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J Neurosci Methods. Author manuscript; available in PMC 2015 December 30.

Published in final edited form as:

J Neurosci Methods. 2014 December 30; 238: 54–69. doi:10.1016/j.jneumeth.2014.09.008.**Animal models of tic disorders: A translational perspective****Sean C. Godar^a, Laura J. Mosher^a, Giuseppe Di Giovanni^{c,d}, and Marco Bortolato^{a,b,*}**^aDepartment of Pharmacology and Toxicology, School of Pharmacy; University of Kansas, Lawrence, KS, USA^bConsortium for Translational Research on Aggression and Drug Abuse (ConTRADA), University of Kansas, Lawrence, KS, USA^cDepartment of Physiology and Biochemistry, University of Malta, Msida, Malta^dSchool of Biosciences, Cardiff University, Cardiff, UK**Abstract**

Tics are repetitive, sudden movements and/or vocalizations, typically enacted as maladaptive responses to intrusive premonitory urges. The most severe tic disorder, Tourette syndrome (TS), is a childhood-onset condition featuring multiple motor and at least one phonic tic for a duration longer than 1 year. The pharmacological treatment of TS is mainly based on antipsychotic agents; while these drugs are often effective in reducing tic severity and frequency, their therapeutic compliance is limited by serious motor and cognitive side effects.

The identification of novel therapeutic targets and development of better treatments for tic disorders is conditional on the development of animal models with high translational validity. In addition, these experimental tools can prove extremely useful to test hypotheses on the etiology and neurobiological bases of TS and related conditions. In recent years, the translational value of these animal models has been enhanced, thanks to a significant re-organization of our conceptual framework of neuropsychiatric disorders, with a greater focus on endophenotypes and quantitative indices, rather than qualitative descriptors.

Given the complex and multifactorial nature of TS and other tic disorders, the selection of animal models that can appropriately capture specific symptomatic aspects of these conditions can pose significant theoretical and methodological challenges. In this article, we will review the state of the art on the available animal models of tic disorders, based on genetic mutations, environmental interventions as well as pharmacological manipulations. Furthermore, we will outline emerging lines of translational research showing how some of these experimental preparations have led to significant progress in the identification of novel therapeutic targets for tic disorders.

Keywords

Tourette syndrome; Tic disorders; Animal models; Dopamine

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1. Introduction

Tics are repetitive, semi-voluntary, sudden movements and/or vocalizations, typically enacted in response to *premonitory urges*, subjective sensations often described as intrusive and uncomfortable feelings of inner tension, which are relieved by tic execution. The production of tics is due to the rapid contraction of discrete muscular groups; while motor tics are often produced by the activation of head, neck and face muscles (although they can also be observed in the trunk and limbs) (Jankovic, 1992); phonic tics are caused by rapid air movements through the larynx, and are sometimes accompanied by syllable repetition (*palilalia*), scatological utterances (*coprolalia*) and imitative reiteration of sounds and words (*echolalia*) (Jankovic, 2001).

Although tics can occasionally occur in every individual, their persistent and pervasive manifestation is regarded as pathological (in view of potentially serious repercussions on psychosocial and professional functioning of the affected subjects) and classified as *tic disorders*. Tic disorders are neurodevelopmental conditions affecting nearly 3% of the population (Knight et al., 2012). The most severe tic disorder, Tourette syndrome (TS), features multiple motor tics and at least one phonic tic (albeit not always simultaneously), within a period longer than 1 year, and with an age of onset younger than 18 years (APA, 2013). TS and other tic disorders are often comorbid with psychiatric disorders, including attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD) and impulse-control disorders (ICDs) (Ghanizadeh and Mosallaei, 2009; Frank et al., 2011).

Although the etiology of tic disorders remains elusive, several findings over the past two decades have elucidated key aspects of their pathophysiology. In particular, converging lines of evidence have convincingly shown that tics reflect functional imbalances within the corticolimbic circuitry, underpinned by dysregulations of dopamine, γ -amino-butyric acid (GABA) and other neurotransmitters. In contrast with this progress, the pharmacotherapy of tic disorders is still often based on the employment of antipsychotic agents (which block dopamine receptors). Indeed, haloperidol and pimozide remain the best-validated drugs to reduce tic severity and frequency in the majority of TS patients with medium and severe TS, but their use often results in poor therapeutic compliance, due to their potentially serious side effects (Silva et al, 1996; Mogwitz et al, 2013; Egolf and Coffey, 2014).

The development of novel drugs for TS and other tic disorders will be accelerated by the validation of more refined animal models of these conditions. Over the past few years, several new findings from genetic and functional studies, as well as conceptual advancements in behavioral neuroscience, have recently led to significant improvements in this area. The goal of the present review is to outline the main animal models of tic disorders, and highlight key methodological and interpretational issues and caveats posed by these preparations, with a particular focus on their translational validity.

As a general premise to the treatment of the key issues related to animal models of tic disorders, we will discuss our current knowledge on key aspects of the phenomenology and neurobiology of tics that are directly relevant in the generation and critical evaluation of animal models. We will then overview the current state of the art on the main behavioral and

neurobiological endophenotypes related to tic disorders, as well as animal models of these conditions based on genetic alterations and environmental manipulations. We will also describe a number of animal models based on pharmacological interventions that simulate specific aspects of pathophysiology. Finally, we will outline a number of experimental lines that have shown how the use of these models can lead to translational progress for the development of novel therapies for TS.

1.1. Phenomenology and neurobiology of tics

The following section will highlight key aspects of tic phenomenology, neurobiology and neurochemistry, which are of importance in the design and validation of animal models of tic disorders. For a more in-depth presentation of these issues see Leckman et al. (2006) and Martino et al. (2013).

Tics are highly heterogeneous phenomena, manifested across different modalities, localizations, frequency, duration and complexity (according to which criterion tics can be defined as either *simple*, if brief and abrupt; or *complex*, if consisting of more sustained, articulated movements or utterances). Irrespective of their presentation, the main distinctive features of tics lie in their repetitive character, their mimicry of normal and purposeful motor or vocal activities (such as eye blinking, touching objects, hopping, uttering meaningful words), and their contextual incongruity (Leckman et al., 2006).

Tics are commonly regarded as isolated or concatenated segments of automatic behavioral sequences, which are dissociated from their original valence and thereby executed in a misplaced, maladaptive and often reverberative fashion. The extraction of these automatic behaviors from their contextually appropriate motor program may reflect deficits in the cortico-striatal-thalamo-cortical (CSTC) loops, which have been extensively documented in TS (Worbe et al., 2012).

Another pathognomonic characteristic of tics, which is commonly used as a key criterion for differential diagnosis from other similar manifestations (such as twitches and myoclonus), lies in their association with *premonitory urges*. These sensations, which precede tic execution, are typically perceived as increasingly intrusive and uncomfortable feelings, sometimes accompanied by a sense of somatic tension (Kwak et al., 2003; Belluscio et al., 2011; Cohen et al., 2013). Although the nature of premonitory urges has not yet been fully clarified, these manifestations have been proposed to reflect an interoceptive “hyperattentional state”, characterized by psychological fixation and excessive awareness of stimuli from specific body parts (Kane, 1994). The intensity of the urges is typically exacerbated by stress and by any attempt to suppress tics, while it is alleviated by tic execution (Leckman et al., 1993); nevertheless, the severities of tics and urges are not correlated (Steinberg et al., 2010; Ganos et al., 2012), and urges appear to be directly linked to obsessive-compulsive and depressive symptoms (Steinberg et al., 2010).

The natural history of tics is highly variable and is characterized by major fluctuations in severity and frequency. Tics often begin appearing at 6–7 years of age as motor, simple manifestations. The appearance of phonic tics begins typically in the next few years (Robertson, 2011). Furthermore, the complexity of tics typically increases, together with a

greater awareness of premonitory urges. Remarkably, stress enhances the severity and frequency of tics (Cohen et al., 2013). After the beginning of puberty, tics often undergo a progressive remission; however, 30–40% TS patients retain tics throughout adulthood (Singer and Walkup, 1991).

