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Modeling tics in rodents: Conceptual challenges and paths forward

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Abstract

Background—Recent advances in our understanding of the neurobiology of tics have led to the development of novel rodent models capturing different pathophysiological and phenotypic aspects of Tourette syndrome. The proliferation of these models, however, raises vexing questions on what standards should be adopted to assess their theoretical validity and empirical utility. Assessing the homology of a rodent motoric burst with a tic remains problematic, due to our incomplete knowledge of the underpinnings of tics, their high phenotypic complexity and variability, limitations in our ability to test key aspects of tic phenomenology (such as premonitory sensory phenomena) in animals, and between-species differences in neuroanatomy and behavioral repertoire. These limitations underscore that any interpretation of behavioral output in an animal model cannot exclusively rely on the recognition of features that bear superficial resemblance with tics, but must be supported by other etiological and convergent phenomenological criteria.

New method—Here, we discuss two complementary approaches for the study and validation of tic-like manifestations in rodents, based respectively on the use of contextual modulators and accompanying features of repetitive motor manifestations and on the reproduction of pathogenic factors.

Results—Neither strategy can by itself provide convincing evidence that a model informatively recapitulates tic pathophysiology. Their combination holds promise to enhance the rigorous evaluation and translational relevance of rodent models of tic disorders.

Conclusions—This systematic consideration of different approaches to the validation and study of animal models of tic pathophysiology provides a framework for future work in this area.

Keywords

tics; Tourette syndrome; stereotypy; grooming; animal model; basal ganglia

Introduction

Clinical phenomenology of tics

Tics are semivoluntary movements or utterances resulting from the contraction of discrete voluntary muscle groups. Providing a comprehensive definition of the clinical characteristics of tics is problematic, given that they are often individually indistinguishable from voluntary movements (Hallett, 2001; Karp et al., 1996; Paszek et al., 2010). Tics are executed in a repetitive, persistent, and contextually inappropriate manner, which can compromise psychological, social, and academic functioning (Leckman et al., 2006). They vary greatly in frequency, severity, anatomical distribution, and duration; for example, while the majority of tics manifest as rapid clonic jerks, they can also have tonic and dystonic features.

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) distinguishes between several types of primary tic disorders (Association, 2013):

- *Tourette syndrome (TS)* is characterized by multiple motor tics and at least one phonic tic that have onset in childhood and persist for at least one year;
- *Persistent motor or vocal tic disorder* is characterized by tics in only one domain (but not both) for at least one year;
- *Provisional tic disorder* is characterized by tics with a duration shorter than one year.

It remains unclear whether these diagnostic categories correspond to discrete pathophysiological entities or exist along a continuum.

Tics are *semivoluntary*; unlike other hyperkinetic phenomena (such as myoclonus, chorea, akathisia, dystonia, and so forth), they can often be volitionally controlled, deferred, and suppressed, at least temporarily. Most adolescent and adult TS patients report that tics are enacted in response to premonitory sensory phenomena (PSP), unpleasant sensations of somatic tension and exaggerated intero- and exteroceptive awareness (Cohen and Leckman, 1992; Houghton et al., 2014). Both PSP and tics can be exacerbated by specific environmental and psychological triggers, including sensory over- or understimulation, fatigue and sleep problems, frustration, and anxiety or stress (Conelea and Woods, 2008; Godar and Bortolato, 2016). A prominent component of PSP is the *premonitory urge*, a sense of incompleteness or tension that produces a strong impulse to tic (Cohen and Leckman, 1992; Leckman et al., 1993) and is aggravated by tic suppression (Himle et al., 2014). Tic execution results in relief from this discomfort (Kwak et al., 2003; Lang, 1991); this process produces negative reinforcement of tics, which may over time make them increasingly habitual (Woods et al., 2009). Thus, although tics have been traditionally framed as purposeless acts, they may in fact be motivated by the need to mitigate PSP.

