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What makes you tic? Translational approaches to study the role of stress and contextual triggers in Tourette syndrome

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Abstract

Tourette syndrome (TS) is a neurodevelopmental condition characterized by multiple, recurring motor and phonic tics. Rich empirical evidence shows that the severity of tics and associated manifestations is increased by several stressors and contextual triggers; however, the neurobiological mechanisms responsible for symptom exacerbation in TS remain poorly understood. This conceptual gap partially reflects the high phenotypic variability in tics, as well as the existing difficulties in operationalizing and standardizing stress and its effects in a clinical setting. Animal models of TS may be highly informative tools to overcome some of these limitations; these experimental preparations have already provided critical insights on key aspects of TS pathophysiology, and may prove useful to identify the neurochemical alterations induced by different stressful contingencies. In particular, emerging knowledge on the role of contextual triggers in animal models of TS may inform the development of novel pharmacological interventions to reduce tic fluctuations in this disorder.

Keywords

Tourette syndrome; tics; premonitory sensory phenomena; animal models; stress

1. Introduction

Tics are sudden, non-rhythmic, repetitive movements and vocalizations, corresponding to the activation of a discrete group of muscles. Both motor and phonic manifestations are characterized by a wide range of phenotypic variability and complexity (Jankovic, 1992): simple tics are brief and repetitive actions, such as nose wrinkling, eye blinking, sniffing or throat-clearing noises; conversely, complex tics engage multiple muscle groups in coordinated patterns, including touching objects or uttering phrases (Jankovic, 1992).

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Another key diagnostic feature of tics is their partial controllability. Indeed, unlike other dyskinetic phenomena, tics can be delayed and camouflaged, even though they cannot be fully suppressed. Although the occasional presentation of tics should not be regarded as pathological, their recurrent and intense display can negatively impact social, educational and occupational functioning (Stokes et al., 1991; Conelea et al., 2013; Gutierrez-Colina et al., 2015), and is therefore classified as a *tic disorder*. The most severe among these nosological entities, Tourette syndrome (TS), is defined by the presence of multiple motor tics and at least one phonic tic, lasting for longer than one year and with an onset prior to 18 years of age. Once regarded as a rare disorder, TS is observed in ~0.5% of the pediatric population according to a recent meta-analysis (Scharf et al., 2015), even though previous studies estimated the international prevalence of the disorder at 1% (Robertson, 2008). About 86% of TS patients exhibit at least one comorbid neuropsychiatric condition (Hirschtritt et al., 2015); in particular, most TS patients are also diagnosed with attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) (Ghanizadeh and Mosallaei, 2009). One of the most prominent features of TS is the high degree of variability in tic severity across different temporal stages of the disorder. Tics emerge in childhood (most typically around 6–7 years of age) and undergo a gradual escalation in intensity and frequency, often followed by a full or partial remission during puberty (Leckman et al., 1998); it is estimated, however, that approximately 24% of TS patients retain moderate and severe tics in adulthood (Goetz et al., 1992). In addition to these diachronic fluctuations, the baseline intensity and frequency of tics oscillate widely, reflecting the impact of multiple contextual and emotional factors. In particular, rich empirical evidence indicates that the severity of tics and associated symptoms increases in the presence of physical and psychological stress (Robertson et al., 2002; O'Connor et al., 2003; Eapen et al., 2004). Indeed, multiple surveys have shown an association between stressful life events and greater severity/earlier onset of tic disorders (Bornstein et al., 1990; Steinberg et al., 2013). This relationship was confirmed by longitudinal studies, which documented that cumulative psychosocial stress predicts for future severity of tics (Lin et al., 2007). On a shorter timescale, several studies have indicated a direct correlation between tic severity and self-report ratings of daily life stress (Findley et al., 2003), as well as negative small events in the same or preceding week (Hoekstra et al., 2004). For such a well-documented relationship, little is surprisingly known about the neurobiological and neurochemical mechanisms whereby tics are exacerbated by stress, and the specific pharmacological and behavioral interventions that may help prevent stress-induced aggravation of tics. An optimal, yet often undervalued tool to overcome these critical barriers is afforded by animal models of TS. The unique advantage of these preparations lies in the possibility to manipulate, standardize and analyze the neurobiological impact of specific stressors in the presence of experimental controls for each of the potential variables involved. In the present review, we will summarize the current knowledge on the effects of stress in TS, and indicate how animal models may help identify the neurobiological mechanisms whereby distinct modalities of contextual stress increase tic severity. In addition, we will overview potential experimental directions that may inform new therapies for the reduction of the impact of stress on TS.