Tics are posited to be caused by the combination of multiple genetic and environmental factors, ultimately resulting in functional deficits of the basal ganglia (Albin and Mink, 2006; Gilbert et al., 2006; Yoon et al., 2007a; Wong et al., 2008; Leckman et al., 2010; Felling and Singer, 2011; Eichele and Plessen, 2013). These structures are key components of the CSTC system, which are directly implicated in the generation of extrapyramidal motor patterns and modulation of automated motor performances. In support of this concept, tic-like behaviors have been shown to emerge following lesions of the basal ganglia (Peterson et al., 1996; Gomis et al., 2008; Ranjan et al., 2011). Tics appear to result from imbalances of the inhibitory and excitatory inputs in these regions, either related to insufficient inhibition from select families of interneurons (Kalanithi et al., 2005; Kataoka et al., 2010), or excessive stimulation of specific neuronal clusters (Albin and Mink, 2006).

Irrespective of the source, the common outcome of these impairments is likely an inadequate “center-on surround-off” interaction in these structures, which leads to the activation of ectopic foci and a partial inability to suppress competing or unwanted motor sequences. It should be noted that most tics tend to involve the activation of facial and neck muscles, possibly suggesting a preferential localization of ectopic foci within the neurons of the ventromedial in the striatum (which represent these regions, based on the somatotopic organization of this brain area; see Maillard et al., 2000; and Nambu, 2011) and their downstream projections.

While multiple lines of evidence have underscored the role of basal ganglia in TS ontogenesis, several findings indicate that the prefrontal cortex may have an equally important role in tics. Indeed, the ability to suppress tics temporarily is likely to reflect the ability of this region to control the automatic functions of the basal ganglia (Peterson et al., 1998). Cortical disinhibition of striatal circuits has been documented in TS (Heise et al., 2010). Furthermore, impairments in cortical activation have also been evidenced in the execution of “go-no go” tasks in TS patients (Ganos et al., 2014; Thomalla et al., 2014), which likely underpin their slower performance in these tests (Eichele et al., 2010).

Although the alterations in CSTC circuits underlying tics involve multiple neurotransmitter systems, a number of neuroimaging studies and postmortem analyses have clearly documented that tics are likely supported by excess activation of dopamine receptors or other alterations of dopaminergic system (Minzer et al., 2004; Gilbert et al., 2006; Steeves et al., 2010). Accordingly, dopamine receptor antagonists, such as haloperidol and pimozide, are highly effective in reducing tic severity (Bloch et al., 2011; Roessner et al., 2013), while dopaminergic agonists have been associated with an exacerbation of tics (Shale et al., 1986). Of note, recent studies indicate that one of the main impairments in the involvement of dopaminergic neurotransmission in tics may lie in the dysregulation of (reduced) tonic and (overactive) phasic dopamine levels in the basal ganglia (Wong et al., 2008; Buse et al., 2013). Tics maybe underpinned by rapid variations in synaptic dopamine content. In

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addition to dopamine, other neurotransmitters are implicated in tic disorders. In particular, post-mortem studies have identified a loss of GABA and cholinergic inhibitory interneurons in the basal ganglia of TS patients (Kalanithi et al., 2005; Kataoka et al., 2010). Given that striatal interneurons exert a modulatory role on dopamine signaling (Ellender et al., 2011), this reduction is likely to contribute to the disinhibition of dopaminergic neurotransmission. The contribution of serotonin and norepinephrine in tics, albeit suggested by pharmacological evidence (see below), is more controversial and may be related to specific subgroups of TS and comorbid manifestations, rather than to the whole spectrum of tic disorders (Steeves and Fox, 2008; Udvardi et al., 2013).

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A host of studies have documented that male patients have a higher predominance (male:female = 4:1), severity and poorer prognosis than females; however, genetic investigations in patients have failed to identify any sex-specific alterations that may account for this sexual dimorphism. On the other hand, emerging evidence suggests that the gender differences in TS may be supported by the implication of androgen hormones in the pathophysiology of tics (for further reading on this topic, see Bortolato et al., 2013a,b).

2. Animal models of tic disorders: validity criteria and endophenotypes

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Similar to other neuropsychiatric disorders, animal models provide a powerful tool to test hypotheses on the biological substrates of TS and other tic disorders in a controlled experimental setting. Given the high complexity of tics and related behavioral phenomena, animal modeling of these condition is generally based on mammalian species, and, in particular, rodents, given their high cost-effectiveness and acceptable degree of neurobiological similarity with humans.

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As in the case of other illnesses, the validation of an animal model of TS is essentially based on three major criteria (Willner, 1986):

1. *Face validity*, which refers to the analogy between the behavioral performance of the animal models and the signs and symptoms in tic disorders;
2. *Construct validity* (encompassing also *etiological validity*), which evaluates the congruence between the etiological and pathophysiological processes in tic disorders and the neurobiological basis of the behavioral manifestations in the animal models;
3. *Predictive validity*, which qualifies the responsiveness of the animal model to treatments validated for tic disorders (such as antipsychotic agents and clonidine).

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The application of each of these criteria to animal models of tic disorders poses a number of challenges. For example, testing an animal model for face validity implies the presentation of tic-like behaviors; nevertheless, given that the behavioral repertoire of rodents is distinctly different from that of humans, and tics reproduce purposeful behaviors in a repetitive and maladaptive fashion, it is to be expected that tic-like behaviors in these species may markedly diverge from those observed in TS patients. For example, it is difficult to predict whether these manifestations should involve vocalizations, in consideration of the different development of laryngeal motor apparatus in humans, as

compared to rats and mice. Thus, it is clear that the substantiation of a potential model of TS based on face validity bears significant risks of anthropomorphic bias, and can lead to numerous confounds. In relation to this issue, Swerdlow and Sutherland (2006) indicated several instances of animal models (such as the stargazer rats and mice) in which spontaneous motor jerks in animals have been sometimes framed as “tic-like” manifestations, even though their neurobiological underpinnings are strikingly different from the substrates of TS. These examples show that, while face validity remains a key criterion in the analysis of animal models of tic disorders, a superficial assessment based uniquely on this parameter has very limited translational value and should not be deemed sufficient for drug development studies. The low reliability of face validity in the evaluation of tic-like manifestations is further underscored by recent studies, showing marked variations in the expression of tic-like behaviors induced pharmacologically across different murine strains (Proietti Onori et al., 2014). Finally, the nature of tic-like behaviors cannot be fully validated due to the impossibility to ascertain the existence of premonitory urges or internal experiences in animals.

While predictive validity can be an effective complement to face validity, excessive reliance upon this criterion should also be avoided, in consideration of the fact that several TS patients do not respond to any of the available treatments. Furthermore, the excessive refinement of animal models and behavioral paradigms aimed at enhancing their responsiveness to well-validated therapies can constrain their translational potential, by reduce their ability to capture the effects of novel treatments based on divergent mechanisms of action.

The most problematic aspect of the verification of construct validity in animal models of tic disorders lies in our limited knowledge of the pathophysiological bases of these conditions. This problem is compounded by the limitations of our current diagnostic classification of tic disorders, which are based on symptomatic parameters, but not on quantitative, measurable indices. Indeed, the diagnostic guidelines of the DSM-5 (APA, 2013) differentiate subtypes of tic disorders based on the severity and pervasiveness of tics, but not on their neurobiological bases. This classification is likely to mix in the same category a number of potentially heterogeneous conditions that share similar symptomatic aspects, but depend on different pathophysiological mechanisms and also respond to different therapies. This reliance on signs and symptoms as central diagnostic criteria may also be applied to several other types of neuropsychiatric conditions.

