTA (Fig. 1) (Haber et al., 2000; McFarland and Haber, 2000; Parent and Hazrati, 1995). Both the striatum and the STN project to the GPi and SNr, either directly or via the GPe. However, these nuclei have opposite effects: the STN transmits excitatory (glutamatergic) projections whereas the striatum sends inhibitory (GABAergic) projections to these nuclei (Haber and Gdowski, 2004). In turn, the GPi and SNr, which form the output structures of the BG, send inhibitory (GABAergic) projections to the brainstem and thalamus. The CBG loop is closed by excitatory projections from the thalamic nuclei which receive BG innervation to the cortex (Hoover and Strick, 1993; Inase and Tanji, 1995; Joel and Weiner, 1994; Middleton and Strick, 1994; Tokuno et al., 1992). The GABAergic projections from the BG to the thalamus and cortex are considered to modulate cortical activation (Albin et al., 1989; DeLong, 1990). A decrease in GPi/SNr activity reduces their inhibition of the thalamus and cortex, thereby facilitating cortical activation, whereas an increase in GPi/SNr activity enhances cortical inhibition.

Information flows through the BG in three feed forward pathways that differ in their effect on the activity of the BG output structures (GPi & SNr) and consequently on the BG's effect on cortical activation. In the "direct" pathway the striatum projects directly to the GPi/SNr, thus decreasing their activity and facilitating cortical activation (Alexander and Crutcher, 1990). The "indirect" and the "hyperdirect" pathways increase GPi/SNr activation, either by increased striatal inhibition of the GPe which reduces GPi inhibition and, via the STN, increases GPi excitation (indirect pathway) (Alexander and Crutcher, 1990), or by excitatory projections from the cortex through the STN to the GPi (hyperdirect pathway) (Nambu et al., 2000) (Fig. 1). Thus, the net effect of these two pathways is suppression of cortical activation. Activation of the different CBG pathways is differentially modulated by DA, through activation

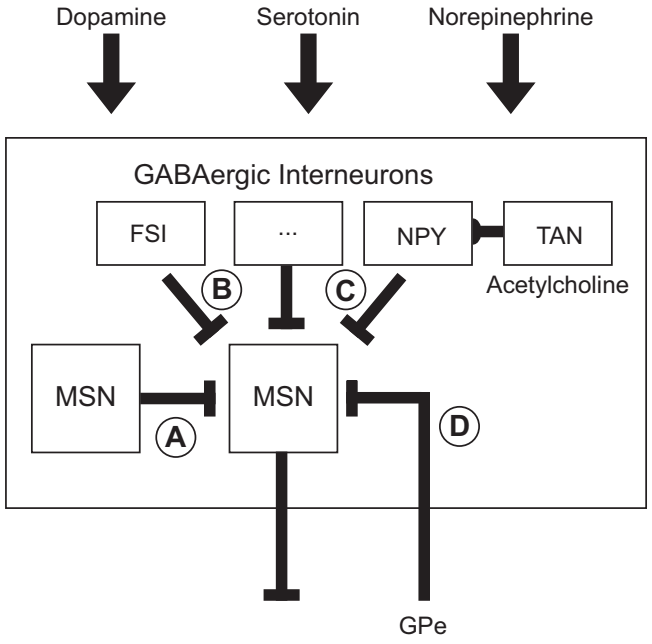

Fig. 2. The striatal network. Simplified diagram of the internal GABAergic network of the striatum. MSNs receive GABAergic inputs from multiple sources: (A) collaterals of other MSNs, (B-C) inputs from GABAergic interneurons, such as (B) FSIs and (C) NPYs, and (D) collaterals of GPe projection neurons. The activity of the network is further modulated by internal and external sources of multiple neuromodulators.

of D1 or D2 receptors in the striatum. DA facilitates the activity of neurons projecting to the direct pathway via D1 receptors while inhibiting the activity of neurons projecting to the indirect pathway via D2 receptors. Thus, the classical CBG model holds that enhanced DA in the striatum increases cortical activation whereas reduced DA levels inhibit cortical activation (Albin et al., 1989; DeLong, 1990).

Input from the cortex to the BG can be subdivided into multiple functional loops which include, amongst others, the motor, associative and limbic pathways. This functional loop structure is maintained by partial anatomical separation of projections throughout all levels of the CBG (Alexander et al., 1986; Parent and Hazrati, 1995). Classically, the ventral regions of the BG (Anterior Cingulate Cortex→Ventral striatum→Ventral pallidum→SNr) are associated with the limbic pathway (Fig. 1), the central BG regions are associated with the cognitive pathway (Dorsolateral Prefrontal Cortex→Caudate→Dorsomedial GPe→Dorsomedial GPi and SNr) and the dorso-lateral regions are associated with the motor pathway (Supplementary Motor Area→Putamen→Ventrolateral GPe→Ventrolateral GPi) (Fig. 1). The motor loop is additionally subdivided into a gross somatotopic organization, including spatially disntict representations of the lower and upper extremities and the orofacial region (Alexander and DeLong, 1985; DeLong et al., 1985). Notably, this functional-anatomical architecture has been most extensively studied in primates, whereas studies in rodents have focused mainly on the division into ventral (limbic) and dorsal (motor) functional loops.

Most BG nuclei mainly contain projection neurons; by contrast, the striatum contains both projection neurons and interneurons, which form a complex internal network (Kawaguchi et al., 1995) (Fig. 2). The vast majority (75–90%) of the striatal neuronal population (Gerfen and Wilson, 1996) are the GABAergic projection neurons, termed medium spiny neurons (MSNs) due to their morphological structure. The activity of MSNs is modulated by local striatal interneurons and by collateral connections between neighboring MSNs (Fig. 2). The striatum contains several different types of interneurons which use GABA as their neurotransmitter and one type of cholinergic interneurons (Tepper and Bolam, 2004). The parvalbumin-positive fast spiking interneurons (FSIs) are the most highly investigated type of GABAergic striatal interneurons. The FSIs population is relatively small (3–5% of the total striatal population) (Kita et al., 1990), but they are able to exert strong inhibition over the MSNs by forming synapses on their somata and proximal dendrites (Bennett and Bolam, 1994; Kita et al., 1990; Koos and Tepper, 1999). The FSIs themselves are connected by chemical and electrical synapses, forming a strongly coupled network (Bolam et al., 2000; Koos and Tepper, 1999). Additional GABAergic striatal interneurons are the neuropeptide Y (NPY)-expressing neurogliaform interneurons. These NPY expressing neurons inhibit the activity of MSNs while being controlled by cholinergic input (English et al., 2012; Ibanez-Sandoval et al., 2011). About 1% of the neurons in the striatum are cholinergic interneurons, termed tonically active neurons (TANs) due to their characteristic *in-vivo* activity pattern (Kimura et al., 1984). The TANs modulate MSNs activity both directly and indirectly by activating GABAergic interneurons (Fig. 2) (English et al., 2012). Post-mortem studies have revealed significant decreases (50–60%) in the FSIs and TANs neuronal population in TS patients, suggesting that changes to the local striatal network may be involved in the TS pathophysiology (Kalanithi et al., 2005; Kataoka et al., 2010).

The activity of the BG is further modulated by neuromodulators, such as DA, 5-HT, NE and ACh. While the sources and connectivity patterns of these neuromodulators are well defined (Lavoie and Parent, 1990; Lavoie and Parent, 1994; Parent et al., 1995), their effects on BG physiology is largely unclear. Amongst the neuromodulators, dopaminergic modulation has generated the most interest among researchers, primarily due to its involvement in Parkinson's disease. The midbrain dopaminergic input to the BG from the SNc and the VTA is the primary source of DA in the BG, with minor sources from local striatal dopaminergic neurons (Ibanez-Sandoval et al., 2010). The BG have a reciprocal effect on dopaminergic neurons, mediated by projections from the striatum (Haber et al., 2000) and the STN to the SNc (Haber and Gdowski, 2004) and projections from the SNc to the striatum, both segments of the globus pallidus and SNr (Charara and Parent, 1994; Hedreen and DeLong, 1991). Anatomical and physiological studies have found serotonergic modulation of BG activity (Kita et al., 2007), originating from raphe nuclei projections to the BG, mostly terminating in the ventral striatum, the substantia nigra and both segments of the globus pallidus (Charara and Parent, 1994; Lavoie and Parent, 1990; Vertes, 1991). ACh affects the BG both by the activity of the striatal cholinergic TANs and via projections from cholinergic neurons of the pedunculopontine nucleus that innervate multiple BG nuclei (Lavoie and Parent, 1994; Mesulam et al., 1992; Parent et al., 1983). Finally, anatomical and physiological studies have shown that the activity of striatal neurons is also modulated by noradrenergic projections from the locus coeruleus (Fujimoto et al., 1981; Parent et al., 1983).