2. Phenomenology and neurobiology of tics

2.1. Sensory antecedents of tics

Although the first clinical description of TS dates back to 1825, a more systematic characterization of the phenomenology and neurobiological basis of tics has been achieved only in the past few years. In particular, while these manifestations were long regarded as neurological entities, recent research has shown that they are the epiphenomenon of a much more complex behavioral sequence, rooted in *premonitory sensory phenomena (PSP)* (Houghton et al., 2014). PSP are uncomfortable sensations, typically characterized by a feeling of oversensitivity and aversion for specific interoceptive and exteroceptive stimuli, with a hyperattentive focus on somatic input (Cohen and Leckman, 1992; Houghton et al., 2014). The source of PSP is not traced back to alterations in sensory transmission efficiency (Belluscio et al., 2011), but may instead depend on perceptual processing dysfunctions. In particular, TS patients exhibit deficits in *gating* functions, which enable the filtering of irrelevant or redundant information (Castellanos et al., 1996; Sutherland-Owens et al., 2011). One of the best-described PSP is the premonitory urge, an intrusive somatic sensation of inner tension and discomfort typically relieved by the execution of tics (Cohen and Leckman, 1992; Leckman et al., 1993; Evers and van de Wetering, 1994). Although these phenomena are not consistently reported in childhood (Banaschewski et al., 2003), they are likely the main negative reinforcers of tics (Woods et al., 2008); indeed, most patients report that tics are primarily executed to alleviate the distress associated with premonitory urges (Lang, 1991; Kwak et al, 2003), and the temporary suppression of tics magnifies the intensity of premonitory urges (Himle et al., 2007).

2.2. Neurobiology of PSP and tics

Recent neuroimaging studies have revealed that tics and their sensory/psychological antecedents result from a sequence of activation patterns across the cortico-striatal-thalamic-cortical (CSTC) loop, a key pathway serving the integration of sensory and motor functions (for a full discussion on the neuroanatomical bases of TS, see Ganos et al., 2013). The functional regulation of the CSTC pathway is based on the integration of topographically segregated networks; in particular, the generation of saliency maps in these sub-circuits is based on “center-on, surround-off” contrasts, in which the stimulation of a network is paralleled by the silencing of competing responses from adjacent tracts via neighboring interneurons (for an overview of the neuronal correlates of these mechanisms in the cortex, see Helmstaedter et al., 2009).

Building on this framework, current interpretations explain PSP and tics as the result of an insufficient inhibitory tone (or excessive excitatory output) in both cortical and striatal areas of the CSTC loop, respectively. Specifically, oversensitivity to stimuli has been shown to reflect the excessive stimulation of the sensorimotor cortex (Wang et al., 2011; Biermann-Ruben et al., 2012); conversely, premonitory urges are rooted in the hyperactivity of the supplementary motor area (SMA), anterior cingulate cortex, insula and parietal operculum (Bohlhalter et al., 2006; Jackson et al., 2011; Wang et al., 2011; Neuner et al., 2014; Worbe et al., 2015). Finally, the negative emotional components associated with the urges appear to be underpinned by the activation of the amygdala (Wang et al., 2011). Some of these

mechanisms have been recently confirmed by the finding that transcranial magnetic stimulation of the SMA produces urges and motor manifestations akin to tics (Finis et al., 2013). While the specific mechanisms underpinning the overactivation of these regions are still unclear, preliminary reports have documented reductions in GABAergic interneurons in the insula of TS patients (Vaccarino et al., 2013). Although these findings await confirmation with larger number of samples and different regions of the CSTC loop, they are in line with other evidence documenting that the GABA content in the somatosensory cortex of TS patients is low and negatively correlated with motor tic severity (Tinaz et al., 2014; Puts et al., 2015). Furthermore, intracortical inhibition has been found to be deficient in TS (Ziemann et al., 1997).