In order to overcome these limitations, researchers have begun dissecting complex neuropsychiatric conditions, such as TS into more elementary “building blocks”. In this respect, a very important innovation in our conceptual framework for animal models of tic disorders is a new focus on *intermediate phenotypes* (Leboyer et al., 1998) which are defined as measurable indices posited to reflect a more elementary set of neuroanatomic, functional or psychological deficits, than the whole array of deficits associated with TS. The best-known example of intermediate phenotypes is afforded by endophenotypes, defined as heritable features corresponding to elements of vulnerability to a given disorder (Gottesman and Shields, 1973). Endophenotypes may encompass behavioral, neuroanatomical, biochemical, neurophysiological, neuropsychological, or cognitive traits related to specific

genetic factors (Gould and Gottesman, 2006; Arts et al., 2008; Viswanath, 2009). Endophenotypes are not inherently pathological, but should be regarded as vulnerability elements, which can facilitate the development of a disorder in the presence of other critical abnormalities (derived from other genetic factors or environmental variables).

It is worth noting that the “atomistic” approach afforded by intermediate phenotypes is more amenable to the implementation of effective translational strategies, particularly when referring to cross-species parameters (which can be dependably measured in both humans and animal models) (Rutter, 2008; Bearden et al., 2009; Markou et al., 2009).

This background highlights that research on animal models of tic disorders and TS refers to two main objectives: (1) the development of animal models based on either genetic mutations or environmental interventions aimed at replicating the key factors associated with the etiology of these disorders; and (2) the confirmation of endophenotypes in TS models across the criteria of face, construct and predictive validity.

3. Neurobehavioral phenotypes relevant to tic disorders

3.1. Stereotyped behaviors

Stereotypies are defined as motor and behavioral sequences that are repeated purposelessly (Ridley, 1994). These behaviors are typically exhibited by most captive animals kept in spatial restriction (which interferes with the expression of behavioral needs) and are interpreted as a spontaneous manifestation of environmental discomfort, likely linked to the expression of functional responses (such as foraging) in the absence of adequate sensory feedback (Dantzer, 1991).

The relevance of animal stereotypies to TS is defined by all three validity criteria; like tics, stereotypies are repetitive, habit-forming motor patterns, which typically mimic purposeful behaviors. As described in Section 6 below, oro-facial and head-bobbing stereotypies can be induced in experimental rodents by several pharmacological agents that impinge on neurochemical substrates related to tics, including agonists for dopamine and serotonin 5-HT₂ receptors. Studies have shown that, like tics, animal stereotypies (either spontaneous or pharmacologically induced) reflect alterations of the basal ganglia (Garner and Mason, 2002); more specifically, the injection of dopaminergic agonists in the dorsal striatum has been shown to evoke stereotyped behaviors in rodents, with a mechanism that involves both D₁-like and D₂-like dopamine receptors. Finally, the predictive validity of stereotyped behaviors with respect to tics, is confirmed by the ability of antipsychotic agents to fully suppress these manifestations (Arnt, 1985; Arnt et al., 1988; Conti et al., 1997).

With respect to the analogy between tics and stereotypies in humans, it should be noted that, while tics used to be regarded as stereotyped behaviors, the DSM-5 has clearly defined a separation between these two phenomena. According to the current diagnostic classifications, stereotypies are defined as more severe and pervasive than tics, and typically associated with intellectual disabilities (such as in fronto-temporal dementia, autism-spectrum disorder and some subtypes of schizophrenia). Furthermore, they are characterized by greater rhythmicity, fewer temporal fluctuations, and no relation to premonitory

antecedents. However, it is worth noting that this distinction has not yet led to a reorganization of the corresponding nomenclature in animal ethology, and thus it is likely that animal stereotypies may correspond to a broader set of phenomena than the human homonyms.

3.2. Prepulse inhibition (PPI) of the startle reflex

PPI is the reduction in startle response elicited by a strong sensory stimulus that occurs when the latter is preceded by a weaker signal (Fig. 1) (Hoffman and Ison, 1980; Braff et al., 1992, 2001). This index is considered a highly dependable measure of sensorimotor gating, the cognitive function that enables the formation of salience maps by filtering out non-relevant information. PPI deficits have been documented in TS (Castellanos et al., 1996; Swerdlow et al., 2001a,b; Zebardast et al., 2013), as well as in OCD (Hoenig et al., 2005; Ahmari et al., 2012). Although the severity of tics and obsessive-compulsive manifestations is not correlated with PPI impairments (Swerdlow et al., 2001a,b; Ahmari et al., 2012), this index is regarded as a key intermediate phenotype for tic disorders. Of note, PPI disruptions are found in several other neuropsychiatric disorders, thus studies that examine the effects of pharmacological manipulations on PPI should be interpreted in this context. The phenomenological connection between sensorimotor gating deficits and PPI is posited to reflect sensory alterations in TS patients, which may also underpin the enhanced sensory feedback and somatic sensitivity in this disorder (Bliss, 1980; Kane, 1994; Biermann-Ruben et al., 2012; Cohen et al., 2013). In addition, the high construct validity of PPI for tic disorders is supported by the overlapping neurobiological and neurochemical substrates of sensorimotor gating with the brain regions involved in TS pathophysiology; indeed, PPI deficits can be induced in rodent models by lesions of the CSTC loops as well as stimulation of dopamine and 5-HT₂ receptors (Geyer et al., 2001; Swerdlow et al., 2001a,b). In parallel, PPI deficits in TS patients have been shown to be associated with altered caudate activation patterns (Zebardast et al., 2013). Finally, PPI deficits in rodents can be reversed by TS medications (Geyer et al., 2001). Nevertheless, it should be noted that the efficacy of antipsychotic agents in reversing PPI alterations has not been validated in TS patients and has produced equivocal results in mental patients with gating disturbances (Kumari et al., 2000, 2002; Graham et al., 2001; Kumari and Sharma, 2002; Xue et al., 2012).

3.3. Neurobiological deficits in the CSTC circuits

As stated above, several findings have elucidated that tics are underpinned by alterations of the basal ganglia. In particular, a host of studies have documented that TS is accompanied by low caudate volume, thinning of sensorimotor cortices and high corticostriatal activity during tic execution (Hyde et al., 1995; Peterson et al., 2003; Bloch et al., 2005; Makki et al., 2009; Plessen et al., 2009; Fahim et al., 2010).

The reduction in caudate volume has been highlighted as a potential predictive measure of tic severity in adulthood (Bloch et al., 2005). Based on the well-documented striatal disinhibition in TS (Baym et al., 2008; Mazzone et al., 2010; Wang et al., 2011; Bronfeld et al., 2013) and the finding of a selective loss in parvalbumin-positive interneurons in the striatum of TS patients (Kalanithi et al., 2005; Kataoka et al., 2010), a number of studies have begun addressing direct neurobiological hypotheses by producing selective lesions

and/or pharmacological treatments in the basal ganglia. Remarkably, selective ablation of D₁-receptor expressing striatal neurons has recently been shown to exhibit tic-like movements sensitive to treatment with the dopaminergic blocker haloperidol, as well as other locomotor impairments and striatal atrophy (Kim et al., 2014).

The thinning of the somatosensory cortex in TS (Fahim et al., 2010) has also appeared to serve as a potential index for symptom severity (Sowell et al., 2008; Fahim et al., 2010), and may underpin the perceptual alterations associated with tics. Interestingly, Steiner and Kitai (2000) found that dopaminergic stimulation activates barrel fields (the rodent equivalent of somatosensory cortex, which regulate the sensory input and activity from vibrissae) through D₁-like receptors in the striatum, suggesting that the connectivity between these two regions may play a key role in the execution of tics.

4. Animal models based on genetic manipulations

The heritability patterns of TS and other tic disorders indicate that the pathogenesis of these conditions is strongly influenced by genetic factors (Scharf and Pauls, 2007). Although no genetic variation and/or mutation has been consistently linked to tic disorders, multiple candidate genes have been associated with TS (for a comprehensive review of this issue, see Paschou, 2013). To study the endophenotypic contribution of these genes with respect to tic disorders, several lines of corresponding knockout (KO) mutant mice have been developed. In addition, a number of genetic models of TS have emerged either based on specific pathophysiological hypotheses (such as the implication of dopamine and its receptors) or by the serendipitous discovery of phenotypic resemblances with tic disorders.