Evidence for the relation between abnormalities in the CBG loop and TS emerges from a variety of studies. Structural imaging studies found a decrease in the volumes of the striatum and globus pallidus of TS patients (Bloch et al., 2005; Peterson et al., 2003). Neurochemical imaging studies found that abnormalities of multiple neuromodulator/neurotransmitter systems, such as the dopaminergic and GABAergic systems, in TS patients were often specifically manifested within different BG nuclei, mainly the striatum and globus pallidus (Albin et al., 2003; Cheon et al., 2004; Lerner et al., 2012; Wong et al., 2008). Functional imaging studies have reported a correlation between tic expression and BG activation levels (Peterson et al., 1998; Wang et al., 2011). Additional evidence for the association between BG abnormalities and TS comes from preliminary results of neurosurgeries performed in TS patients which indicate that high-frequency stimulation of the

GPi can significantly reduce tic severity (Ackermans et al., 2006; Diederich et al., 2005; Hariz and Robertson, 2010; Houeto et al., 2005; Welter et al., 2008).

1.3.2. The cerebral cortex

The involvement of the cerebral cortex in TS has been studied extensively in the context of both tic manifestation and the premonitory urges appearing prior to the tics Reduced inhibition, resulting in increased cortical neuronal activity, is hypothesized both types of symptoms. According to this model, reduced inhibition in the sensory and limbic areas leads to an inability to suppress the sensations and premonitory urges whereas reduced inhibition in motor cortical areas leads to inability to control the expression of the tic. The involvement of the cortex was hypothesized to arise from reduced inhibition of cortical networks (Ziemann et al., 1997) which may arise from abnormal changes in either subcortical innervation, primarily from the BG, or intrinsic changes in cortical networks, specifically abnormalities of the cortical GABAergic interneurons. Imaging studies of TS patients primarily point to hyperactivity in cortical regions which participate in two CBG circuits (Fig. 1): limbic areas such as the anterior cingulated cortex (ACC) and the orbitofrontal cortex, and motor areas, primarily the supplementary motor area (SMA) (Braun et al., 1995). Studies designed to detect the neurophysiological abnormalities underlying the tics in human patients are confounded by large changes in neuronal activity in the motor cortices and large movement-related artifacts induced by the tics themselves. Some recent articles have addressed this concern by comparing the neuronal activity recorded from TS patients during tic expression with that of normal subjects performing voluntary movements resembling the tics. This type of comparison points to activity within the SMA as the primary difference between TS patients and normal subjects (Hampson et al., 2009). Other studies using the same methodology added non-motor areas such as the ACC and prefrontal cortex (Wang et al., 2011). Structural neuroimaging also indicated that TS was associated with changes in both the limbic and motor cortical systems, with the greatest changes observed in the somatosensory and primary motor areas (Sowell et al., 2008) and in limbic areas such as the ACC (Fahim et al., 2009).

2. TS pharmacological animal models

Modeling human disorders in animals refers to the process of using animals for the study of pathological phenomena occurring in humans. There are two main goals for animal models in neurobiological research of disorders: (1) Developing new therapeutic means or targets for improving the treatment of human patients; (2) Uncovering the pathogenesis of the disorder; i.e., achieving a better understanding of the neuropathological processes underlying the human condition (LeDoux, 2005). Pharmacological animal models involve the administration of substances that affect different neurochemicals in the nervous system to induce a pathological state in the model animal. In this section we present the general principles commonly used for the evaluation of animal models, highlight specific aspects of modeling TS in animals and describe the major pharmacological animal models of TS.

2.1. Estimation and validation of TS animal models

Several conceptual frameworks have been suggested to assess the validity of animal models of psychiatric and neurological disorders. Most of these methods share a few basic principles, and the most commonly used approaches define three types of validation levels: face, predictive and construct validity. *Face validity* refers to the phenomenological similarity between the animal model and the human clinical condition. It requires that symptoms observed in the animal model be reasonably similar to specific features or symptoms of the modeled disorder (Jinnah and Hess, 2005). Some researchers have emphasized that the significance of the specific modeled symptom within the overall clinical picture of the human condition should also be addressed in the evaluation of the model (Matthysse, 1986). In animal models of TS, face validity is usually achieved by the induction of abnormal tic-like movements in animals. *Predictive validity* is generally defined as the degree to which the performance of the model animal on any kind of test or measured parameter accurately predicts some aspect of the modeled condition. In practice, predictive validity is usually based on response to medication; i.e., an evaluation of how well the effects of drugs on some aspect of the model predicts their effect in human patients (Matthysse, 1986). The predictive validity of animal models of TS is usually based on responses to antipsychotic drugs and/or α2-adrenergic agonists, which are the two most commonly used pharmacological treatments of TS. *Construct validity* refers to the theoretical rationale of the animal model, and describes models that were designed to evaluate a specific theory regarding the etiology of the human condition (theory-driven models) (Joel, 2006; Swerdlow and Sutherland, 2005). As such, construct validity requires that the model be consistent with what is known about the pathophysiology of the disorder in humans.

A valid animal model does not require that all three types of validity be established. For example, animal models with well-established predictive or construct validity may not display any of the symptoms observed in human patients (e.g., Freedman and Giarman, 1956). Models with different types of validity are used for different purposes, and should be evaluated according to different criteria. Models that rely on face validity should be more rigorously evaluated in relation to accepted definitions and diagnostic criteria of the human syndrome (Jinnah and Hess, 2005). The predictive validity of animal models should be assessed by parameters such as the sensitivity, specificity and relative potency of the model's response to different pharmacological agents (Swerdlow and Sutherland, 2005). As such, good predictive models may be the most useful for guiding therapy (Jinnah and Hess, 2005). Establishing the construct validity of a model is largely dependent on the strength of currently available findings, hypotheses or conceptual models regarding the pathology underlying the human disorder. This requirement may pose a particular problem for the evaluation of animal models of TS, as there is still substantial ambiguity regarding TS etiology and pathophysiology (Burke and Lombroso, 2005; Swerdlow and Sutherland, 2005).

2.2. Common principles underlying TS animal models

The most distinctive aspect of TS used in animal models is the existence of abnormal movements which resemble motor tics. The definition of tics in human patients covers a broad spectrum of movements and behaviors, ranging from brief jerk-like movements (simple tics) to sequential complex behaviors (complex tics) (American Psychiatric Association, 2000; Barbeau et al., 1981). Accordingly, a wide range of seemingly different abnormal movements or behaviors have been classified as tics in animal models (Crossman et al., 1988; Handley and Dursun, 1992; McCairn et al., 2009; Tarsy et al., 1978) based primarily on behavioral observations (Corne et al., 1963; Slater and Dickinson, 1982). Tic-like movements or behaviors in animals are generally characterized by their spontaneous and sudden, relatively brief and repetitive nature, which makes them easily identified even in animals simultaneously displaying other movements and behaviors (Crossman et al., 1988; Handley and Dursun, 1992; McCairn et al., 2009) (see supplementary video). These simple motor tics typically manifest as jerk-like movements that are usually restricted to a single muscle group or body part. Parameters such as the anatomical location,

intensity, duration and frequency of these abnormal movements in animals may vary significantly between different models. These parameters can be measured and quantified by off-line analyses of video recordings of the animal's behaviors (McCairn et al., 2009) and by electromyography (EMG) recordings. Recordings of EMG activity from multiple muscles can be used to identify the exact timing of tic-onset and the pattern of muscular activation associated with the tic-like movement (Bronfeld et al., 2011; McCairn et al., 2009; Muramatsu et al., 1990). These detailed behavioral observation and analyses methods can be used to distinguish putatively tic-like movements in animals from potentially similar movement abnormalities such as myoclonus, chorea or dystonia (McCairn et al., 2009). The definition of complex motor tics in TS (American Psychiatric Association, 2000; Barbeau et al., 1981) broadens the definition of tic-like movements in animals to include stereotypic behaviors. Behavioral stereotypies in animals include behaviors which are part of the animal's normal behavioral repertoire (e.g., sniffing, rearing, grooming) which are repeatedly and excessively performed, often outside of their normal context (Dantzer, 1991; Eilam et al., 2006; Mason, 1991; Ridley, 1994).