Along similar lines, several studies have documented the reduction and altered distribution of parvalbumin-positive GABAergic and cholinergic interneurons in the dorsal striatum of TS patients (Kalanithi et al., 2005; Kataoka et al., 2010), as well as decreased binding of GABA-A receptors in the striatum, globus pallidus, thalamus, amygdala and insula (Lerner et al., 2012). These changes may partially reflect metabolic dysfunctions of striatal interneurons, as suggested by transcriptomic alterations (Lennington et al., 2016). Deficits in interneurons and GABA-A receptors are posited to result in the formation of *ectopic foci* in the dorsal striatum (Mink, 2001; Albin and Mink, 2006). An excessive cortical and/or amygdalar output (corresponding to intense and discomforting PSP) would lead to the transient activation of these neuronal clusters, engendering tics through the stimulation of downstream pathways in the thalamus and primary motor cortex (Neuner et al., 2014). Recent findings indicate that the stimulation of the primary motor cortex may reduce the excitability of the somatosensory cortex (Enomoto et al., 2001; Seyal et al., 2005), providing a tentative mechanism accounting for the reduction in PSP following tic execution.

2.3. The role of dopamine in tics

Activation of the striatum is directed by dopamine, a key neurotransmitter in the regulation of motor output in the CSTC. The role of dopamine in TS is indicated by the anti-tic effects of dopamine receptor antagonists, such as haloperidol and pimozide (Roessner et al., 2013); furthermore, dopaminergic agonists have been shown to increase TS symptom severity (Shale et al., 1986). Differences in dopaminergic functions between TS patients and non-affected individuals have been shown by Steeves and colleagues (2010), who reported that the dopamine releaser amphetamine led to a significantly more widespread activation in several CSTC areas of TS patients. Although the exact contribution of dopamine in tic ontogeny is partially unclear, several authors have hypothesized that tics may reflect an excessive phasic release and reduced tonic transmission of dopamine in the basal ganglia (Wong et al., 2008; Buse et al., 2013), which could result in the activation of ectopic foci by virtue of volume-transmission mechanisms and activation of extrasynaptic dopamine receptors. This mechanism would imply a primary role of D_1 receptors in TS pathophysiology, given that they are posited to mediate phasic dopamine signaling in the dorsal striatum and are predominantly extrasynaptic (Caillé et al., 1996; Dreyer et al., 2010). From this perspective, it is worth noting that D_1 receptor antagonism has been recently found to have therapeutic efficacy in TS (Gilbert et al., 2014). Several other lines of research point to the involvement of D_1 receptors: first, these receptors have been recently shown to

regulate recurrent efferent feedback from the somatosensory cortex and facilitate detection of behavioral stimuli (Happel et al., 2014); second, activation of D_1 receptors in the striatum is instrumental in the induction of striatal synaptic plasticity processes, such as long-term potentiation (Kerr and Wickens, 2001; Centonze et al., 2003), and has been shown to have a widespread facilitatory effect on the connectivity between thalamus and somatosensory cortex (Steiner and Kitai, 2001).

These mechanisms may be instrumental in the pathophysiology of TS by facilitating habit formation, a core adaptive process that appears to be hyperactive in TS (Delorme et al., 2016) and is also accelerated by D_1 receptor activation (Nelson and Kilcross, 2013). In this respect, it should be noted that activity-dependent dopaminergic feedback appears to play a major role in the reinforcement of tics (Albin and Mink, 2006). Although these premises may apparently suggest that the neurobiological bases of TS are well-defined, it should be noted that this disorder may encompass multiple distinct entities with only partial mechanistic overlap. Initial attempts to qualify different subtypes of TS are ongoing (Grados et al., 2008; Eapen and Robertson, 2015), but little to no neurobiological information about the neurobiological underpinnings of phenotypic differences is currently available.