4.1. Mice with mutations of candidate genes for TS and tic disorders

To date, only a few genes have been convincingly implicated in the pathogenesis of TS (Table 1). Nevertheless, the current availability of high-throughput techniques is rapidly increasing the number of candidate genes for TS. In this perspective, Scharf et al. (2013) recently published the results of the first genome-wide association study in TS, which involved 1496 TS patients and 5249 non-affected individuals. Although no association reached the significance threshold, the study identified strong signals in the genes *COL27A1* and *POL3B* (encoding type XXVII collagen alpha chain and RNA polymerase III, respectively) (Scharf et al., 2013).

The main lines of murine mutants of genes involved in tic disorders are outlined below.

4.1.1. Dopamine transporter (DAT) KO and knockdown mice—The gene *DAT1* (also termed *SLC6A3*) encodes one of the primary regulators of synaptic dopamine content (Kurian et al, 2009). The main function of DAT is to facilitate the reuptake of dopamine into the presynaptic terminal. A reduction in DAT function and expression is conducive to a significant enhancement of dopamine synaptic levels in the striatum; thus, several studies have sought a potential relation between genetic variants of *DAT1* and TS. Although the results of these studies have not been consistently replicated, several independent lines of research have pointed to *DAT1* as a potential risk factor for TS susceptibility (Comings et al., 1996; Diaz-Anzaldúa et al., 2004b; Tarnok et al., 2007; Yoon et al., 2007b).

In line with this evidence, DAT KO mice mimic some of the biochemical abnormalities in TS and show TS-like behaviors, including perseverative behaviors, hyperlocomotion and attentional alterations (Giros et al., 1996; Ralph et al., 2001; Zhuang et al., 2001; Berridge et al., 2005; Fox et al., 2013). In addition, DAT KO (but not knockdown) mice exhibit PPI deficits, which were ablated by antagonists of D₂ dopamine and 5-HT_{2A} serotonin receptors, as well as the blockers of norepinephrine transporter (Ralph et al., 2001; Ralph-Williams et al., 2003; Barr et al., 2004; Yamashita et al., 2006). Conversely, the perseverative patterns exhibited by these mutants appear to be sensitive to D₁-like receptor blockers (Ralph et al., 2001). Notably, DAT-deficient mice display lower surface expression and binding of D₁ receptors, in comparison with wild-type (WT) mice (Dunmartin et al., 1999; Fernagut et al., 2003). Overall, although DAT mutants do not exhibit spontaneous tic-like manifestations, the available results appear to indicate that these lines of transgenic mice may have high validity for TS-related endophenotypes.

4.1.2. Monoamine oxidase A (MAOA) KO and hypomorphic mice—MAO A is the key enzyme serving the metabolism of serotonin and norepinephrine, and plays an important contributory role in the degradation of dopamine (Bortolato et al., 2008a). The implication of the *MAOA* gene as a potential genetic vulnerability for TS has been shown by a few studies (Gade et al., 1998; Diaz-Anzaldúa et al., 2004a,b). In humans, a nonsense point mutation of *MAOA* has been shown to result in aggressive behavior (Brunner et al., 1993). Furthermore, low-activity variants of a functional VNTR polymorphism of *MAOA* promoter have been associated with a greater predisposition to aggressive temperament, particularly in boys with a history of early trauma (Caspi et al., 2002). Although aggressive manifestations are relatively frequent in TS (Stephens and Sandor, 1999; Budman, 2006), to the best of our knowledge no studies have addressed the potential link between MAOA variants and aggressive trait in tic disorders.

Multiple lines of MAOA KO and hypomorphic mice have been generated (Cases et al., 1995; Scott et al., 2008; Bortolato et al., 2011); in line with human data (Buckholtz and Meyer-Lindenberg, 2008), these lines of transgenic mice exhibit alterations in environmental and social processing, which lead to maladaptive behaviors in the presence of environmental challenges (Bortolato et al., 2011; Godar et al., 2011). MAO A KO, but not MAO A hypomorphic mice exhibit spontaneous aggression (Cases et al., 1995; Scott et al., 2008; Bortolato et al., 2011; Bortolato and Shih, 2011). In addition, recent analyses have ascertained that MAOA mutants feature a number of other phenotypic characteristics, some of which may be relevant to the pathogenesis of TS, such as a higher proclivity to manifest spontaneously repetitive behaviors (Bortolato et al., 2011, 2013a,b). The effects of treatments of TS on the repetitive behaviors in this line have not yet been tested. In preliminary data, we found that treatment with low, intrinsically ineffective doses of apomorphine, a non-selective dopaminergic agonist, induced a significant increase in stereotyped behaviors in MAO A KO mice (Godar and Bortolato, unpublished observations). Although neither MAO A KO nor hypomorphic mice exhibit spontaneous PPI deficits, both lines are hyperresponsive to the PPI-disruptive properties of NMDA glutamate receptor antagonists in this paradigm (Godar and Bortolato, unpublished observations), possibly reflecting alterations in the subunit composition of this receptor in

the prefrontal cortex (Bortolato et al., 2012). Of note, MAO A KO mice feature a prominent disruption of somatosensory cortex (Cases et al., 1995), possibly suggesting a template for the neuroanatomical alterations of this region in TS patients.

4.1.3. Contactin-associated protein-like 2 (CNTNAP2) mutants—The CNTNAP2 protein plays a key role in the cell-adhesion pathways and cortical development (Ip et al., 2010; Anderson et al., 2012; Clarke et al., 2012). Mutations for *CNTNAP2* gene have been recognized in a rare, familial form of TS (Verkerk et al., 2003). In addition, a trend for an association between SNP variants of this gene and TS has been reported (Scharf et al., 2013). CNTNAP2 mutant mice display autistic-like phenotypes and hyperactivity (Penagarikano et al., 2011). While these phenotypes are not directly reminiscent of those observed in TS, it should be noted that many genetic bases of autism-like behaviors are also shared with TS (Lewis and Kim, 2009; Clarke et al., 2012). CNTNAP KO mice also display abnormalities in neuronal migration, reduced number of interneurons and abnormal neuronal network activity. Furthermore, the highly repetitive behaviors of these animals were reduced by the antipsychotic risperidone (Penagarikano et al., 2011), which has high effectiveness in TS (Bruun and Budman, 1996; Bruggeman et al., 2001). Interestingly, a recent study found that CNTNAP2-deficient mice exhibit increased levels of dopamine release into the striatum, as well as a reduction in GABAergic interneurons and altered inhibitory signaling (Karayannis et al., 2014). These changes were accompanied by excessive grooming behaviors that were responsive to haloperidol treatment (Karayannis et al., 2014).

4.1.4. SLIT and NTRK-like (SLITRK) family mutant mice—The SLITRK family consist of 6 genes that encode leucine-rich transmembrane proteins, involved in axonal targeting and neuronal differentiation. While the function of SLITRK1 in the brain is still unclear, recent studies have shown that this molecule is dynamically associated with CSTC circuits (Stillman et al., 2009) and regulates neurite growth (Kajiwara et al., 2009).

Notably, *SLITRK1* has been identified as a candidate gene responsible for rare, familial forms of TS (Abelson et al., 2005; Deng et al., 2006; O’Roak et al., 2010); furthermore, few recent studies have shown an association between these gene and TS (Miranda et al., 2009; Karagiannidis et al., 2012; but see Keen-Kim et al., 2006; Scharf et al., 2008; and Zimprich et al., 2008 for contrasting evidence). In addition, this gene has been implicated in comorbid disorders, such as OCD and trichotillomania (Abelson et al., 2005; Zuchner et al., 2006; Ozomaro et al., 2013).

In mice, the overexpression of SLITRK1 induces neuronal outgrowth, whereas the other members of the SLTRK family appear to inhibit the same process (Aruga and Mikoshiba, 2003). The SLITRK1 KO mice has been developed and exhibits high norepinephrine levels, as well as anxiety-like responses which are sensitive to clonidine (Katayama et al., 2010); nevertheless, these mutants do not exhibit tic-like or related motor manifestations.