Another significant feature of TS is the sensory or psychic experience–the premonitory sensations or urges (Kwak et al., 2003). While tic-like movements can be directly detected and characterized in animals, it is impossible to know whether these movements are preceded by premonitory sensations. However, premonitory urges were suggested to reflect deficient SMG processes (reviewed in: Swerdlow et al., 1999; Swerdlow and Sutherland, 2005), which may more readily be tested. One experimental technique used to estimate SMG in both human subjects and animals is the prepulse inhibition (PPI) of the startle reflex, which has been extensively applied in the study of TS (Castellanos et al., 1996; Swerdlow et al., 2001a,b). The startle response is the reflexive response to a sudden, relatively intense sensory stimulus. Data show that the magnitude of the startle response is reduced (inhibited) when presentation of a weaker stimulus briefly (typically by 30–500 ms) precedes the presentation of the startling stimulus (Graham, 1975; Ison et al., 1973). A failure of the weak pre-stimulus to reduce the magnitude of the startle response to the ensuing strong stimulus is regarded as a deficient PPI response indicating a sensorimotor deficit (Swerdlow et al., 1999; Swerdlow and Sutherland, 2005; Weiss and Feldon, 2001).

2.3. GABA-related models

GABA is an inhibitory neurotransmitter regulating neuronal activity throughout the CNS. The GABAergic animal model of TS focuses on the disruption of local GABAergic transmission within the BG, which are part of the neural circuit implicated in human TS, by specifically targeting the striatum. Early studies found that unilateral local application of $GABA_A$ antagonists such as picrotoxin or bicuculline into the rat striatum induced the appearance of abnormal movements in the contralateral limbs or face (Patel and Slater, 1987; Tarsy et al., 1978). Similar abnormal movements were induced in the monkey following application of a $GABA_A$ antagonist specifically into the putamen, which is the striatal component of the BG motor loop (Crossman et al., 1984, 1988; McCairn et al., 2009). The abnormal movements induced by this striatal GABAergic manipulation were characterized as repetitive myoclonic jerks consisting of sudden, rapid and brief flexion of the contralateral limb followed by a slower relaxation (Fig. 3A and supplementary video) (Crossman et al., 1988; Marsden et al., 1975; McCairn et al., 2009; Patel and Slater, 1987). Facial movements could also be observed, which in rats included contralateral facial grimacing, teeth chattering and tongue protrusions (McKenzie et al., 1972), and in monkeys consisted of brief contralateral contractions of orofacial musculature (Fig. 3A and supplementary video) (McCairn et al., 2009). These sudden, rapid and repetitive movements bear a phenomenological resemblance to the simple motor tics of TS patients, and could likewise be blocked by administration of antipsychotic drugs (e.g., haloperidol) (McKenzie et al., 1972). In monkeys, a minority of the injections led to complex tics involving sequential activation of multiple muscle groups resulting in repetitive complex movements (Fig. 3B and supplementary video). In both rats and monkeys tics usually appeared within minutes following administration of the $GABA_A$ antagonist (mostly 2–10 min, average ~5 min), and lasted for up to 2 h (Crossman et al., 1988; Marsden et al., 1975; McCairn et al., 2009; Patel and Slater, 1987; Tarsy et al., 1978). The frequency of the tics fluctuated during the duration of the effect, but was usually around 0.5 Hz (one tic every 2 s) (Marsden et al., 1975; McCairn et al., 2009; McKenzie and Viik, 1975; Patel and Slater, 1987; Tarsy et al., 1978). Tics tended to be highly localized, appearing in isolated muscle groups against a backdrop of otherwise normal behavior and motor functions (Crossman et al., 1988; McCairn et al., 2009; Tarsy et al., 1978). In rats, a somatotopic organization was observed between the striatal microinjection sites and the body part in which the abnormal movements were expressed. Microinjections into the anterior, central or posterior parts of the striatum induced abnormal movements predominantly affecting orofacial (Nakamura et al., 1990), forelimb (Patel and Slater, 1987; Tarsy et al., 1978) or hindlimb (Tarsy et al., 1978) muscles, respectively. However, no somatotopic organization of the injection sites was observed in monkeys (Bronfeld et al., 2011; Crossman et al., 1988; Worbe et al., 2009).

The local GABAergic animal model revealed an interesting link between motor tics and their common comorbid symptoms (OCD/OCB and ADHD). A similar pharmacological manipulation; i.e., localized microinjections of $GABA_A$ antagonists, into different functional territories of the striatum and GPe induced complex domain-specific behaviors similar to compulsive, hyperactive or attention deficit symptoms (Grabli et al., 2004; Tarsy et al., 1978; Worbe et al., 2009) (Box 1).

$GABA_A$ antagonists may affect multiple GABAergic transmission pathways within the striatum, including projections from MSN collaterals and from local GABAergic interneurons (Fig. 2). Recently, Grittis and colleagues (Gittis et al., 2011) demonstrated that abnormal movements could be elicited in mice by a more selective suppression of GABA transmission in the striatum. In their study, the researchers blocked the activity of a specific type of GABAergic striatal interneuron–the FSIs. This form of selective striatal GABAergic manipulation induced contralateral twisted dystonia-like postures together with jerk-like repetitive movements. Combined with findings showing a selective loss of FSIs in TS patients, these findings suggest a major role for loss or dysfunction of FSIs GABAergic inhibition in the pathophysiology leading to motor tics (Kalanithi et al., 2005).

Electrophysiological recordings in the localized GABAergic animal model have enabled the exploration and characterization of the neural mechanisms associated with the expression of motor tics. Initial studies that used electroencephalography (EEG) or local field potentials to assess the activity of large cortical neuronal populations found large slow spike-like transient deflections in the cortical electrical activity that appeared synchronously with the tics (Muramatsu et al., 1990; Tarsy et al., 1978). Later studies that recorded the activity of individual cortical neurons found that tics were associated with phasic bursts of spiking activity in these neurons (McCairn et al., 2009). Tic-related activations of cortical neurons could be detected around the time of the tic, usually with a latency of ±50 ms around tic onset (Bronfeld et al., 2011). In the striatum, projection neurons (MSNs) displayed phasic bursts of activity around the time of each tic (Bronfeld et al., 2011). These tic-related activations tended to precede both the motor tic and the cortical tic-related activation (Bronfeld et al., 2011). Only