TS affects 0.5–1.0% of youth (Robertson, 2008; Scahill et al., 2001; Scharf et al., 2012) and can vary in severity from a mild inconvenience to a functionally debilitating condition (Kurlan, 2010; Leckman, 2002). TS is commonly comorbid with other disorders, such as obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), impulse-control disorders, and anxiety (Hirschtritt et al., 2015). Like autism-spectrum

disorder, TS has a marked male preponderance, with a sex ratio reported as high as 3:1 (Scahill et al., 2001; Scharf et al., 2012). TS, like tic disorders more generally, is more common in youth, with symptoms typically peaking between the ages of 10 and 12 (Leckman et al., 1998). Symptoms often improve with age, even though approximately 30% of patients continue to exhibit clinically significant tics in adulthood (Singer and Walkup, 1991).

Neurobiology and genetics of tics

Although our understanding of the neurobiological underpinnings of tics remains incomplete (Bronfeld and Bar-Gad, 2013; Leckman et al., 2010; Pittenger, 2017b), certain principles have emerged that help to constrain the construction and interpretation of pathophysiological models (Pittenger, 2017b). A comprehensive summary of this growing literature is beyond our scope here, but a brief review of relevant findings helps to contextualize the discussion that follows.

Convergent data implicate dysregulation of the corticostriatal circuitry in the pathophysiology of TS (Leckman et al., 2010). Structural imaging data have revealed slightly but significantly decreased caudate and putamen volume in both adults and children with tics (Peterson et al., 2003). This may be explained by the loss of specific populations of interneurons, which has been observed *post mortem* in adults with severe TS: the cholinergic tonically active neurons (TANs) and the GABAergic interneurons expressing either parvalbumin or neuronal nitric oxide synthase (nNOS) (Kalanithi et al., 2005; Kataoka et al., 2010; Lenington et al., 2016). In contrast, other populations of interneurons and the striatal principal cells, the medium spiny neurons (MSNs), appear to be normal in the TS striatum (Kataoka et al., 2010), implying some specificity to the interneuronal deficit.

Functional imaging data is somewhat limited, due in part to the challenge of subject movement during tic emission. Some of the best functional data come from studies of tic suppression, which have been associated with activity in both prefrontal cortex and caudate (Peterson et al., 1998).

Within the striatum, several lines of evidence suggest that dysregulation of modulatory dopamine (DA) neurotransmission plays a prominent role. A number of positron emission tomography (PET) studies, though not all, suggest increased tonic striatal DA levels in adults with TS (Singer et al., 1992; Wong et al., 2008). There again appears to be some specificity to this effect: evidence for elevated basal DA is seen in patients with TS but not in those with OCD (Denys et al., 2013). Antagonism of D2-like DA receptors is the most efficacious pharmacotherapy for tics (Bloch, 2008; Kurlan, 2014), and challenge with high doses of DA-elevating psychostimulants can enhance tics in patients (Denys et al., 2013; Feinberg and Carroll, 1979), as well as in animal models (Canales and Graybiel, 2000; Castellán Baldan et al., 2014; Xu et al., 2015a).

Several mechanistic models have been proposed to explain striatal dysregulation in tic disorders; these are not mutually exclusive (Pittenger, 2017b). One influential model is that tics derive from focal disinhibition within the striatum (Albin and Mink, 2006; Bronfeld and Bar-Gad, 2013; Mink, 2001); this is consistent with the deficits in inhibitory interneurons

that have been observed post-mortem (Kalanithi et al., 2005; Kataoka et al., 2010; Lenington et al., 2016). Another proposal is that tics, and hyperkinetic motor conditions more generally, derive from an imbalance between the dopamine D1-receptor expressing MSNs of the striatal direct pathway and the D2-receptor expressing MSNs of the indirect pathway. More specifically, elevated tonic striatal DA may preferentially act on D2 receptors, which have a higher DA affinity than D1 receptors, and thereby inhibit the indirect pathway (Mink, 2003; Pittenger, 2017b); since the indirect pathway is thought to inhibit off-target movements (Albin and Mink, 2006; Cui et al., 2013), either global or focal disinhibition thereof may produce impaired inhibition, manifesting as tics (Albin and Mink, 2006; Mink, 2003).