3. Animal models of TS

Rodent models of TS offer an interesting complementary experimental platform to investigate the neurobiological basis of tics. The main advantage of these preparations lies in the possibility to test for specific mechanistic hypotheses that may emerge from correlational clinical data, and identify the neurochemical bases of different symptoms. At the same time, due to the obvious neurobiological differences, animal models can only approximate the dynamic complexity of human pathophysiology. Furthermore, subjective phenomena cannot be interrogated in animals, and can only be investigated by means of indirect proxy endophenotypes based on overlapping neurobiological mechanisms.

Over the past few years, one of the most common approaches to model TS in rodents has been based on the development of genetic mutations found in TS patients. The first notable example of this strategy was the generation of mice with a nonsense mutation for the gene *Slitrk1* (Katayama et al., 2010), following the identification of an association between the human gene and rare, familial forms of TS (Abelson et al., 2005). While these mouse mutants did not exhibit tic-like manifestations, they showed increased anxiety- and depression-like phenotypes (Katayama et al., 2010), which may be linked to the comorbidity between TS and these psychiatric conditions (Coffey et al., 2000; Hirschtritt et al., 2015). A similar approach was followed after the discovery of a rare mutation for the gene encoding histidine decarboxylase (*HDC*) in a TS pedigree (Ercan-Sencicek et al., 2010). *Hdc*-deficient mice exhibit elevated levels of dopamine in the striatum, as well as information-processing deficits akin to those observed in TS patients (Castellan-Baldan et al., 2014). While tic-like repetitive responses are not spontaneously exhibited by these mutants, they can be elicited by a challenge with the dopaminergic indirect agonist *d*-amphetamine or an acute stress (Castellan-Baldan et al., 2014; Xu et al., 2015a).

In this section, we will briefly examine how animal models are strengthening our neurobiological views on the mechanisms underpinning PSP and tics. For comprehensive reviews on animal models of TS and tic disorders, the interested reader is referred to Bronfeld et al. (2013a), Macrì et al. (2013) and Godar et al. (2014).

3.1. Model-based approaches to PSP

Animal models cannot properly reproduce PSP, given their subjective nature; thus, the most common approach to study these phenomena is based on indices of perceptual efficiency that may share common neurobiological substrates with PSP. In particular, great emphasis has been placed on sensorimotor gating, given the deficits in this domain documented in TS patients. The best-validated, cross-species paradigm for gating measurement is the prepulse inhibition (PPI) of the startle reflex, which represents the reduction of a startle response enabled by a weak signal immediately preceding the startling stimulus (Hoffman and Ison, 1980; Braff et al., 1992; Braff et al., 2001). Clinical reports have documented PPI disruptions in TS patients throughout different paradigms (Castellanos et al., 1996; Swerdlow et al., 2001). While PPI cannot be considered a direct index of PSP severity, it may serve as a phenomenological proxy for the information-processing impairments that underpin sensory antecedents of tics (Swerdlow, 2013).

Converging lines of research on the anatomical and psychophysiological bases of PPI have revealed that the substrates of this endophenotype largely overlap with those of TS (Swerdlow, 2013): first, in TS patients, PPI is correlated with activity of the superior parietal cortex and associated with deficits in the dorsal striatum (caudate) and other regions responsible for integration of somatosensory stimuli, such as the prefrontal cortex (Buse et al., 2016a); second, neuroimaging studies have shown that PPI and PSP are based on overlapping neuroanatomical circuits in the somatosensory cortex and caudate nucleus (Neuner et al., 2010; Wang et al., 2011; Zebardast et al., 2013); third, clinical and preclinical reports have documented that PPI is impaired by dopaminergic agonists (Braff et al., 2001; Geyer et al., 2001; Swerdlow et al., 2008), whereas PPI deficits are improved by dopaminergic antagonists (Braff et al., 2001).