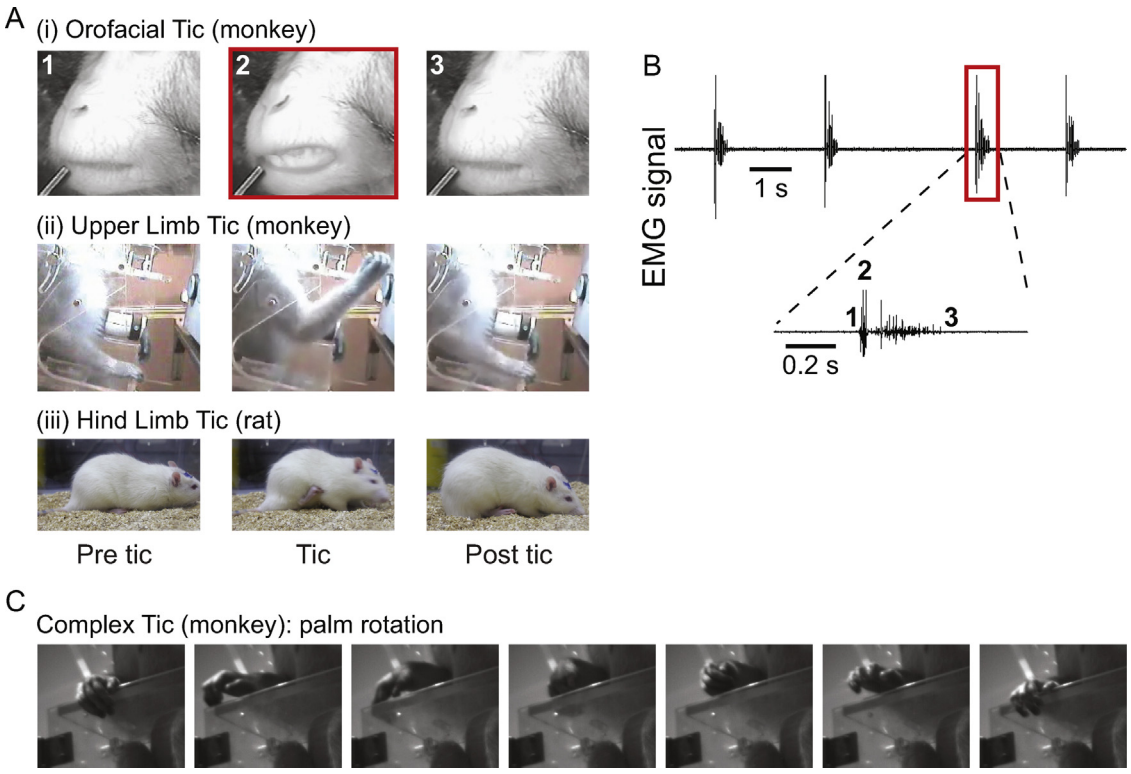

Fig. 3. Tic expression in the local striatal GABAergic model of TS. Video and EMG recordings of motor tics induced by local microinjections of a $GABA_A$ antagonist into the striatum of the monkey and rat. (A) Frames taken from three video recordings depicting a simple motor tic expressed in different muscles: (i) orofacial (ii) upper limb and (iii) hind limb. (B) Simultaneous EMG recordings from a facial muscle during the expression of orofacial motor tics in a monkey. The red square denotes the same time period in both A and B (Based on: Bronfeld and Bar-Gad, 2012). (C) A sequence of frames taken from a video recording depicting the progress of a complex motor tic manifested as a rotation of the palm.

neurons recorded from the somatotopic sub-region representing the body part in which tics were expressed were activated around the time of the tic. However, within this somatotopic domain a large fraction of the recorded neurons expressed tic-related activations (Bronfeld et al., 2011). Phasic tic-related modulations of activity could also be observed in the striatal cholinergic interneurons (TANs). The pattern of TANs tic-related activity was similar to the stereotypic activity modulations observed in these neurons in relation to other behavioral events (Kimura et al., 1984). Previous studies have shown that the event-related activity of these neurons is strongly modulated by DA (Graybiel et al., 1994). These properties suggest that the tics induced by pharmacological manipulation of $GABA_A$ transmission in the striatum also involve the dopaminergic system, which has been implicated in TS pathophysiology. In particular, this also suggests that the dopaminergic dysfunction related to TS may be induced by a primary dysfunction within the BG. Downstream from the striatum, phasic tic-related activity could be detected both in the GPe and in the BG output structures – the GPi and SNr. Tic-related activity was expressed as phasic increases or decreases of the baseline high-frequency firing rate of neurons in these structures around the time of each tic. Phasic rate increases were more common in GPe neurons, while rate decreases, often expressed as brief periods of complete cessation of spiking activity, were predominant in the GPi and SNr (Bronfeld et al., 2011; McCairn et al., 2009; Muramatsu et al., 1990). A large fraction of neurons (over 70% of the recorded neurons) in these structures expressed tic-related activity, and the tic-related neurons were widely distributed throughout each nucleus (Bronfeld et al., 2011; McCairn et al., 2009; Muramatsu et al., 1990). GPe and GPi tic-related activity occurred later than the onset of both the motor tic and tic-related cortical activation (Bronfeld et al., 2011). Notably, recent recordings of GPi neurons performed in TS patients undergoing neurosurgery have revealed similar patterns of tic-related activity to those observed in the animal model (Zhuang et al., 2009).

2.4. Dopamine-related models

The 'DA hypothesis' of TS has been extensively studied in animal models through pharmacological manipulations of the dopaminergic system, which lead to multiple and complex behavioral effects. Most studies have focused on two main aspects of DA-mediated behavioral abnormalities: motor and sensory alterations. The motor aspect is tested via the effect of excess DA on the formation of excess behavior, and the sensory aspect involves using the PPI paradigm as a measure of altered SMG processes.

Early studies indicated that systemic administration of a dopaminergic agonist (e.g., amphetamine) to rodents induced stereotypic behaviors such as sniffing, licking or biting (Randrup et al., 1963), which could be blocked by DA antagonists (Del and Fuentes, 1969; Randrup et al., 1963; Randrup and Munkvad, 1965). These behavioral effects were dose dependent, with increasing dosages of DA agonists leading to prolonged periods of stereotypic behavior accompanied by greater suppression of normal activities (Porrino et al., 1984; Russell and Pihl, 1978). Different dopaminergic agonists produce similar behavioral effects (Fog, 1969), but amphetamine is the most commonly used drug in this model. Amphetamine can also induce species-specific stereotypic behaviors in other animals including mice, guinea pigs, cats and monkeys (Randrup and Munkvad, 1967; Ridley et al., 1982). Additionally, administration of apomorphine (a dopaminergic agonist) to healthy humans was found to induce yawning and increase blinking (Blin et al., 1990).

Box 1: Hyper-behavioral abnormalities induced by local disruption of GABA transmission in the basal ganglia

The anatomical organization of neuronal afferents to the BG and their internal circuitry supports the concept of a functional subdivision of the BG into functional domains devoted to the processing of sensorimotor, associative and limbic information (Alexander et al., 1986; Alexander and Crutcher, 1990). Local pharmacological manipulations of BG information transmission in animals can induce different abnormal behavioral symptoms, whose nature is dependent on the type of pharmacological manipulation, the target nucleus and the specific functional domain within the nucleus. A local blockade of GABAergic transmission within the motor territory of the striatum in rats and monkeys induces tic-like movements (see Section 2.1). A similar pharmacological manipulation in non-motor BG functional domains can induce hyper-behavioral abnormalities resembling the behavioral symptoms of some of the most common TS comorbid conditions including hyperactivity, attention deficits and compulsive behaviors.

Hyperactivity and attention deficits: A hyperactive state was observed in rats following microinjections of a $GABA_A$ antagonist into the GPe (Ikeda et al., 2010; Tarsy et al., 1978; Williams and Herberg, 1987; Wisniecki et al., 2003), and in monkeys following microinjections into the associative territories of the GPe (Francois et al., 2004; Grabli et al., 2004) or the striatum (Worbe et al., 2009). The overall manifestation of hyperactivity was similar in monkeys and rats: the animals displayed a general increase in exploratory/locomotor activity, a larger behavioral variability with frequent and rapid alterations between different types of behavior, and in some cases the animals exhibited unidirectional rotation behavior (circling) towards the contralateral side to the injected hemisphere. In monkeys performing a behavioral task the hyperactive state was accompanied by specific perturbations of task performance which may reflect spatial attention disturbances (Grabli et al., 2004).

Compulsive-like behaviors: In monkeys, two types of repetitive, compulsive-like behaviors were induced by local $GABA_A$ antagonist microinjections. Microinjections in the limbic territories of the GPe (Francois et al., 2004; Grabli et al., 2004) or the striatum (Worbe et al., 2009) induced behavioral stereotypies expressed as repetitive licking or biting of the tail or fingers. Another type of compulsive-like behavior was expressed as part of the hyperactive state in monkeys, following microinjections into the associative striatal or GPe territories. These behaviors were expressed as frequent and repetitive touching aimed at a specific location or object in the cage or experimental setup, often located at the contralateral side to the microinjection (Bronfeld et al., 2010; Grabli et al., 2004; Worbe et al., 2009).

The local GABAergic modulation animal model directly demonstrates the role of disrupted BG GABA-related transmission in the pathogenesis of abnormal movements and behaviors. The observation that qualitatively different hyper-behavioral symptoms may be induced by the same pharmacological manipulation in different functional domains of the BG suggests that a common neuronal pathology may underlie different disorders including TS, OCD and ADHD. The different behavioral manifestations of these disorders may be attributed to the identity and extent of the affected functional territories. Thus, very different behavioral effects may actually be derived from a common pathology simply because of the different afferent/efferent connectivity of the affected brain area. A common neural pathology may also account for the high rates of comorbidity between these disorders observed in human patients.