The genetics of TS are less developed but are advancing rapidly (Fernandez et al., 2017). Particularly exciting is the identification of rare but high-penetrance mutations in several genes (Abelson et al., 2005; Ercan-Sencicek et al., 2010); while the population risk attributable to such rare mutations is small, they have particular utility in probing and modeling pathophysiology, as further discussed below.

Animal models of tics: validity criteria and conceptual framework

Animal models of tic disorders are potentially valuable tools for the investigation of their biological and neurochemical substrates, the identification of novel therapeutic targets, and the early testing of experimental treatments (Godar et al., 2014; Pittenger, 2014; Yael et al., 2016). Rodent models are particularly popular across many fields of translational research, due to their cost-effectiveness, sophisticated genetics, and neuroanatomy that is reasonably comparable to that of primates. Over the past decade, progress in genetics and new insight into the pathophysiology of TS, aspects of which are summarized above, have given new impetus to the development of novel animal models that seek to test specific hypotheses of tic mechanism and to provide platforms for ongoing translational investigations (Godar et al., 2014; Pittenger, 2014, 2017b).

However, attempts to study the pathophysiology of tics, or any complex neuropsychiatric phenomenology, raise daunting interpretive challenges. It is important to recognize that the pathophysiology and phenomenology of TS, like that of any human neuropsychiatric disease, will never be fully recapitulated in a rodent model, for several reasons. First, aspects of the phenomenology of neuropsychiatric diseases cannot be assessed in an animal, even if they could be recapitulated; in the case of tic disorders, this is most obviously true of PSP. Second, even when aspects of disease phenomenology, like tics, can be plausibly observed in an animal model, such observations will always be fraught with interpretative ambiguity – as in the case of excessive grooming, which has been interpreted as being isomorphic to a range of neuropsychiatric symptomatology (Kalueff et al., 2016). Third, there are enough differences between primate and rodent neuroanatomy that even if pathophysiology were perfectly recapitulated, the downstream consequences might differ. For example, a larger fraction of the basal ganglia output targets the midbrain, rather than the thalamus and thereby the cortex, in rodents than in primates, and this will inevitably influence aspects of the behavioral consequences of striatal pathology. Finally, neuropsychiatric nosology is itself imprecise and in a state of flux – for example, it is as yet unclear whether the distinction

between TS and chronic motor and vocal tic disorders represents a true distinction between natural kinds. It would be unrealistic to expect animal models of disease pathophysiology to map faithfully onto clinical entities that are themselves heterogeneous, and perhaps artificial.

In light of these complexities, it is important to operationalize what characteristics make an animal model of any disease worthy of investigation. This is traditionally considered with respect to different aspects of model *validity* (Nestler and Hyman, 2010; Willner, 1986).

Face validity refers to the degree of phenomenological isomorphism between tics, as characterized in humans, and abnormal hyperkinetic or repetitive behaviors in an animal model. It is simultaneously the most intuitive and the most problematic form of validity. Face validity was prioritized in early work, but analogies between animal behaviors and human symptomatology are inherently subjective interpretations and are thus problematic (Geyer and Markou, 1995; Mosier, 1947). In particular, it is not obvious *a priori* what sort of behavior in a rodent can be considered homologous to a tic. Claims to face-valid behavioral models of tics may rely on such characteristics as phasic, non-rhythmic character, unilaterality, bias towards face and upper body, temporal fluctuation, and so forth. However, not every repetitive movement is representative of a tic. Repetitive movements, such as elevated grooming (Kalueff et al., 2016), have been described as recapitulating tics (Xu et al., 2015a; Xu et al., 2015b; Xu et al., 2016); but dysregulated grooming has also been argued to recapitulate obsessive-compulsive symptoms (Ahmari et al., 2013; Greer and Capecchi, 2002; Shmelkov et al., 2010; Welch et al., 2007), trichotillomania (Feusner et al., 2009), autistic stereotypies (Peca et al., 2011; Zhou et al., 2016), Rett syndrome (Yasui et al., 2014), psychostimulant-related behavior (Berridge et al., 2005), and other clinical conditions (Kalueff et al., 2016). Given the evolutionary divergence between rodents and humans, it is unlikely that homologs of tics in mice will fully recapitulate all clinical characteristics of tics. For example, it is unclear whether rodents can exhibit vocal tics, given the divergent development of the laryngeal musculature and corresponding neural machinery in humans. Similarly, the quadrupedal posture of rodents may entail differences in the somatic distribution of tics.