It is worth noting that mice with a null-allele mutations for the SLITRK5 gene display excessive autogrooming and high anxiety-like responses, which appear to be underpinned by the overactivation of the orbitofrontal cortex. In addition, these mutants feature abnormal

morphology of striatal cells, and fluoxetine-sensitive changes in the subunit composition of glutamate receptors (Shmelkov et al., 2010).

4.1.5. L-Histidine decarboxylase (HDC) KO mice—HDC plays a role in histaminergic signaling (Fernandez et al., 2012) by facilitating the conversion of histidine into histamine (Haas et al., 2008). Similar to the above genes, a mutation of the HDC gene was found in a familial type of TS (Ercan-Sencicek et al., 2010; Karagiannidis et al., 2013). This discovery led to the generation of Hdc-deficient mice; these mutants do not exhibit spontaneous stereotypies, but display elevated levels of dopamine in the striatum, which lead to a marked increase in amphetamine-induced stereotypies. Notably, these phenomena are attenuated by D₂ dopamine receptor blockade, as well as intracerebral histamine infusion. In addition, HDC deficiency was found to result in PPI deficits and up-regulated brain D₂/D₃ receptor binding in both humans and mice (Castellan Baldan et al., 2014). The role of histamine in the pathophysiology of TS remains unclear, but it may reflect the ability of this neurotransmitter in exerting a modulatory role on striatal dopaminergic transmission (Ellender et al., 2011).

4.1.6. Neuroligin (NLGN) family mutant mice—Neuroligins are postsynaptic cell-adhesion molecules, which have been implicated in the regulation of synaptic plasticity and in the pathogenesis of autism-spectrum disorder (Tabuchi et al., 2007; Sudhof, 2008; Dahlhaus et al., 2010).

A rare, familial form of NLGN4 deletion has been associated with tic disorders and autism (Lawson-Yuen et al., 2008); however, no further studies have identified associations between this gene and TS to date. Mutants of *NLGN4* gene, which encodes for neuroligin-4, a synaptic cell adhesion protein have been shown to display autistic-like behaviors, including social interaction deficits and alterations of ultrasound communication in early developmental stages (Jamain et al., 2008; Ju et al., 2014); to the best of our knowledge, however, no TS-related endophenotypes have been tested in these mutants. Interestingly, NLGN4 KO mice feature decreased excitability in the somatosensory cortical networks (Delattre et al., 2013); further studies are needed to establish whether these functional deficits may be related to the observed thinning of somatosensory cortex in TS patients (Fahim et al., 2010; see Section 3.3).

Of note, recent findings indicate the potential implication of neuroligins in the regulation of dopaminergic neurotransmission, indicating a potential connection with aspects of TS pathophysiology. Indeed, neuroligin 3 mutant mice were recently shown to exhibit acquired repetitive behaviors, which were underpinned by the selective impairment of synaptic inhibition on medium spiny neurons expressing D₁, but not D₂ receptors in the ventral striatum and nucleus accumbens (Rothwell et al., 2014).

4.1.7. SAP90 associated protein 3 (SAPAP3) KO mice—The *SAPAP3* gene (also termed *DLGAP3* in humans) encodes for a key scaffolding component of the post-synaptic density (PSD) protein complex (Scannevin and Huganir, 2000). Recent studies have highlighted this gene as a promising candidate for TS (Crane et al., 2011) and OCD (Bienvenu et al., 2009; Zuchner et al., 2009). Mouse mutants of this gene have been shown

to exhibit excessive grooming, as well as a number of functional and neuroarchitectural abnormalities, which were rescued by reinstatement of the protein through lentiviral vectors (Welch et al., 2007; Xu et al., 2013) or optogenetic stimulation of lateral orbitofronto-striatal circuits (Burguiere et al., 2013). The impact of anti-tic agents on excessive grooming in this line, however, remains to be tested.

4.2. Other genetic mutant models of TS

As stated above, a different approach to TS is based on the identification of murine genetic mutants that feature alterations akin to those manifested in this disorder. One of these models, the D1CT-7 mice, are currently regarded as one of the TS models with highest face and predictive validity, in view of their unique “tic-like” manifestations that respond to the main pharmacotherapies approved for TS (see below). Another interesting example is afforded by mice with mutations of the *Hoxb8* gene, which exhibit grooming and marked abnormalities in the projection neurons of the CSTC and brainstem loops (Greer and Capecchi, 2002; Reilly, 2002); these characteristics may have relevance to TS and related disorders, such as trichotillomania.

In spite of the resemblance between the behavioral repertoires of these models and TS symptoms, the construct validity of these animals is questioned, given the lack of current knowledge on the relevance of their mutations in the pathophysiology of TS.

4.2.1. D1CT-7 mice—D1CT-7 mice harbor a transgene that was generated via the attachment of the cholera toxin intracellular enzymatic subunit A1 to the human dopamine D₁ receptor promoter (Campbell et al., 1999). This construct was found to result in the chronic potentiation of the activity of a subset of D₁-harboring neurons, located in layer II of the piriform cortex, layers II and III of the somatosensory cortex, and intercalated nucleus of the amygdala (Campbell et al., 1999).

D1CT-7 mice exhibit a number of TS-related phenomena. Most notably, these mutants are among the few mutants that exhibit spontaneous tic-like manifestations, consisting in sudden axial jerks (Fig. 2), from the third week of postnatal life (a period roughly corresponding to the age of onset of TS). These manifestations are counteracted by treatment with benchmark drugs for TS, including antipsychotic drugs and clonidine (Nordstrom and Burton, 2002). In parallel with the above-discussed aspects of TS patients, D1CT-7 mice exhibit sexual dimorphism, with greater severity and complexity of tic-like behaviors in males (Nordstrom and Burton, 2002). In addition to TS-related phenotypes, D1CT-7 mice also display hyperlocomotion, leaping and other psychomotor abnormalities, as well as perseverative responses, which have been likened to compulsive manifestations of OCD.

In contrast with the high face and predictive validity of D1CT-7 mice, their construct validity has been questioned, due to the artificial nature and anatomical localization of their transgene (Swerdlow and Sutherland, 2006). Pyramidal cells in layers II and III are the main source of intracortical horizontal projections (Hess and Donoghue, 1994) and receive an abundant input from dopaminergic neurons (Gaspar et al., 1995; Lu et al., 1997), which enhance excitatory post-synaptic currents through D₁ receptor activation (Gonzalez-Islas and Hablitz, 2003). While this construct suggests that tic-like phenomena may result from

corticostriatal hyperactivity, this possibility is in direct conflict with the observations of cortical hypoactivation in TS, casting doubts on the relevance of these manifestations with respect to tics (Swerdlow and Sutherland, 2006).

The relevance to the neuropotentiation of D₁-positive neurons in the intercalated nucleus of the amygdala in TS is also elusive; however, this localization may be related to the OCD-like manifestations in DICT-7 mice, given the well-documented involvement of this brain region in the regulation of fear extinction (Likhtik et al., 2008), a functional domain that is typically impaired in OCD (Milad et al., 2013). Indeed, the neurons of the intercalated nucleus of the amygdala work as relay cells for intra-amygdaloid signals, by regulating the traffic between the input from the orbitofrontal cortex and the basolateral amygdala and the output stations in the central nucleus (Royer et al., 1999; Ghashghaei and Barbas, 2002), which allow for the expression of fear.

The validation of the construct of DICT-7 mice for TS awaits future evaluations on key endophenotypes related to tic disorders, including PPI and neurobiological alterations of the basal ganglia.

5. Animal models based on environmental etiology

The development of animal models of tic disorders based on environmental manipulations relies on two complementary strategies aimed at maximizing the construct and etiological validity of these preparations:

1. the replication of environmental factors associated with a documented higher risk for TS (such as prenatal or early postnatal exposure to stress or inflammation); and
2. the simulation of specific aspects of TS pathophysiology with pharmacological interventions related to the main neurotransmitter systems involved in tic ontogeny.