Animal studies that used localized microinjections of DA agonists have demonstrated the importance of the BG system in mediating DA-induced stereotypies. Amphetamine microinjections into ventral regions of the striatum, which belong to the limbic CBG circuit (Fig. 1) elicited oral stereotypies, whereas microinjections targeting dorsal striatal regions did not produce these behaviors (Kelley et al., 1988). Recordings of neuronal activity indicate that apomorphine-induced behavioral abnormalities in monkeys are associated with a reduction in the firing rate of neurons in the SNr, which is the main output structure of the CBG limbic circuit (Fig. 1) (Nevet et al., 2004). Furthermore, high frequency stimulation targeting the GPi, which is the main output structure of the motor CBG circuit, was reported to reduce tic severity in TS patients (Welter et al., 2008), but high frequency stimulation targeting the entopeduncular nucleus (the rat homologue of the GPi), did not significantly reduce amphetamine- induced sniffing behaviors (Posch et al., 2012). These findings point to the specific involvement of the limbic CBG domain in mediating the behavioral effects of DA dysregulation, and suggest that they may be primarily associated with the non-motor rather than the motor aspects of TS.

Dopaminergic pharmacological manipulations were also found to affect SMG processes, studied by the PPI paradigm. Systemic administration of DA agonists induces PPI deficits in animals (Lind et al., 2004; Mansbach et al., 1988; Ralph et al., 2001; Yee et al., 2004) as well as in humans (Hutchison and Swift, 1999), which may be abolished by co-administration of DA antagonists (Hoffman and Donovan, 1994; Mansbach et al., 1988). The effect of DA agonists on PPI is highly variable. The same dose can induce opposite effects in different rat strains (Rigdon, 1990; Swerdlow et al., 2007; Swerdlow et al., 2003), and both an increase or a decrease in the paired pulse response can be induced in the same rat strain, depending on the stimulus condition and drug doses (Swerdlow et al., 2001b). Regions within the BG have been shown to be involved in DA-related PPI deficits. An anatomically targeted study of localized amphetamine infusion into rat nucleus accumbens resulted in a disruption of PPI (Swerdlow et al., 2007; Wan et al., 1995; Wan and Swerdlow, 1996) pointing to potential ventral striatal involvement in SMG changes. Other studies have indicated that lesions, as well as high frequency stimulation of the rat entopeduncular nucleus, prevent an apomorphine-induced PPI deficiency (Lutjens et al., 2011; Posch et al., 2012).

While the dopaminergic animal model clearly demonstrates the involvement of a central DA dysfunction in motor and sensorimotor abnormalities, its relation to TS is currently unclear. Administration of DA agonists is often used to model other disorders with a suspected DA dysfunction (e.g., schizophrenia) (Kokkinidis and Anisman, 1981; Weiss and Feldon, 2001), and the behavioral outcomes of stereotypies and PPI deficits are also studied in relation to other disorders (e.g., schizophrenia, OCD, ADHD) (Eilam et al., 2006; Geyer, 2006).

2.5. Serotonin-related models

Brief and repetitive movements were described in rodents following systemic administration of drugs which increase CNS levels of 5-HT or serotonergic activity. In mice, these behaviors took the form of head shakes or twitches, which are brief and sudden rotations of head (Corne et al., 1963). In rats, central systemic administration of serotonergic agonists induced “wet-dog-shakes” which are single or multiple rotation movements involving the head, neck, shoulders and upper trunk, reminiscent of the shaking movements seen in dogs emerging from water (Bedard and Pycock, 1977). These behaviors can be seen in normal animals as part of the grooming repertoire or following some physiological stimuli such as wetting of the animal (Tse and Wei, 1986).

However, following serotonergic manipulation the frequency and the probability of the behaviors increased, usually up to an approximate range of 1–10 shakes/twitches per minute during peak effect period, and they were performed spontaneously outside of their normal context (Bedard and Pycock, 1977; Corne et al., 1963; Dursun and Handley, 1996). The animals appeared to exhibit no control over these movements, and typically displayed otherwise normal behavior between each shake/twitch (Bedard and Pycock, 1977; Corne et al., 1963).

Systemic administration of serotonergic agonists was initially suggested as a model for TS based on the tic-like properties of the induced behaviors; i.e. their sudden, brief, repetitive and stereotypic nature (Handley and Dursun, 1992). Subsequent studies have indicated that this pharmacological manipulation could also model the SMG deficits observed in TS patients, since serotonergic agonists also reduce the PPI response (Kehne et al., 1996; Sipes and Geyer, 1994). Studies in the serotonergic animal model have mostly focused on uncovering the specific pharmacological mechanisms and anatomical localization related to the 5-HT-induced TS-like abnormalities. For example, studies found that both the 5-HT-induced abnormal movements and the PPI deficits in animals were specifically mediated by the 5-HT_{2A} receptor subtype (Dursun and Handley, 1996; Farid et al., 2000; Kennett and Curzon, 1991; Padich et al., 1996), which was also implicated in the tics of TS patients. Sipes and Geyer suggested that 5-HT_{2A} receptors within the ventral pallidum are specifically important for the observed modulation of PPI (Sipes and Geyer, 1997).

The animal model of 5-HT-induced behaviors has also highlighted the complex relationship between different neuromodulator systems in the context of TS psychopharmacology. A wide variety of substances can induce abnormal movements or PPI deficits similar to those induced by serotonergic agonists (Handley and Dursun, 1992), including agents affecting DA (Dickinson et al., 1984; Mansbach et al., 1988), NE (Handley and Brown, 1982; Swerdlow et al., 2006), ACh (Gaynor and Handley, 2001; Yeomans et al., 2010), GABA (Handley and Singh, 1985; Yeomans et al., 2010), and other neurotransmitter/neuromodulator systems (Handley and Dursun, 1992; Johansson et al., 1995; Varty et al., 1999). Furthermore, serotonergic agents can attenuate behavioral abnormalities induced by manipulations of other neuropharmacological systems, and non-serotonergic agents can modulate behavioral abnormalities induced by serotonergic manipulations (e.g., Corne et al., 1963; Dursun and Handley, 1996; Egashira et al., 2004; Handley and Singh, 1985; Sallinen et al., 1998a; Shilling et al., 2004; Tizabi et al., 2001; Varty et al., 1999). These non-specific cause and effect relationships between the pharmacological manipulation and resulting behaviors may confound our ability to use this model to explore the specific role of 5-HT in TS.

2.6. Norepinephrine-related models

Pharmacological manipulations of the NE system do not directly induce tic-like behaviors in animals. However, this system is involved in modulating the PPI response in animals, which is hypothesized to model SMG deficits in TS patients (Swerdlow et al., 2001a). Systemic administration of adrenergic agonists resulted in PPI deficits in rats and mice (Carasso et al., 1998; Sallinen et al., 1998b), and this effect was shown to be mediated by activation of central rather than peripheral adrenergic receptors (Alsene et al., 2006). Multiple adrenergic receptor subtypes were implicated in the observed PPI deficits (Carasso et al., 1998; Lahdesmaki et al., 2004; Sallinen et al., 1998b). Recently, an attempt was made to identify the discrete brain regions involved in NE-related PPI deficits, with the use of localized microinjections rather than systemic administration of NE agonists (Alsene et al., 2011). This study indicated that NE affects PPI through its activation of a ventral forebrain network and a thalamo-cortical network. However, only a limited set of brain regions was examined, and further research is required to identify and characterize the PPI-related neural pathways affected by NE and its mechanisms of action. Animal studies have also shown that NE activity can modulate PPI deficits induced by pharmacological manipulations of other neuromodulators such as DA and 5-HT (Alsene et al., 2010; Lahdesmaki et al., 2004; Sallinen et al., 1998a). Attempts have been made to identify the distinct and common neural pathways involved in PPI modulations by the different systems (Alsene et al., 2010, 2011; Swerdlow et al., 1990). Although studies have indicated that different brain regions and neural pathways may be involved in mediating the effects of different neuromodulators on PPI (Alsene et al., 2011), a few common neural pathways have also been identified. Specifically, regions within the BG limbic pathway (ventral striatal/ventral pallidal regions) were shown to mediate the interacting effects of different neuromodulators on PPI (Alsene et al., 2011; Swerdlow et al., 1990).

3. Critical assessment of TS pharmacological animal models

Pharmacological animal models of TS rely on different conceptual or phenomenological resemblance to the disorder to establish their validity. However, all models should ultimately be evaluated based on their potential contribution for advancing our understanding of the neural mechanisms underlying the disorder and its potential therapeutic targets. In this section we discuss the advantages and limitations of different pharmacological methods used to model TS in animals.

3.1. TS symptoms addressed by the models

TS lies between two large domains of neuronal disorders: its primary symptom, motor tics, would lead to its classification as a *movement disorder* (Barbeau et al., 1981), whereas its accompanying premonitory urges and comorbid disorders place it in the spectrum of *psychiatric disorders* (American Psychiatric Association, 2000). Animal models of TS mirror this dichotomy, with different models focusing on either the motor or the limbic facets of the disorder.