An alternative strategy to study the neurobiology of PSP lies in the employment of animal models that reproduce the neurobiological correlates of these manifestations, such as the over-activation (or under-inhibition) of the somatosensory, insular and prefrontal cortex. Along these lines, a recent study showed that local infusion of low-dose picrotoxin (a GABA-A receptor antagonist) in the sensorimotor cortex of mice led to tic-like responses, associated with increased exploration, sniffing and paw-licking behaviors. These phenotypes underwent sensitization with repeated interventions, and were abrogated by local activation of GABA-A receptors in the dorsolateral striatum (Pogorelov et al., 2015). While these results cannot ultimately verify whether activation of the sensorimotor cortex is directly responsible for premonitory urges, the tight association with tic-like responses and generalized motor phenomena suggests that local disinhibition of the somatosensory cortex may indeed underlie PSP. Given that this region has inhibitory processes overlapping with PPI (Nakagawa et al., 2014), it would be interesting to verify whether pharmacological disinhibition of the somatosensory cortex would impair sensorimotor gating. It should be

noted, however, that tactile, rather than acoustic PPI, may be best suited to capture these impairments, given the nature of the sensory information processed in this area. The notion that insufficient GABAergic inhibition in cortical areas may impair information processing is supported by multiple lines of preclinical evidence: for example, recent findings have demonstrated that maturation of GABAergic circuits in the insula are essential for sensory integration (Gogolla et al., 2014); furthermore, previous research has indicated that lesions of the medial prefrontal and entorhinal cortex disrupt acoustic PPI (Yee, 2000; Goto et al. 2002).

Some initial studies have taken advantage of optogenetic tools to show the behavioral consequences of the activation of corticostriatal connections. In particular, repeated hyperactivation of the connectivity between the orbitofrontal cortex and the ventromedial striatum produced a progressive, long-lasting increase in grooming compulsions, potentially indicating that repetitive motor manifestations may be the result of a chronic enhancement in the activity of select cortical regions (Ahmari et al., 2013). Of the currently available TS animal models, the one that perhaps best recapitulates the relevance of cortical hyperactivation in PSP is the D1CT-7 transgenic mouse, which was generated by the insertion of a cholera toxin subunit A1 gene behind the promoter of dopamine D_1 receptor (Campbell et al., 1999; Nordstrom and Burton, 2002). This construct leads to the constitutive activation of Gs proteins in a subset of D_1-positive neurons in the layers II and III of the somatosensory cortex, layer II of the piriform cortex, as well as the intercalated nucleus of the amygdala (Campbell et al., 1999). The activation of output neurons in these two regions is thought to reproduce some of the neural events that occur during premonitory urges and sensory phenomena (Nordstrom et al., 2015). Accordingly, D1CT-7 mice exhibit spontaneous tic-like manifestations, consisting in sudden axial jerks, which emerge during early neurodevelopmental stages and appear with a sexual dimorphism reminiscent of that observed in TS (Nordstrom and Burton, 2002). In addition to their high face validity, D1CT-7 mice show a high predictive validity for anti-tic therapies, including clonidine and haloperidol (Nordstrom and Burton, 2002). Further validation that the phenotypes of D1CT-7 may be relevant to the link between PSP and tics is provided by our recent results that these animals (but not their wild-type littermates) exhibited PPI deficits and exacerbations of their tic-like manifestations in response to a mild acute stress (Godar et al., 2016). These results indicate that the neuropotentiation of somatosensory cortex and amygdala may increase the predisposition to respond to stressful contextual triggers with tics.

3.2 Model-based approaches to tics

Given the differences in motor pattern organization between humans and rodents, it is extremely difficult to define the phenotypic equivalences of tics in non-primate animal models. In general, one of the most common experimental proxies for tics in experimental animals is provided by the repetitive motor responses induced by dopaminergic agonists. Activation of dopamine receptors in the dorsal striatum has been shown to result in repetitive responses, which are facilitated by deficits of cholinergic interneurons in the same area (Arnt, 1985; Arnt et al., 1988; Conti et al., 1997; Aliane et al., 2009; 2011; 2012). Notably,

these phenomena have been shown to be responsive to most TS therapies across multiple species (Rotrosen et al, 1972; Asper et al., 1973; Dewey and Fibiger, 1983).