These two different approaches will be described in this and the next section, respectively.

5.1. Models of early stress and obstetric complications

Several epidemiological studies suggest that early exposure to a number of critical environmental factors may play a role in the pathogenesis of TS and other tic disorders. In particular, the risk for TS has been shown to be significantly enhanced in patients with a history of adverse events and/or stress in the prenatal and perinatal period (Leckman et al., 1990; Motlagh et al., 2010; Bos-Veneman et al., 2011), as well as maternal smoking (Mathews et al., 2006). Given that obstetric complications and maternal smoke have been linked to multiple mental disorders, several animal models have been developed in the attempt of reproducing the pathophysiological sequence leading to their sequelae (Boksa, 2004; Yochum et al., 2014). Most of these preparations, however, have not been specifically tested from the perspective of tic disorders, and their translational validity for TS awaits to be comprehensively examined. Nevertheless, the majority of these models may reproduce salient phenomenological aspects of tic disorders, given that they feature alterations in dopaminergic signaling, as well as higher susceptibility to stereotyped behaviors and PPI deficits (Boksa, 2004).

5.2. Models based on early neuroinflammation

The best-documented environmental factor of TS etiology that has been investigated in animal models is the implication of neuroinflammatory events, and, in particular, infections during prenatal or early postnatal life. Several lines of evidence have documented a possible relation between the exposure to Group A β -hemolytic streptococci (GAHBS) and tic disorders (Swedo et al., 1998; Mell et al., 2005), as well as other neuropsychiatric disorders (Leslie et al., 2008). The finding of antibodies for GAHBS in a subgroup of children with acute-onset tic disorders led to the definition of a novel entity, named PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection) (Leonard and Swedo, 2001; Swedo and Grant, 2005; Swedo and Leonard, 1994; Swedo et al., 1998, 2010). Subsequent research, however, has significantly challenged the idea of this entity as a separate disorder from TS/OCD, also due to the inconclusive support for an etiological role of GAHBS in this condition. For these reasons, PANDAS is not currently recognized as a distinct entity by either the DSM or the ICD; alternative nomenclatures, which no longer emphasize the causal role of GAHBS or other infectious agents, have been recently proposed to describe related neuropsychiatric disorders characterized by sudden onset during childhood (Singer et al., 2012; Swedo et al., 2012).

Irrespective of these diagnostic issues, the link between inflammatory agents and TS pathogenesis has been investigated in rodent models. For example, mice immunized for group A streptococci were found to exhibit TS-related manifestations, such as increased grooming and rearing (Hoffman et al., 2004; Yaddanapudi et al., 2010; Brimberg et al., 2012). In addition to these behavioral changes, these animals displayed anti-brain antibodies in their serum, as well as increased IgG concentrations in several brain regions, such as the striatum, cerebellum, and hippocampus (Hoffman et al., 2004; Yaddanapudi et al., 2010).

In an attempt to demonstrate that TS pathogenesis may be linked to the presence of autoantibodies, serum from TS patients has been injected into the striatum of rats. This treatment has been shown to lead to motor and oral stereotypies, as well as episodic vocalizations and increased genital grooming (Hallett et al., 2000; Taylor et al., 2002; Singer et al., 2005), in association with IgG deposits (Hallett et al., 2000). Rats treated with serum from TS patients were also found to exhibit increased levels of dopamine and reduced DAT expression (Jijun et al., 2010). Interestingly, an increase in stereotyped movements and tic-like responses was observed in rodents treated with TS sera with immunoreactivity for the potassium/sodium hyperpolarization-activated cyclic nucleotide channel 4 (HCN4) (Yeh et al., 2012). HCN4 belongs to a family of channels that regulate GABA release in the globus pallidus (Hallworth and Bevan, 2005; Boyes et al., 2007; Boyes and Bolam, 2007). Although no direct link between HCN4 and TS has been reported, polymorphic variants of the gene encoding for this protein have been associated with OCD and mood disorders (Kelmendi et al., 2011).

While these animal models are highly valuable to understand the immune contributions in TS pathophysiology, their validation is complicated by poor reproducibility. The phenotypical spectrum of the behavioral and neurobiological sequelae of TS serum administration and/or antigens related to infectious agents in rodents are highly heterogeneous. This variability likely reflects differences in the content of the antibodies,

procedure of transmission and/or susceptibility of different animals. Furthermore, other groups have failed to identify a clear effect of TS sera on the phenotypes of rat models (Loiselle et al., 2004). In addition, the predictive validity of these models is currently unknown.

Based on the finding that TS patients often exhibit alterations in their cytokine content in serum (Gabbay et al., 2009) and basal ganglia (Morer et al., 2010), several animal models have been developed to reproduce the phenotypic implications of early exposure to key candidate cytokines, such as IL6 and IL2. Treatment of pregnant female mice with IL-2 during mid-gestation results in behavioral alterations, including self-grooming and rearing (Ponzio et al., 2007); conversely, IL6 treatment results in decreased PPI (Smith et al., 2007). Furthermore, recent evidence has shown that treatment with specific subunits of the soluble receptors for these cytokines results in stereotyped movements and multiple alterations of locomotor activity (Patel et al., 2012; Zalcman et al., 2012).

6. Pharmacological models of tic disorders

In line with the multifactorial nature of tic disorders, multiple neurotransmitters have been implicated in the pathophysiology of TS by brain-imaging studies, postmortem analyses, and, above all, the effectiveness of specific pharmacological agents in reducing tic severity and frequency. In addition to the well-known implication of dopamine in tics, deficits in GABAergic neurotransmission are a likely concurring factor of TS pathogenesis, as signified by the reduction in GABAergic interneurons documented in this disorder (Kalanithi et al., 2005; Kataoka et al., 2010). While the implications of other neurotransmitters in TS are less well-documented, it is likely that both serotonin (at least through 5-HT_{2A} receptor activation) and norepinephrine may exert a modulatory function on the alterations of the CSTC circuitry observed in tic disorders.

Based on these notions, systemic or intracerebral treatment with drugs that can reproduce some of the neurochemical alterations observed in TS can afford a rapid, cost-effective way to investigate the pathophysiology of tic disorders and screen for novel potential therapies. Nevertheless, the limited construct validity of these preparations for TS raises doubts about their translational relevance.

6.1. Models based on dopaminergic stimulation

The stimulation of dopamine receptors through non-selective indirect (i.e., *d*-amphetamine) or direct (apomorphine) agonists is known to produce stereotypies as well as PPI deficits (Randrup et al., 1963; Ridley et al., 1982; Mansbach et al., 1988; Geyer et al., 2001; Ralph et al., 2001; Lind et al., 2004). In addition, both D₁-like and D₂-like receptor activation plays a role in these two phenomena (Doherty et al., 2008; Frau et al., 2013). The impact of D₁-like and D₂-like receptor agonists on PPI varies depending on the species and strain of experimental animals (Ralph and Caine, 2005); however, it appears that, in most cases, these phenotypes are contributed by both families of dopamine receptors. The mechanisms supporting the cooperation between D₁ and D₂ receptors in the striatum remain partially unclear, but are likely to reflect their confinement on striatonigral neurons of the direct pathway and striatopallidal neurons of the indirect pathway, respectively (Gerfen et al.,

1990; Robertson et al., 1992; Levey et al., 1993; Planert et al., 2013). In this perspective, it is worth noting that the stereotypies induced by stimulant drugs, such as amphetamine and cocaine, have been shown to reflect the disequilibrium of activation in the striosomes (which display abundant D₁ receptors) with respect to the matrix (which features high levels of D₂ receptors) (Canales and Graybiel, 2000). Conversely, PPI deficits in response to dopaminergic agonists have been shown to reflect the activation of D₁ and D₂ receptors in the nucleus accumbens (Wan et al., 1995; Wan and Swerdlow, 1996; Swerdlow et al., 2007). As expected, the behavioral changes produced by dopaminergic stimulation are sensitive to antipsychotic agents, signifying high predictive validity for these preparations (Arnt, 1995; Geyer et al., 2001; Gilbert et al., 2014).