The defining motor symptoms of TS are tics, and as such may be regarded as the crucial feature for establishing the face validity of TS animal models. TS pharmacological animal models differ significantly in their ability to induce tic-like movements (Table 1). Only the localized striatal GABA-related model can reliably induce repetitive abnormal movements similar to motor tics. In this model, tics usually manifest as brief jerking movements (simple tics) (Fig. 3A), but abnormal sequential movements resembling complex tics are also observed (Fig. 3C). Importantly, the pattern of prolonged and relatively high frequency repetitive expression of abnormal movements in this model enables the analysis of specific neuronal activity patterns related to the expression of the tics (Bronfeld et al., 2011; McCairn et al., 2009). The only other pharmacological animal model whose behavioral manifestation partially resemble motor tics (Handley and Dursun, 1992) is the serotonergic model. However, the extent to which 5-HT-induced behaviors can truly be regarded as a model for tics is unclear. The induced behaviors in this model are often expressed at a low frequency (sometimes repeating only a few times in a time span of several hours, e.g., Corne et al., 1963), they may be expressed in normal or sham-treated animals (Corne et al., 1963), and they are observed in animal models of multiple other pathological conditions, such as opiate (Azizi et al., 2012) or alcohol (Unsalan et al., 2008) withdrawal syndromes, epilepsy (Shin et al., 2009) and others. Furthermore, the surprisingly wide range of pharmacological manipulations, physiological stimuli and

Table 1
Pharmacological models of Tourette syndrome.

Pharmacological system	Pharmacological manipulation	Administration	Tic-like movements	PPI-deficits	Comorbid Behavioral Symptoms		
					Stereotypies	Hyperactivity	Attention-deficits
GABA	$GABA_A$ Antagonists	Localized–motor striatum	+	?	+[a]	+[b]	+[b]
Dopamine	D2 (primarily) Agonists	Systemic, Localized–limbic striatum	–	+	+	+	-
Serotonin	5-HT_{2A} (primarily) Agonists	Systemic	–/+	+	+	–	-
Norepinephrine	Agonists	Systemic	–	+	–	–	-

[a] Elicited by localized $GABA_A$ antagonist microinjections into the limbic domains of the striatum/GPe.
[b] Elicited by localized $GABA_A$ antagonist microinjections into the associative domains of the striatum/GPe.

conditions which elicit the same pattern of behavioral abnormality as 5-HT administration (see: Handley and Dursun, 1992, for a partial list) makes it extremely difficult to pinpoint the specific neural pathways underlying these behaviors, much less to establish which of these potential mechanisms is associated with the behavioral abnormalities observed in TS patients. Neither the dopaminergic nor noradrenergic animal models elicit tic-like movements, but administration of DA agonists induces stereotypic behaviors and a general increase in locomotor activity (hyperactivity) in animals (Table 1). Both of these motor abnormalities may be related to TS, given the high rates of comorbid compulsive and hyperactive behaviors reported in TS patients. However, these symptoms are not unique to TS and may not necessarily reliably represent TS-specific pathological processes.

Although motor tics are the most striking feature of TS symptomology, and perhaps the most easily evaluated in animals (see Section 2.2), the focus on this motor aspect of the disorder does not accurately capture the overall clinical picture of TS. Almost all TS patients report experiencing uncomfortable sensations or urges which "compel" them to express the tics (Kwak et al., 2003). While tic-like movements can be observed in animals, it is difficult to deduce whether these movements are also preceded by any abnormal urges or sensations. One indirect measure of these sensory or psychic phenomena that has been tested in studies of TS is the PPI response. PPI deficits have been reported in almost all pharmacological animal models of TS (Table 1). To date, PPI deficits have not been evaluated in the GABA-related TS models but pharmacological studies have shown that GABA is involved in mediating PPI deficits (Kodsi and Swerdlow, 1995; Yeomans et al., 2010). The study of PPI has yielded valuable results regarding the neural basis of SMG processes (Swerdlow et al., 1999), but its potential contribution to an understanding of the neural mechanisms of TS may be inherently confounded. One issue is the observation that PPI deficits can be induced by pharmacological manipulations of multiple neuromodulator systems, which may modulate PPI via different neural pathways. This heterogeneity of causes leading to the same outcome precludes our ability to determine which neural pathway or system is associated with the PPI deficits observed in TS patients. Furthermore, PPI deficits are not unique to TS, and have been reported in many different neurological and psychiatric disorders such as Huntington's disease, Alzheimer's disease, schizophrenia, depression, OCD, ADHD and others (reviewed in: Geyer, 2006). The highly non-specific manifestation of PPI deficits makes it impossible to rely on this symptom as a major validating feature of a TS animal model.

A review of TS pharmacological animal models reveals a disturbing dissociation between the study of motor and non-motor aspects of the disorder. Specifically, different researchers use the same pharmacological manipulation but report either its motor outcomes or its effects on PPI. This dissociation is particularly detrimental in studies focusing on PPI, as it is unclear how and to what extent the altered behavioral state influences different parameters of the PPI paradigm. An integrated approach to both types of symptoms may be highly beneficial in bridging the gap between the sensory and motor aspects of TS. This will enable the identification of the common and distinct neural mechanisms related to these phenomena, and uncover the relationship between them. Given the strong association between sensory experience and the motor manifestation in TS patients, this relationship is likely to be crucial to a better understanding of the x basis of TS.

3.2. Neural components affected by pharmacological manipulations

Multiple levels of resolution can be considered when describing the neurobiological basis underlying a particular disorder. The neuropathology can be described at the level of a dysfunctional neuromodulator system, a particular neural pathway or region, specific cell types, or even specific sub-cellular components (e.g., receptor, ion channel, etc.). Pharmacological manipulations may have complex effects on any one of these levels, and may be used to varying degrees to study some of these neural components, depending on the methodology they employ. Understanding the potential implications and limitations of different methodologies is particularly important in the study of TS, where there are multiple animal models targeting different neuromodulatory systems.

The most widely used technique in TS pharmacological studies is systemic administration of drugs affecting a particular neuromodulator system. The underlying assumption is that any behavioral changes induced by this manipulation in the animals would correspond to a primary dysfunction in this neuromodulatory system in the human patients. The use of substances with variable capacities to cross the blood-brain barrier or direct intracerebral administration has shown that TS-related behavioral effects in animals are mediated by their activity on receptors in the CNS rather than in the periphery (Alsene et al., 2006; Corne et al., 1963). However, it is impossible to know which specific brain region mediates the effects of the drugs, as they bind to receptors located throughout the CNS. This non-specific spatial distribution does not allow for a detailed investigation of the specific neural pathways mediating the behavioral effects. Furthermore, this feature of the method may also confound its most basic assumption; i.e. the attribution of the behavioral effects to the manipulated neuromodulatory system. Complex cross-effects between different neuromodulatory systems are well documented for practically all systems (Di Matteo et al., 2008; Drago et al., 2011; Foote et al., 1983; Morgane and Jacobs, 1979; Nanopoulos et al., 1982). Systemic manipulations of one neuromodulator can induce measurable changes in others (e.g.

(Dayan and Finberg, 2003; Di Matteo et al., 2008; Meltzer and Nash, 1991), and the behavioral effects induced by manipulation of one system can be modulated by substances affecting other systems (see Sections 2.5 and 2.6). These interactions confound attempts to attribute observed behavioral effects induced by systemic drug administration to a specific system.