These behaviors have been traditionally described as “stereotypies”, in relation to their repetitive nature; however, this definition may be poorly suitable to a translational framework, given that, in humans, this term refers to a very specific type of behavioral phenomenon, characterized by invariant, highly rhythmic presentation, as well as lack of premonitory urges (Crosland et al., 2005; Singer, 2013). The clinical distinction between tics and stereotypies is so important that the DSM-5 has included the latter manifestations in the differential diagnostic criteria for tics.

The ambiguity in the current nomenclature is also problematic as it fails to distinguish between spontaneous, drug-induced and stress-induced repetitive behaviors, even though their neurophysiological mechanisms may be at least partially divergent (for a more detailed analysis of this issue, see Lewis and Kim, 2009). Taken together, these premises highlight the need for a more precise classification of repeated behaviors in animal models, also in consideration of the potentially relevance of each of these responses to multiple neuropsychiatric conditions in humans.

A different approach to model tics in animals is based on the generation of artificial “ectopic foci” in the striatum, resulting from either excess activation, or functional deficits in the inhibitory components, of this region. In particular, GABA-A receptor blockade in the dorsal striatum of rodents and primates has been found to elicit tic-like manifestations (McCairn et al., 2009; Bronfeld et al., 2013b). Bronfeld and colleagues (2013b) showed that the injection of the GABA-A receptor antagonist bicuculline in the striatum of rats; this experiment led to a somatotopically organized pattern of movements, which began as a jerk-like phenomenon, became gradually more pronounced, and finally decreased in intensity until reaching complete cessation. Notably, the temporal properties of tic expression in this model of focal disinhibition were recently found to be influenced by the frequency and amplitude of the stimulation of the motor cortex and the ensuing striatal activation (Israelashvili and Bar-Gad, 2015).

Overall, these findings lend strong support to the idea that local deficits in GABAergic interneurons may lead to tics through activation of ectopic foci, but also qualifies that fluctuations of tics in frequency and intensity may be under direct cortical control. These mechanisms have been implemented in the development of novel mouse models of TS based on the selective ablation of cholinergic and parvalbumin-positive, GABA-ergic interneurons (Xu et al., 2015b; Xu et al., 2016). These preparations aimed at studying the functional relevance of the lack of striatal interneurons in TS, as documented by post-mortem findings (Kalanithi et al., 2005; Kataoka et al., 2010). In both models, targeted deletion of either subpopulations of interneurons in the dorsal striatum predisposed to repetitive sniffing and grooming and sensitization to stress following short-term stress (Xu et al., 2015b; 2016).

Taken collectively, the evidence in animal models of TS indicate that local disinhibition in the somatosensory cortex and in the dorsal striatum predisposes to phenomena directly related to PSP and tics; however, these responses are directly triggered by acute stress,

highlighting the critical role of this factor in eliciting and modulating the expression of TS symptoms. In the next section, we will explore this relationship in greater detail, and review the main lines of translational evidence from clinical and preclinical studies indicating the role and mechanistic bases of specific stressors in symptom fluctuations in TS.

4. Contextual and emotional triggers as exacerbating factors in TS

As noted in the previous sections, tics and PSP are exacerbated by various *stressors*, defined as environmental factors that force the organism to transiently operate beyond its physiological capacity. Similarly, psychological stressors increase the perceived gap between a challenging environmental contingency and the ability to successfully react to it (Lazarus, 1966). Irrespective of the nature of the stressor, the brain orchestrates an *allostatic* response, i.e., a complex series of autonomic, neuroendocrine, neuroimmune and behavioral changes aimed at re-establishing a homeostatic balance (McEwen, 2007; McEwen and Wingfield, 2010). In this context, *homeostasis* refers to the ability to maintain the organism within a narrow range of survival-promoting functional conditions. The phenomenological link between acute stress and exacerbation of PSP and tics has been the object of several studies. In particular, a number of recent meta-analyses have reviewed the current knowledge on the specific environmental triggers associated with tic exacerbation (Conelea and Woods, 2008; Caurin et al., 2014; Hoekstra et al., 2013), and generally confirmed that TS symptoms are worsened by several (but not all) modalities of acute stress. Nevertheless, the analysis of this relationship is complicated by a number of methodological and theoretical restrictions: first, the lack of an operationalized definition of acute stress in TS pathophysiology limits our ability to recognize which stressors are specifically able to exacerbate urges and trigger tics; second, the standardization of the role of stressors in TS is complicated by the vast heterogeneity of clinical presentations, socio-cultural background and experiential factors in patients; finally, while the execution of tics often reduces the stress associated with PSP, it can also compound the sensation of psychological stress, depending on the context. These limitations notwithstanding, certain generalizations can be made on the main contextual factors associated with rapid variations in TS symptom severity. The bulk of available clinical evidence indicates that tic fluctuations predominantly occur in relation to four types of partially overlapping scenarios: 1) high or low sensory stimulation; 2) anxiogenic situations; 3) frustrating and anger-inducing contingencies; 4) fatigue and sleep loss. The allostatic mechanisms enacted to withstand these stressors are likely to interact with the neurobiological mechanisms of TS. A synoptic diagram of the key areas that may be activated by different contextual trigger is presented in Table 1 (for details, see below). Strikingly, manipulations related to these contextual factors have also been shown to trigger or intensify TS-related phenotypes in animal models.