6.2. Models based on GABAergic antagonism

The local infusion of GABA-A receptor antagonists such as bicuculline into the caudate-putamen of primates and rodents has been shown to induce tic-like movements in the orofacial region and limbs (McKenzie et al., 1972; Patel and Slater, 1988; Tarsy et al., 1978; Crossman et al., 1984, 1988; McCairn et al., 2009; Bronfeld et al., 2013). Furthermore, blockade of GABA-A receptors in the striatum and ventral globus pallidus has shown to result in PPI impairments (Kodsi and Swerdlow, 1995).

Recent studies have investigated the specific striatal structures implicated in these effects (hyperactivity, stereotyped behaviors and repetitive behaviors) (Worbe et al., 2013). Neuronal labeling patterns of activation and associated target areas were confined to the CSTC circuitry. The inactivation of GABA-A receptors in the basal ganglia is thought to simulate the deficits in striatal GABAergic interneurons observed in TS (Kalanithi et al., 2005; Kataoka et al., 2010; Lerner et al., 2012; Bronfeld et al., 2013). Accordingly, the selective inactivation of specific population of GABAergic striatal interneurons in mice has been shown to produce abnormal movements (Gittis et al., 2011). Electrophysiological studies revealed that these manifestations coincided with alterations in the firing rate within the basal ganglia (Muramatsu et al., 1990; McCairn et al., 2009; Bronfeld et al., 2011). Although these data collectively support a robust face and construct validity of bicuculline-induced tic-like manifestations with respect to TS, further studies are needed to test the predictive validity of these behaviors.

6.3. Models based on serotonin and norepinephrine stimulation

Evidence on the involvement of serotonin and norepinephrine in TS is inconclusive (Singer et al., 1982, 1990; Baker et al., 1990; Bornstein and Baker, 1990; Leckman et al., 1995; Heinz et al., 1998; Muller-Vahl et al., 2005; Wong et al., 2008). Nevertheless, several data support that tic severity can be reduced by blockade of 5-HT_{2A} receptors by atypical antipsychotics (Leysen et al., 1994) and activation of α_2 presynaptic adrenergic autoreceptors, which reduces norepinephrine synaptic levels (Leckman et al., 1991; Aoki et al., 1994; Szabo et al., 2001). Based on these concepts, administration of 5-HT_{2A} receptor agonists such as 2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI) has been used to produce head shakes in mice (Corne et al., 1963; Bedard and Pycock, 1977; Dursun and Handley, 1996) and rats (Pranzatelli, 1988; Berendsen and Broekkamp, 1990; Fone et al., 1991), as well as PPI deficits in rats (Sipes and Geyer, 1994; Kehne et al., 1996). Some of

these effects can be countered by both antipsychotic administration (Kohnomi et al., 2008) and mGlu2/3 receptor stimulation (Wischhof et al., 2012).

Similarly, cirazoline, an α_1 adrenergic agonist, has been shown to cause PPI deficits, which are prevented by clonidine (Carasso et al., 1998; Swerdlow et al., 2006). Nevertheless, DOI and cirazoline are posited to act through independent mechanisms to modulate sensorimotor gating and locomotor activity (Baisley et al., 2012).

7. Translational applications of TS models for therapeutic development

The current armamentarium for the therapy of tic disorders is based on drugs that target the key neurotransmitter systems implicated in TS, such as dopamine receptor antagonists and the α_2 receptor agonist clonidine. In addition, GABA-A receptor positive allosteric modulators (such as clonazepam) (Jimenez-Jimenez and Garcia-Ruiz, 2001; Reid, 2004), GABA-B receptor agonists (baclofen) (Singer et al., 2001) and blockers of 5-HT₂ receptors (such as atypical antipsychotics) (Bruud and Budman, 1996; Budman et al., 2001) have shown some therapeutic efficacy in TS. Nevertheless, the lack of diagnostic biomarkers for TS dictates that the bases for the therapeutic management of this disorder are empirical, often resulting in suboptimal clinical outcomes and insufficient patient compliance. In this perspective, the recent advances in our understanding of the endophenotypic architecture and multifactorial nature of TS, may facilitate the development of novel therapeutic agents tailored for specific “neurobiological subtypes” of tic disorders, with greater tolerability and fewer side effects. Animal models capturing a distinct set of deficits related to specific genetic and environmental vulnerability factors promise to afford highly valuable experimental platforms for the development of more selective and effective therapeutic strategies for tic disorders.

Although only few lines of research have employed animal models of tic disorders for the development and validation of novel treatments, the past few years have witnessed a number of promising advances in this direction. For example, the discovery that histamine synthesis deficiency is a likely contributing factor in the pathogenesis of TS (Castellan Baldan et al., 2014), which has been strongly supported by the characterization of HDC KO mice (see Section 4.1.5), is currently leading to the clinical validation of histamine-targeting drugs. Specifically, the recent findings that H₃ histamine receptor antagonists enhance PPI (or prevent PPI deficits induced by dopaminergic agonists) in rodents (Fox et al., 2005; Southam et al., 2009; Raddatz et al., 2012; but see Burbán et al., 2010 for contrasting results), have led to the initiation of clinical trials aimed at the assessment of the safety, tolerability and effectiveness of selective H₃ inverse agonists in TS patients.

The work of our laboratory (in collaboration with the University of Cagliari, Italy) in the past decade has also led to a translational line of work (encompassing preclinical and clinical research) aimed at the validation of novel therapies based on the role of androgen steroids in tic disorders. The male predominance of TS prompted us to study the involvement of 5 α -reductase (5 α R), the key enzyme catalyzing the metabolism of testosterone into 5 α -dihydrotestosterone (DHT), in tic disorders (Paba et al., 2011). Our preclinical studies began with the analysis of 5 α R inhibitors (finasteride and dutasteride) on

PPI deficits and stereotypies induced by *d*-amphetamine and apomorphine (Fig. 3A and data not shown) in rats (Bortolato et al., 2008b). While finasteride exerted antidopaminergic properties across these behavioral outcomes, it did not show any of the side effects associated with haloperidol, such as catalepsy (Bortolato et al., 2008b). Further investigations revealed that the effects of finasteride were not supported by the gonads, but were instead likely supported by the nucleus accumbens/ventral striatum (Devoto et al., 2012) (Fig. 3B). The anti-tic mechanisms of finasteride were also found to be related to the attenuation of the effects of D₁, but not D₂ receptors in both rats and mice (Frau et al., 2013; Frau et al, submitted for publication). In addition, we found that abiraterone, a potent blocker of androgen synthesis, produced similar, yet less robust effects (Frau et al., 2014). Taken together, these results led us to study the therapeutic potential of finasteride in adult male TS patients. Following our first positive result in a treatment-refractory TS patient (Bortolato et al., 2007), we studied the effects of finasteride in an open trial, which showed that this drug induced a significant reduction in the severity of tics and compulsive (but not obsessive) symptoms by the sixth week of therapy (Muronì et al., 2011; Bortolato et al., 2013a,b). A double-blind, placebo-controlled clinical trial on the effects of finasteride in adult TS male patients is currently ongoing at the University of Cagliari, Italy.

While finasteride is not likely to be an optimal therapy for TS, given its potentially serious side effects on masculinization in boys, ongoing studies in our laboratory are currently analyzing the contribution of different androgen steroids in the anti-tic mechanisms of finasteride, using animal models. These investigations may yield important contributions to our understanding of the neuroendocrine alterations underpinning tic disorders. Another corollary of our study has led to the analysis of association of TS and *SRD5A2*, the gene encoding 5 α R type 2 (the primary target of finasteride in humans). Indeed, the location of this gene on chromosome 2p23 (Morissette et al., 1996) is directly proximal to one of the regions with high linkage for TS, as recognized by the largest linkage study for tic disorders to date (TSCAIG, 2007).