One way to overcome the limitations of systemic drug manipulations is the use of localized administration methods (e.g., microinjections or microinfusions). Localized administration can be used to identify the specific brain regions mediating the observed behavioral effects, and reduce concerns regarding cross-effects between different neuromodulator systems. In the case of TS, localized pharmacological manipulations have supported the hypothesis that the CBG system and specifically the striatum play an improtnat role in mediating both motor and non-motor aspects of TS (Alsene et al., 2011; Bronfeld et al., 2011; Kelley et al., 1988; McCairn et al., 2009; Sipes and Geyer, 1997; Wan et al., 1995; Wan and Swerdlow, 1996). The specific sub-regions involved in different types of TS-related behavioral abnormalities (SMG deficits, tics, compulsive behaviors, hyperactivity) could also be identified using this method. Despite the advantages of localized pharmacological methods, they have a number of limitations. First, they are highly dependent on the a-priori selection of targeted brain regions (e.g., Alsene et al., 2011). TS studies have mostly targeted different regions within the CBG because of the hypothesized involvement of this system in TS. While this is certainly a valid approach, it cannot exclude the potential involvement of other unexplored brain regions. Another limitation of localized administration methods pertains to the technical features of the method. Localized administration requires the insertion of a delivery cannula to the targeted area that passes through and may damage other brain region in its path. Furthermore, the injection apparatus or process may cause mechanical damage to the injected brain area itself. The identity of brain regions affected in this way and the extent of the possible damage might influence the behavioral outcome. Such effects were specifically investigated in the case of the GABAergic model of TS, but the findings were inconclusive. Some studies have indicated that the physical damage to the motor cortex overlaying the targeted striatal region was an important element in the tic-inducing mechanism (Tarsy et al., 1978), but other studies have failed to replicate these findings (Patel and Slater, 1987). Nevertheless, future studies should attempt to minimize brain damage, and the potential effects of any damage should be evaluated by targeting the investigated regions via different trajectory paths.

Even within a specific region, pharmacological manipulations may influence different components of the local neuronal population. One example is the local GABergic model, in which a blockade of $GABA_A$ transmission is likely to affect multiple nodes of the local striatal network (Fig. 2). Understanding which of these disrupted connections is responsible for the observed behavioral effects induced by the pharmacological manipulation, and in what way it affects striatal information processing is crucial to determining the TS-related neural mechanism (see Section 4.1). This could be achieved by using more selective substances that can affect a specific and restricted neuronal population (Gittis et al., 2011), or by employing advanced methods of selective activation or inhibition of specific neuronal subtypes, such as optogenetics (Boyden et al., 2005).

Finally, the identity of the specific sub-cellular components mediating the effects of neurotransmitters/neuromodulators on neuronal activity such as receptors and transporters might also be an important feature of the underlying neural pathology. Dysfunction of different types of these elements may have substantially different effects on neuronal activity, even if they are part of the same neuropharmacological system. Therefore, the precise action sites of the drugs used in pharmacological manipulations should be taken into account when interpreting their behavioral effects. However, pharmacological manipulations can also induce dynamic changes in sub-cellular components which might significantly change their effects on neuronal activity. These include changes in the expression or sensitization of different receptor subtypes, changes in the activity of transporters, etc. (e.g., Overstreet et al., 2000; Overstreet and Westbrook, 2001; Richerson and Wu, 2003). These changes can occur over multiple time scales; they may immediately follow an acute pharmacological manipulation, or otherwise be expressed following variable periods of chronic drug administration. These dynamics should therefore be considered when using pharmacological models to explore the neural mechanisms of a disorder, as they may substantially change the behavioral and/or neuronal effects of the drugs.

4. Implications of TS pharmacological animal models

Dysfunction of the CBG system is generally regarded as the underlying cause of TS, but the exact neural substrates involved in the disorder and the abnormal neural activation patterns associated with its symptoms are still largely unknown. Animal models provide a powerful tool for a detailed exploration and characterization of the neural mechanism of TS. In this section we present the possible implications of results obtained from pharmacological animal models for shedding light on the neurobiological basis of TS and for advancing new conceptual frameworks of the disorder.

4.1. The neurobiological basis of TS

Current knowledge about the neurobiological basis underlying TS and its specific symptoms is very limited. Most of the data still comes from studies performed on human subjects, both clinical studies of the effects of different pharmacological agents and imaging and histological studies assessing the differences between TS patients and healthy subjects. However, pharmacological animal models have made important contributions to our understanding of the basis of the disorder, primarily by providing novel information about the involvement of CBG malfunction in TS, and specifically the role of the striatal GABAergic network.

There are multiple sources of GABAergic synapses on striatal MSNs: collaterals from other MSNs, inputs from GABAergic interneurons and feedback from the GABAergic projection neurons of the GPe (Fig. 2). The tics evoked by local microinjections of $GABA_A$ antagonists to the striatum may thus result from disruption of any one of these sub-systems. By far, the most numerous type of GABAergic synapse on the MSNs arises from collaterals of other MSNs. These MSN-MSN collaterals are mostly located on distal dendrites and exert relatively weak somatic inhibition (Jaeger et al., 1994; Tunstall et al., 2002; Wilson and Groves, 1980). Although the effect of these individual synapses on MSNs is small, they may have major effects on transmission within the dendrites, by allowing them to modulate the effects of excitatory cortical inputs (Wilson, 2007). Hence, blockade of these synapses might induce uncontrolled transmission of cortical inputs from the dendrites to the MSN soma, and potentially lead to a significant depolarization of the neuron.

The second source of GABA mediated inputs to MSNs comes from any one of the multiple groups of striatal GABAergic interneurons. The most extensively studied type of GABAergic interneurons is the FSIs which exert powerful inhibition on the MSNs through synaptic connections located on their soma and proximal dendrites (Bennett and Bolam, 1994; Kita et al., 1990; Koos and Tepper, 1999). FSIs themselves are interconnected by chemical and electrical synapses, and the blockade of their transmission may reduce the coordinated inhibition of MSNs (Koos et al., 2004). Recently,

an animal model demonstrated that selective inhibition of the FSIs was able to elicit abnormal motor activity (Gittis et al., 2011), thus further pointing to the specific involvement of these interneurons in the induction of motor abnormalities. Another type of recently identified interneurons is the neuropeptide-Y expressing neurogliaform GABAergic interneurons (Ibanez-Sandoval et al., 2011). The activity of these neurons, which can exert strong inhibition over MSNs, is modulated by cholinergic inputs from the local TANs population (English et al., 2012), thereby providing a potential GABAergic pathway mediating reward-related signals. Blockade of this transmission pathway would cause a partial detachment of the striatal activity from the reward signals. Additional GABAergic interneurons have been described, and new types of interneurons are continually being characterized, but their role within the local striatal network and their effects on MSN activity are currently poorly understood.

Around 30% of GPe projection neurons send collaterals that terminate in the striatum, thereby providing another source of GABAergic striatal inhibition (Bevan et al., 1998; Kita and Kitai, 1994). Although the neurophysiology of these inhibitory connections is not well understood they have the potential to provide feedback to the striatum from downstream activity. The "double inhibition" structure of the striatal-GPe-striatal feedback loop may be used to selectively amplify MSN activity.

The pharmacological blockade of local striatal $GABA_A$ transmission which leads to tic expression in animals might mimic naturally occurring damage to any one of the above mentioned sources of striatal GABA transmission leading to tics in TS patients. Evidence for one possible reduction in GABA transmission in the striatum is the reduced number of GABAergic interneurons identified in post-mortem studies of TS patient (Kalanithi et al., 2005; Kataoka et al., 2010).

In addition to deficits directly affecting striatal GABAergic transmission, another source for dysfunction of the local striatal network might be altered internal or external neuromodulatory inputs. The internal striatal network is modulated by the activity of local cholinergic (Bolam et al., 1984) and dopaminergic interneurons (Ibanez-Sandoval et al., 2010), as well as by external DA, 5-HT, ACh and NE projections which have been shown to modulate MSN activity (Di Chiara et al., 1994; Fujimoto et al., 1981; Gerfen et al., 1990; Miller et al., 1975; Olpe and Koella, 1977). Animal models have shown that many of the behavioral changes induced by pharmacological manipulations of these neuromodulators are mediated by their effect on the striatum (Alsene et al., 2011; Kelley et al., 1988; Sipes and Geyer, 1997; Wan et al., 1995; Wan and Swerdlow, 1996). However, there are few physiological studies exploring the effects of these pharmacological manipulations on the activity of striatal neurons. Thus, while dysfunction of the normal striatal activity is a likely neural mechanism underlying the tics of TS patients, it may be induced either by direct deficits of the local GABAergic network or by deficits in the neuromodulators affecting its activity.