4.1. Sensory over- or understimulation

Tics are generally exacerbated by conditions that entail either too much or too little sensory stimulation (generally classified as “boredom” by most patients). The most common scenarios associated with overstimulation include watching TV and playing videogames (Silva et al., 1995; Caurin et al., 2014; Barnea et al., 2016). Interestingly, engaging in multitasking activity has also been linked to tic exacerbation (O’Connor et al., 1994); this

phenomenon may be interpreted as a consequence of overstimulation, but also reflect the greater difficulties encountered by TS and TS+ADHD patients in executive functions (Channon et al., 2003). The mechanisms underpinning tic exacerbation in response to overstimulation are still elusive but likely reflect an information overload contributed by gating deficits. From this perspective, it is worth noting that PPI responses elicited by monaural prepulses are greater than their binaural counterparts (Marsh et al., 1976; Hoffman and Ison, 1980; Kumari et al., 2005), probably indicating that sensory integration lowers filtering ability.

Low environmental stimulation is also likely to distort information processing, possibly by shifting attentive focus towards interoceptive stimuli and the pursuit of alternative goals (Bench and Lench, 2013). In keeping with this idea, boredom is associated with negative self-awareness (Seib and Vodanovich, 1998) and a greater risk for impulsivity (Watt and Vodanovich, 1992). While the association between boredom and tics has been shown in a small subset of TS patients in several studies (Robertson et al., 2002; Eapen et al., 2004), the neurobiological underpinnings of this link remain elusive. In agreement with clinical data, a moderate spatial confinement has been shown to worsen TS-related behaviors in animal models, particularly in the presence of other predisposing factors. For example, spatial restriction of the testing arena has been shown to increase repetitive responses induced by *d*-amphetamine (Fowler and Mahoney, 2010). Furthermore, our group recently showed that spatial confinement within a familiar environment (home cage) greatly exacerbates tic-like responses and causes PPI deficits in D1CT-7 mice (Godar et al., 2016). Interestingly, these phenomena were reduced by dopaminergic antagonists, as well as by clonidine, supporting that these behavioral manifestations are likely supported by enhancements in catecholamine neurotransmission (Godar et al., 2016).

From this perspective, it is worth noting that one of the best-validated stressors in the lab setting is physical restraint, an extreme situation of spatial restriction. This manipulation has been shown to induce PPI deficits in mice and rats (Conti and Printz, 2003; Guercio et al., 2014) as well as an initial increase of dopamine release in the ventral striatum (Puglisi-Allegra et al., 1991).