The term *predictive validity* has been used in different ways by different authors. In a broad sense, it can describe the ability of a model to predict anything about the human condition that it seeks to recapitulate. The term is frequently used in a narrower sense, to denote the modulation of putatively ‘tic-like’ behaviors by therapeutic manipulations, most commonly therapeutic drugs. This raises three challenges. First, the medications used to treat TS and other tic disorders are not specific to these conditions; for example, D2 antagonists reduce tic frequency and severity, but are also widely used to treat psychosis, affective disorders, and other conditions. Second, no medications for tics are 100% effective; thus, responsiveness to a pharmacological agent does not guarantee that the observed behaviors are faithfully recapitulating tic pathophysiology, and failure to respond to a therapeutic agent does not prove that they are not. Finally, basing a model too strictly on responsiveness to established treatments creates the risk of modeling known therapeutic mechanisms, rather than disease pathophysiology. This may hamper the testing of novel therapeutic strategies.

Construct validity refers to the congruence of a manipulation in an animal model with a hypothesized disease-associated theoretical construct. This most commonly takes the form of *etiologic* or *pathophysiological validity*, meaning that an animal model recapitulates a hypothesized disease etiology. The major limitation here lies in our rudimentary knowledge of the etiology of tics: in the absence of a clearly delineated understanding of the causes of disease, etiologic validity is difficult to achieve. As our understanding of the causes and pathophysiology of tic disorders advances, it is to be hoped that models with robust construct validity will become increasingly available. When etiology and/or pathophysiology is convincingly captured in a model, explorations of downstream consequences, moderators of disease, and novel treatment strategies can be performed with greater confidence.

Ultimately, the value of an animal model of disease pathophysiology lies in its ability to shed light on human disease – its ability to advance our knowledge of pathophysiology, diagnosis, treatment, or prevention. However, the road from the hypothesis, through a model, to a change in clinical practice that improves patients' lives is a long one, and it has yet to be completed in any study of tic disorders. It is, therefore, important to establish shorter-term criteria by which we can determine what approaches and models are most likely to lead to the ultimate goal of clinical insight and treatment advance. In a sense, this is an economic question: given limitations of time, money, and intellectual resources, where should we focus our efforts? Operationalizing model validity is one approach to this question. Model validation gives reason to believe that a model is capturing pathophysiology in a meaningful way, making it more likely to lead to translational insight than a model that is not validated.

It is also important to consider the question of model utility: specifically, what does study of the model seek to achieve, and what questions does it seek to answer? It is difficult to imagine a model being utile without being valid, but it is possible for a model to be valid without being particularly useful. One frequent goal of tests in animal models is to test specific pathophysiological hypotheses: to investigate, with a level of experimental control and rigor not possible in clinical studies, whether a defined insult produces disease-relevant consequences. When this is the goal, validation studies may themselves be of primary importance: convincing demonstration of sufficient parallels between the model system and the human disease state provides evidence in support of the motivating hypothesis. A second frequent goal is the mechanistic analysis of a validated model system, using invasive approaches that are not available in clinical studies, to generate novel mechanistic insight and hypotheses for subsequent testing in humans. A third is the testing, again in a well-validated system, of novel therapeutic strategies. Keeping these specific questions in mind is critical to leveraging translational studies in pathophysiologically grounded models, with the ultimate goal of producing meaningful clinical insight and developing new therapeutics.