The clinical presentation of TS includes both motor abnormalities (i.e., tics), non-motor dysfunctions such as the SMG deficits, and multiple common psychiatric comorbid conditions (OCD/OCB, hyperactivity and attention deficits). A link between these different types of symptoms has also been observed in pharmacological animal models of the disorder. Models utilizing localized injections in the brain have typically shown that the same pharmacological manipulation can induce different behavioral effects based on the site of injection. This division was most explicit in the GABAergic animal model: while injections into the motor domain of the striatum produced motor tics (Crossman et al., 1988; McCairn et al., 2009; Tarsy et al., 1978), injections into the limbic domain resulted in stereotypic behaviors and other effects which were clearly non-motor (Kodsi and Swerdlow, 1995; Worbe et al., 2009). This coexistence of limbic and motor deficits suggests that the same type of functional dysfunction may underlie both types of symptoms. The BG and specifically the striatum are a likely location for this association since the histological and functional properties of its internal network are very similar across different functional domains. The defining feature differentiating functional domains is their different input/output connectivity patterns (Fig. 1). Thus, a similar type of neuronal pathology leading to the same deficits in striatal network information processing may yield very different behavioral outcomes, based on the type of cortical information being processed. Moreover, a distributed manifestation of the neuronal damage causing the functional dysfunction of the network across multiple striatal functional domains may account for the comorbid expression of movement (motor domain) and psychiatric (limbic domain) symptoms.

Overall, further studies pointing to the specific neuronal elements participating in the manifestation of the different TS symptoms are crucial for identifying the exact neural mechanism underlying TS. Progress in developing animal models that utilize advanced and more specific pharmacological methods may be the key to disentangling the complex interactions between different functional domains and different neuronal substrates of the striatum.

4.2. Theoretical constructs of TS

One of the validation criteria of animal models is construct validity which relates the association between the manipulation used to generate symptoms in the animal model and a theoretical construct accounting for the pathogenesis of symptoms in the human condition. However, models and constructs have a reciprocal relationship, in which the validity of a model may be based on its association with a construct and the findings of the model may support or weaken a pre-existing construct. Multiple hypothetical constructs explaining the underlying neural mechanism of TS currently exist, and have thus prompted the development of multiple animal models. However, since none of these constructs have been unequivocally established, the validity of these models should be evaluated both in terms of their face and/or predictive value and as regards to their contribution to the hypothetical construct.

Constructs attributing a primary dysfunction of a particular neuromodulator system to TS etiology were mostly based on responses to medication. These prompted the 'DA hypothesis' of TS, as well as hypotheses regarding the involvement of NE and 5-HT in the disorder. Based on these constructs, gross pharmacological manipulations of these neuromodulator systems were suggested to represent TS in model animals. However, these models have generally provided little support for these constructs. The main difficulty lies in the non-specific relationships between TS and both the neuropharmacological abnormality and the induced abnormal behaviors. The same pharmacological manipulations used to model TS have also been used to model disorders such as schizophrenia, OCD, ADHD, anxiety disorder, etc. To date, none of these models have addressed the specific features of the potential neuropharmacological dysfunction that could determine the nature of the different ensuing symptoms. Overall, this suggests that the specific symptoms of TS are not generated solely by a dysfunction of a particular neuromodulator system. Rather, either such pharmacological abnormality does not exist at all, or it is accompanied by dysfunction of other neural systems. In either case the beneficial effects of pharmacological treatments might be attributed to modulation of the damaged neural system by the manipulated neuromodulator. In the case of TS the effects of different neuromodulator systems may be mediated by their effects on the CBG system.

Dysfunction of the CBG system is currently the leading hypothesis regarding the neural mechanism underlying TS (see Section 1.3.1). However, the exact nature of the CBG pathophysiology related to TS and the causes for this dysfunction are still poorly understood. The different constructs suggested over the years to explain the CBG-TS association have mostly been derived from general theoretical models of the structure and function of the CBG system and its effect on normal and abnormal behaviors. Early theoretical models of the CBG system described all the neurons of a nucleus as a single entity which affects its downstream targets by either an excitatory or inhibitory effect (Albin et al., 1989; DeLong, 1990). According to this model, hypokinetic disorders (such as Parkinson's disease) are a result of enhanced BG output leading to reduced cortical activity whereas hyper-kinetic disorders (such as TS) are the result of reduced BG output leading to enhanced cortical activity. The modulating effects of DA on CBG activity were specifically addressed by this model. According to the model, an increase in the dopaminergic innervation to the striatum decreases the net output of the BG, by facilitating activity within the direct pathway and reducing activity in the indirect pathway (see Section 1.3.1). This shift in the balance between the two pathways reduces the inhibition exerted on the cortex by the BG, thereby increasing cortical activity and leading to hyper-kinetic symptoms. However, the model failed to account for the qualitative difference between different hyper-kinetic symptoms (tics, chorea, ballism) induced by this dopaminergic dysfunction. The dopamine pharmacological model of TS is consistent with this hypothesis, as dopamine agonists applied either systemically or locally within the striatum serve as animal models for the disorder. However, currently there is no direct evidence for a reduction in BG output following DA agonists application, since no electrophysiological studies have been conducted in this model.

Later theoretical and conceptual models of the BG pathway focused on their role in performing action selection (Mink, 1996). According to these models the BG receive cortical inputs representing multiple potential actions (behaviors). The information sent back to the cortex from the BG signals ("selects") which actions should be performed while inhibiting all other potential actions. This selection process within the BG may be mediated by the activity of the internal striatal inhibitory network and/or by the integration of feedforward and feedback projections from multiple BG nuclei. According to these models, hyper-kinetic and hyper-behavioral disorders are attributed to malfunctions in the action selection process (Mink, 2003). Specifically, it was hypothesized that in TS an aberrant area in the striatum (representing the tic action) fails to be inhibited by other actions and thus is performed in addition to the normal actions selected by the BG. This hypothesis is partially supported by the GABA antagonist animal model. In this model, a specific area in the striatum cannot be inhibited due to the binding of GABA antagonists. Electrophysiological recordings indicating that neurons in this area are indeed active surrounding the time of the tic (Bronfeld et al., 2011) support the action selection theoretical model. However, there is evidence that neurons downstream from the striatum and specifically in the BG output structures encode the tic in a distributed, rather than a focal manner (Bronfeld et al., 2011; McCairn et al., 2009; Muramatsu et al., 1990). This pattern of activity is in contrast with the classical notion of the action selection model in which each neuron or a small group of neurons are expected to encode a specific action, in this case a tic.

Theoretical models can lead to the formulation of new animal models of the disorder by pointing to potential brain areas and neurochemicals that can be manipulated to achieve TS-like symptoms. Animal models also have the potential to engender novel theoretical models by pinpointing the specific elements whose manipulation changes the computation performed by the neuronal system, and hence help uncover the patterns of abnormal neuronal activity associated with these symptoms. Taken together, the combination of theoretical conceptual models of TS and experimental animal models of the disorder may provide new concepts and data that should lead to a better understanding of the mechanisms underlying TS.

5. Summary and conclusions

Pharmacological animal models of TS focus on three properties associated with the disorder: motor tics, a hyper-behavioral state, and SMG deficits. These models can be broadly divided into two categories: systemic manipulations of neuromodulators (dopamine, serotonin or NE), and localized manipulation of GABAergic transmission within the motor domain of the striatum. Neuromodulator manipulations induce either a hyper-behavioral state (including stereotypic behaviors and hyperactivity) or SMG deficits, whereas local GABAergic manipulation induces motor tics. Furthermore, the involvement of a GABAergic dysfunction in hyper-behavioral phenomena associated with TS has been suggested by the induction of behavioral stereotypies and hyperactivity following disruption of GABA transmission in the non-motor striatal domains. All the pharmacological animal models indicate that the CBG loop is the main neural pathway mediating the TS-related behavioral effects of the pharmacological manipulation. Within the CBG, different functional sub-circuits appear to mediate different aspects of TS. The dorsal pathway involving the motor domain is primarily associated with tic manifestations and the ventral pathway involving the limbic domain is associated with premonitory urges and abnormal SMG.

Pharmacological animal models have mainly focused on a phenomenological description of the pharmacological manipulation and the ensuing behavioral effects, and less attention has been paid to the underlying modulation of neuronal activity. Recent neurophysiological studies using the localized striatal GABAergic model have led to advances in our understanding of the neural mechanism associated with the manifestation of motor tics. The application of advanced neurophysiological methods in other animal models may shed further light on additional properties of the disorder.

A major issue hindering the progress of TS research is the current lack of a conceptual (or even theoretical) model of the disease mechanism or the functionality of its underlying brain areas. This has impeded both the assessment of existing animal models and the development of new models. Novel data collected from human patients, combined with new neurophysiological data collected in animal models should help build a bottom-up conceptual model of TS. The future combination of novel pharmacological, electrical and genetic methodologies for selective manipulation of specific neural components with recordings of the associated neurophysiological activity is needed to uncover the neural mechanisms underlying TS and suggest new therapeutic targets.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2012.09.010.

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