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Review

Animal models of tic disorders: A translational perspective

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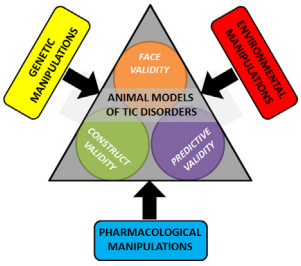
HIGHLIGHTS

- 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.

GRAPHICAL ABSTRACT



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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

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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.

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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.