Studying tic-like movements using a phenomenological approach

It has been emphasized above that repetitive behaviors in animals are not necessarily homologous to tics (just as not all repetitive behaviors in humans are tics). Nevertheless, careful consideration of some of the more fine-grained clinical characteristics of tics allows a principled and systematic approach to behavioral analysis, when potentially tic-like behaviors are observed in an animal, either serendipitously or in response to a hypothesis-

motivated experimental manipulation. In a patient, consideration of a diagnosis of a tic disorder is typically prompted by the presence of hyperkinetic symptomatology. Verification of a tic disorder entails careful observation of the specific movements and accompanying symptomatology, accompanied by systematic consideration of its modulation by environmental variables or pharmacological manipulations. For example, tics are worsened by stress (Conelea and Woods, 2008; Godar and Bortolato, 2016); modulation of observed symptoms by stress in a particular patient, therefore, supports a tic disorder diagnosis. Analogously, the potential relevance of an observed repetitive behavior to tics is strengthened if it is similarly modulated by stress.

Some studies have focused on the fine-grained motor characteristics of tics as critical to behavioral analyses. For example, simple tics are spasmodic contractions of single muscle groups and are typically phasic. They typically resemble normal movements, or at least fragments of normal motor patterns. They are non-rhythmic, which distinguishes them from seizures. They are typically unilateral. They fluctuate over time, are distractible, and are alleviated during sleep. The presence of some or all of these characteristics may increase the face validity of a particular tic model. That said, our view is that *a priori* insistence on some specified subset of these phenomenological characteristics before a model can be accepted as recapitulating tics is overly restrictive and risks producing false negatives. It is impossible to know with precision, *a priori*, what behaviors would be produced by a faithful recapitulation of TS pathophysiology in a mouse; and the behaviors might look quite different, in their fine-grained details, in two equally valid and informative models. It is better, in our view, to note a wide range of hyperkinetic or repetitive behaviors as potentially tic-like, and to seek convergent support in investigations of environmental modulation and other analyses. Such convergent characterization provides more robust evidence that the model is of relevance to the understanding of tics than any single phenotype can in isolation. Repetitive hyperkinetic behaviors in isolation are subject to a range of interpretations; but such characteristics as sexual dimorphism, modulation by stress, and drug responsiveness help to build an overall case for validity.

The consideration of hyperkinetic movements in an animal model can be complicated by issues of nomenclature. Neurologists have developed precise terminology to categorize pathological movements in patients, but the application of this terminology to animals is not straightforward. This is particularly true with respect to the term ‘stereotypy’. In mice and rats, stereotypies are defined as rhythmic sequences of repetitive movements, typically inappropriate to the behavioral context (Ridley, 1994). In humans, stereotypies denote a much narrower set of behaviors: they are typically involuntary, invariant, highly rhythmic, and often associated with developmental disabilities. Stereotypies in this latter sense are explicitly distinct from tics – indeed, they are listed in the DSM-5 as part of the differential diagnosis for tic disorders (Association, 2013). This can lead to confusion: clinically, stereotypies in patients are not tics, by definition; but translationally, the relevance of stereotypies observed in any particular animal model to the pathophysiology of tics should be treated as an empirical question.

Indeed, stereotypies in rodents share neurobiological mechanisms with tics (Muehlmann and Lewis, 2012). Both have been associated with deficient inhibitory control within the basal

diagnosis (Kohl et al., 2013). PPI in mice and rats is impaired by direct or indirect DA agonists, which can exacerbate tics (Denys et al., 2013; Feinberg and Carroll, 1979), and is improved by efficacious TS pharmacotherapies (Geyer et al., 2001). While the precise relationship between PPI deficits and PSP in patients with TS remains unclear (Swerdlow et al., 2001), these observations, coupled with the consistency of experimental paradigms across species, makes PPI an attractive and powerful analytic tool in translational studies of TS.