8. Concluding remarks

In summary, the pathogenesis of TS is underpinned by the interaction between genetic risk factors and environmental insults; however, the neurobiological mechanisms that underlie this disorder are still unclear. Several key questions still remain unanswered, including: the neurobiological bases of sex differences in TS; the mechanisms that contribute to the developmental trajectory of tic disorders; and the identification of potential biomarkers and premorbid signs. This scenario highlights the need for animal models that can capture specific symptomatic traits. Careful consideration into animal model selection based on key criteria will be essential to further our understanding of TS pathogenesis and identify translational leads for the development of future therapies.

Acknowledgments

This work was supported by grants from the National Institute of Mental Health (NIH R01 MH104603) National Institute of General Medical Sciences (NIH P20 GM103638) and Tourette Syndrome Association. The authors are indebted to the EU COST Action CM1103 “Structure-based drug design for diagnosis and treatment of neurological diseases: dissecting and modulating complex function in the monoaminergic systems of the brain” for

supporting their international collaboration. None of the institutions had any further role in the decision to submit the paper for publication.

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HIGHLIGHTS

- Animal models of Tourette syndrome and other tic disorders (TD) are reviewed.
- TD models are based on genetic mutations and environmental interventions.
- TD models are validated across criteria of face, construct and predictive validity.
- Endophenotype testing is essential to enhance the translational value of TD models.
- TD models may assist in the identification of new therapeutic targets.

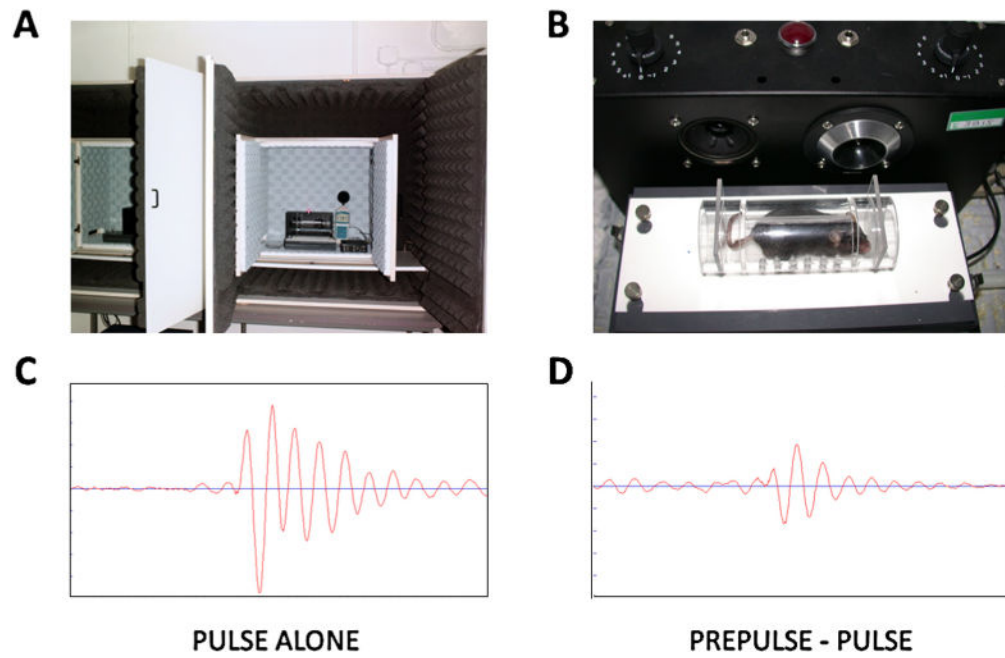


Fig. 1. Prepulse inhibition (PPI) of the acoustic startle reflex. (A) Photograph of acoustic startle apparatus (Med Associates, St. Albans, VT). (B) Image of a mouse placed into the testing cage, mounted across a speaker and on a piezoelectric platform for signal transduction. (C and D) Examples of pulse-alone and prepulse-pulse waves during PPI testing.



Fig. 2.
Frame-by-frame image of a “tic-like” manifestation in a D1CT-7 mouse model of Tourette syndrome.

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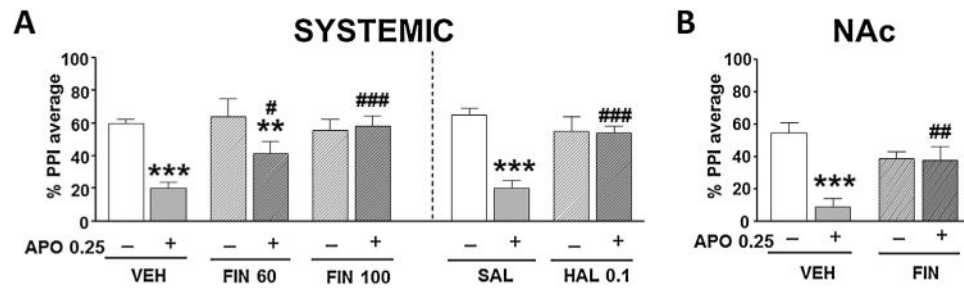


Fig. 3.

Systemic (A) and intra-accumbal (B) administration of finasteride counters the deficits in the prepulse inhibition of the startle induced by the dopaminergic agonist apomorphine. Readapted from Bortolato et al. (2008a,b) and Devoto et al. (2012). Values are displayed as mean %PPI (average of three different prepulse loudness levels) \pm SEM. *** P <0.001 and ** P <0.01 compared to animals treated with saline and vehicle. ### P <0.001, ## P <0.01 and # P <0.05 compared to animals treated with apomorphine and vehicle. Abbrev.: FIN, Finasteride; VEH, Vehicle; APO, Apomorphine; SAL, Saline; HAL, Haloperidol; NAc, Nucleus accumbens.

Table 1

Tourette syndrome candidate genes and corresponding animal models.

Candidate genes	References	Animal model	Face validity	Predictive validity	References
<i>DAT1</i>	Comings et al., 1996 Diaz-Anzaldúa et al., 2004b Tarnok et al., 2007	DAT KO	PPI deficits Perseverative behaviors Hyperlocomotion	PPI deficits respond to antipsychotics PPI deficits reversed by D2, not D1 blockade Perseverative behaviors attenuated by D1 blockers Hyperlocomotion reversed by haloperidol	Giros et al., 1996 Spielewoy et al., 2000 Ralph et al., 2001 Powell et al., 2008 Fox et al., 2013
<i>MAO A</i>	Gade et al., 1998 Diaz-Anzaldúa et al., 2004a, b	MAO A KO MAO A hypomorphic	Stereotyped behavior Perseverative behaviors Perseverative behaviors	Unknown Unknown Unknown	Zhuang et al., 2001 Berridge et al., 2005 Cases et al., 1995 Scott et al., 2008 Bortolato et al., 2011
<i>SLITRK1</i>	Abelson et al., 2005 Deng et al., 2006 O'Roak et al., 2010 Karagiannidis et al., 2012	SLITRK KO	None reported	Unknown	Katayama et al., 2010
<i>NLGN4</i>	Lawson-Yuen et al., 2008	NLGN4KO	None reported	Unknown	Jamain et al., 2008
<i>IMMP2L</i>	Boghosian-Sell et al., 1996	N/A			
<i>CNTNAP2</i>	Verkerk et al., 2003 Scharf et al., 2013	CNTNAP2	Stereotyped behavior Perseverative behaviors Excessive grooming	Risperidone reverses stereotyped and perseverative behaviors Excessive grooming is responsive to haloperidol	Penagarikano et al., 2011 Karayannis et al., 2014
<i>HDC</i>	Ercan-Sencicek et al., 2010	HDC KO	Stereotyped behaviors	Haloperidol reduced stereotyped behaviors	Castellan Baldan et al., 2014
<i>DLGAP3 (Sapap3 in mice)</i>	Crane et al., 2011	SAPAP3 KO	Excessive grooming		Welch et al., 2007 Burguiere et al., 2013
<i>COL27A1</i>	Scharf et al., 2013	N/A			
<i>POLB</i>	Scharf et al., 2013	N/A			