The complexity of a behavior-based analytic approach is illustrated by studies over the past two decades of the D1CT-7 mouse, which carries a transgene expressing the cholera toxin enzymatic subunit A1 under control of the dopamine D1 receptor promoter (Campbell et al., 1999; Nordstrom and Burton, 2002). This transgene enhances activity in a subset of neurons in layer 2/3 of frontal cortex, the amygdala, and other structures that project to the striatum and thus potentiates activity in the corticostriatal circuitry. These mice exhibit sudden axial jerks and other hyperkinetic movements (Campbell et al., 1999; Nordstrom and Burton, 2002). The presence of such movements in a model that has a degree of construct validity (in that it recapitulates corticostriatal hyperactivity) provided early support for its relevance to TS.

Convincing validation of the D1CT-7 mouse as an informative recapitulation of TS pathophysiology has proven a complex goal, and the model has been critiqued (Swerdlow and Sutherland, 2006). To reiterate, however, the goal of analysis in such a model should not be aimed at proving that they perfectly capture all aspects of TS phenomenology – no model can – but rather, to establish that they recapitulate some measurable characteristics of disease sufficiently to be taken as supportive of the motivating construct and to justify further study.

The presence of repetitive hyperkinetic behavior in the D1CT-7 mice supports the underlying hypothesis that corticostriatal hyperactivity is linked to such effects. More nuanced phenotyping is required to provide clearer support for a specific relationship with TS. For example, jerking movements are sexually dimorphic, appearing more prominently in males; they appear early in life; they fluctuate in severity over time; and they are reduced by several drugs that mitigate tics in TS patients, including haloperidol and clonidine (Nordstrom and Burton, 2002). These subtleties increase confidence that the observed behaviors do indeed reflect tic-relevant abnormalities. More recently, further parallels with tics have been documented: hyperkinetic movements in D1CT-7 mice have been shown to be exacerbated by acute stress (Godar et al., 2016), and the mice have been shown to exhibit PPI deficits (Godar et al., 2016) and deficits in sensorimotor integration (Fowler et al., in press).

Modeling tics based on specific pathophysiological hypotheses

An alternative to focusing on the nuances of putatively tic-like behaviors is to construct models based on specific pathophysiological hypotheses. The D1CT-7 mice were generated to recapitulate hyperactivity of the corticostriatal circuitry, and to this extent they are based on a hypothesis of disease mechanism. Translating such hypotheses to animal model systems allows us to test whether they produce disease-relevant effects. However, the details

of corticostriatal hyperactivity in TS are not well understood, and there is no reason to believe that D1CT-7 mice recapitulate them with particular fidelity. The more precisely a model system recapitulates specifics of pathophysiology, the more we can be confident that other observations in the model will be relevant to disease.

Of course, a pathophysiology-based modeling approach is limited by the availability of plausible and tractable hypotheses; and until recently these were lacking in the case of tic disorders (as in the case of most complex neuropsychiatric disorders). In recent years, however, several plausible and translationally tractable hypotheses have emerged, and models testing them have been described. This new generation of models holds great promise for the development of new insights into the genesis, mechanisms, and treatment of tic disorders.

As noted above, one network-level theory of tic disorders is that they arise from foci of ectopic disinhibition within the striatum (Albin and Mink, 2006; Mink, 2001, 2003). This has been experimentally tested in monkeys, rats, and mice through the targeted intra-striatal infusion of GABA-A antagonists (Bronfeld and Bar-Gad, 2013). Local striatal disinhibition in macaques leads to contralateral phasic jerks with an average duration of ~250 ms and a frequency of 20–50/minute (McCairn et al., 2009). These have good face validity for tics: they are phasic, non-rhythmic, are associated with short bursts of activation of isolated muscle groups, and do not interrupt ongoing performance of other activities. The topography of the tic-like movements depends on the location of the focal disinhibition, suggesting a somatotopic organization. Similar phenomenology has been observed after local striatal disinhibition in rats (Bronfeld et al., 2013) and mice (Pogorelov et al., 2015). In rats, the tic-like movements are accompanied by hyperactivity (walking, rearing, sniffing, etc.) and locomotor rotation bias, contraversive to the injected hemisphere (Bronfeld et al., 2013). They appear first as small jerks, which then increase in amplitude, reach a sustained stereotypic shape, and then gradually decrease until their cessation (Bronfeld et al., 2013).

The documentation of tic-like phenomenology after local striatal disinhibition (Bronfeld et al., 2013; McCairn et al., 2009; Pogorelov et al., 2015) provides validation for the model and supports the underlying hypothesis (Albin and Mink, 2006; Mink, 2001, 2003). It also provides a platform for ongoing work, using experimental approaches that are not accessible in patients. For example, ongoing work in the monkey model after local striatal disinhibition has mapped the propagation of tic-associated neural activity through the cortico-striatal circuit and have revealed coordinated activity in the cerebellum (McCairn et al., 2009; McCairn et al., 2013). In rodents, simultaneous manipulation of the striatum and its cortical afferents have elucidated the relationship between these structures during tic production, indicating that cortical activity triggers tics and determines their timing, while striatal dysregulation determines their topography (Israelashvili and Bar-Gad, 2015; Pogorelov et al., 2015). Such studies are not possible in humans and illustrate the analytical power of work in animal models.

Post-mortem studies in adults with refractory TS have documented reductions in specific populations of interneurons (Kalanithi et al., 2005; Kataoka et al., 2010; Lenington et al., 2016); this may represent the substrate of pathological striatal disinhibition. The causal

relationship of interneuron pathology to TS-relevant behaviors has recently been tested in animal models. Targeted depletion of parvalbumin-expressing GABAergic interneurons (Xu et al., 2016) or of cholinergic interneurons (Xu et al., 2015a) in the dorsal striatum does not produce stereotypic movements at rest, but elevated and dysregulated grooming emerges after acute stress. Given the ability of stress to trigger or worsen tics (Conelea and Woods, 2008; Godar and Bortolato, 2016), this provides good support for the causal relevance of the interneuronal pathology to TS.

Work in animals allows levels of experimental control not possible in human studies. For example, the fact that experimental depletion of interneurons was performed in developmentally normal mice (Xu et al., 2015a; Xu et al., 2016) suggests that interneuronal pathology, independent of developmental miswiring of the striatal circuitry, is sufficient to produce tic-relevant pathology; such dissociation of developmental from adult mechanisms is difficult to achieve in clinical studies. Recently, conjoint depletion of both interneuron populations has been shown to produce spontaneous tic-like phenomenology in mice, even without acute stress (Rapanelli et al., in press). This suggests that disruption of either interneuron population alone destabilizes the circuitry, but sufficient compensatory or homeostatic mechanisms are present to prevent behavioral abnormalities until an additional disruptive event (i.e. acute stress); disruption of both populations produces sufficient destabilization that such compensation is no longer possible.

A final example of a tic model derived from a specific pathophysiological hypothesis derives from recent advances in the genetics of TS. As noted above, TS is substantially genetic, but important risk alleles and causative mutations have been slow to emerge (Fernandez et al., 2017). The genetic abnormalities best suited to pathophysiological modeling are those that produce a large effect, even if they are individually rare. One such mutation, an inactivating nonsense mutation in the gene *histidine decarboxylase (Hdc)*, was described in 2010 (Ercan-Sencicek et al., 2010). *Hdc* encodes the enzyme for the biosynthesis of histamine from the amino acid histidine. The neurotransmitter histamine is produced in the posterior hypothalamus and modulates neural circuits throughout the brain, including in the basal ganglia (Bolam and Ellender, 2015; Haas et al., 2008; Panula and Nuutinen, 2013; Pittenger, 2017a). *Hdc* knockout mice, which recapitulate the biochemical abnormality produced by the disease-associated mutation, have been studied as a putative model of the pathophysiology of tics (Pittenger, 2017a). This model has inherent construct/etiologic validity, in that it is based on a large effect-size disease-associated mutation (Castellan Baldan et al., 2014; Ercan-Sencicek et al., 2010).

Hdc-KO mice do not exhibit obvious stereotypy at baseline, but they show hyperkinetic repetitive behaviors after stress (Xu et al., 2015b) or amphetamine challenge (Castellan Baldan et al., 2014). The emergence of repetitive behaviors after manipulations that worsen tics (Conelea and Woods, 2008; Denys et al., 2013; Feinberg and Carroll, 1979; Godar and Bortolato, 2016) provides validation of the motivating hypothesis, that *Hdc* deficiency produces TS-relevant effects. *Hdc*-KO mice also show impaired PPI (as do TS patients carrying a mutated *Hdc* allele), providing further validation (Castellan Baldan et al., 2014). Parallel studies in these mice and in patients carrying the *Hdc* mutation have identified abnormalities in DA modulation of the striatum and in dopamine D2/D3 receptors in the

substantia nigra as a potential locus of pathology and/or homeostatic regulation in tic disorders (Castellan Baldan et al., 2014; Rapanelli et al., 2017; Rapanelli et al., 2014).

Work is ongoing in this model system on several fronts, which are described in detail elsewhere (Pittenger, 2017a). In the current context, it is most relevant to focus on the characteristics of the model that provide validation – that is, that encourage confidence that *Hdc* KO mice faithfully recapitulate tic-relevant pathophysiology, and thus that ongoing investment in the characterization of this model is likely to produce clinically relevant insights, in the long run. Of most importance, the model is based on a clear, well-specified, and translationally tractable hypothesis of disease etiology: that TS can, in rare cases, derive from deficiency in the *Hdc* gene and in neuronal histamine production. This hypothesis is supported by the development of tic-relevant behavioral and neurochemical abnormalities in *Hdc* knockout mice (Castellan Baldan et al., 2014; Rapanelli et al., 2014; Xu et al., 2015b). Ongoing investigations in this validated model system are allowing analysis of pathophysiology at a level of resolution not possible in clinical studies (Pittenger, 2017a).

Conclusion: combining phenomenology- and pathophysiology-based analyses

In the discussion above, we have presented phenomenology- and pathophysiology-based modeling strategies as complementary perspectives; but, in practice, they synergize and, in the most convincing studies, reinforce one another. Behavior in an animal that resembles tics in multiple ways (e.g. hyperkinetic repetitive behaviors; male bias; exacerbation by stress) but has no validated link to established principles of tic pathophysiology will appropriately face a high burden of proof before it can be accepted as being of relevance to the understanding of human tic disorders. And any model with unimpeachable construct or etiologic validity that produces no behaviors that are even slightly reminiscent of tics will gain little traction. Ideally, both pathophysiological grounding and nuanced phenomenological analysis are present.

This is clear in the specific examples developed above. The D1CT-7 mice have face validity for tics along several dimensions (Campbell et al., 1999; Fowler et al., in press; Godar et al., 2016; Nordstrom and Burton, 2002), but the case for their relevance is also bolstered by the fact that they recapitulate the corticostriatal hyperactivity associated with tic disorders (Hallett, 2001; Leckman et al., 2010). Similarly, models based on specific pathophysiological hypotheses – local striatal disinhibition; interneuronal pathology; or histamine deficiency – have been validated by the production of repetitive behavior when this pathophysiology is recapitulated in an animal (Bronfeld and Bar-Gad, 2013; Pittenger, 2017a; Xu et al., 2015a; Xu et al., 2016); in several cases this analysis has entailed examination of modulators of tic phenomenology, such as acute stress or psychostimulant challenge (Castellan Baldan et al., 2014; Xu et al., 2015a; Xu et al., 2015b; Xu et al., 2016), providing nuance to the behavioral characterization.

No rodent model system is likely to entirely recapitulate the phenomenology of complex neuropsychiatric disease. When considering a particular model of tic disorders, the goal should not be to establish whether it perfectly captures all aspects of TS symptomatology,

but rather to judge how likely it is to produce translationally and clinically useful insights – that is, what its utility may be in addressing important translational questions. From this perspective, there is a balance between the two perspectives elaborated here. When a model captures a clear and well-defined cause of tics, even a rare one, we can take a somewhat relaxed stance with respect to the precise details of the resulting behaviors. On the other hand, if a model recapitulates the phenomenology of tics in great detail, it may prove to be of substantial interest even if the underlying causes are not known at the outset.

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