4.2. Anxiety

A host of studies have documented that feelings of anxiety increased the severity of tics (Bornstein et al., 1990; O'Connor et al., 1994; Silva et al., 1995) and premonitory urges (Rozenman et al., 2015) in TS patients. In particular, anxiety has been recently shown to trigger "tic attacks", episodic bouts of severe, continuous and non-suppressible tics, in a subset of TS patients (Robinson and Hedderly, 2016). Although the detrimental impact of anxiety on TS pathophysiology is well supported, recent evidence indicates that this relationship may not be generalized to all anxiogenic contexts. For example, a recent experimental study has documented that the Trier social stress test *reduces* tic frequency, even though it enhances neuroendocrine and physiological indices of the stress response (Buse et al., 2016b). On the other hand, other studies reported that socialization and anticipation of social events are associated with tic exacerbation (Steinberg et al., 2013; Caurin et al., 2014; Himle et al., 2014). The relationship between anxiety-like responses and

TS-related endophenotypes is also not consistently straightforward in animals. On one hand, fear-inducing experimental stimuli in the lab setting, such as a mild footshock, have failed to induce PPI deficits in experimental animals (Guercio et al., 2014). On the other hand, anxiogenic stimuli (such as sudden acoustic bursts or fear-conditioning procedures) were sufficient to trigger tic-like behaviors in animal models with reductions of striatal interneurons (Xu et al., 2015b; 2016).

These contrasting findings may signify that, while anxiety may be intrinsically insufficient to trigger TS-related deficits, it may synergize with other predisposing factors to increase these phenotypes. In particular, anxiety may trigger tics only in a subset of individuals with a greater proclivity to engage in externalizing, rather than internalizing responses (such as those with a comorbid diagnosis of ADHD or disruptive behavior disorder). A similar possibility has been examined to interpret the complex interplay existing between anxiety and reactive/defensive aggression (Bubier and Drabick, 2009; Neumann et al, 2010). Indeed, these two manifestations are often associated in children and share common risk factors, neuroendocrine correlates and temperamental styles (Bubier and Drabick, 2009). An alternative/complementary explanation may be that the association between anxiety and tics may be particularly relevant in situations of intense emotional tension. Indeed, Franklin and colleagues (2009) found that anxiety-spectrum constructs are negatively correlated with PPI. Furthermore, PPI deficits were found in relation to high-trait anxiety in college students (Duley et al, 2007) and panic disorder patients (Ludewig et al, 2002). Considering that the prevalence of anxiety disorders is high in TS patients (Coffey et al., 2000; Hirschtritt et al., 2015), it is possible that a subset of TS patients may over-react to specific stimuli, and that the ensuing exaggerated responses may lead to the exacerbation of PSP and tics. Irrespective of the specific contingencies, most available evidence supports the possibility that the contribution of anxiety to the severity of TS manifestations may be primarily contributed by the amygdala, the key region for the regulation of fear response. Indeed, TS patients display morphological and functional alterations of this region, including an increased volume (Peterson et al., 2007), as well as an elevated activity during tics (Wang et al., 2011) and exposure to emotional face expression (Neuner et al., 2010).

4.3. Frustration

Frustration can be conceptualized as the emotional response to the omission of a desired goal (Abler et al., 2005) or the absence of reinforcement to an expected reward (Amsel, 1992). Psychological experiences of frustration may generate anger and aggressive behaviors (Pawliczek et al., 2013). Aggression and conduct disorder has been frequently associated with TS (Comings and Comings, 1987; Wand et al., 1993; Dehning et al., 2015; Kano et al., 2015).

Although very few studies have examined the neural bases of frustration, a recent report has shown that brain activity patterns during frustration closely mirrored those reported in acute stress experiments, including the prefrontal cortex, insula, dorsal striatum and cingulate cortex (Bierzynska et al., 2016). In another neuroimaging study, frustration increased activity along the prefrontal cortex, insula, amygdala and midbrain (Yu et al., 2014), a network that closely aligns with rage circuitry (Panksepp, 2005). Although only a few

studies have studied frustration in experimental animals, novel paradigms have been recently developed to study this construct in reference to operant tasks (Burokas et al., 2012). Notably, changes in the predictability of food delivery can increase frustration (Bassett and Buchanan-Smith, 2007) and have been linked to an increase in spontaneous repeated behaviors (Waitt and Buchanan-Smith, 2001). In addition, preliminary observations in our lab indicate that the frustration of a conditioned reward exacerbated tic-like responses in D1CT-7 mice. Future studies will be needed to verify how the application of operant paradigms to reproduce frustrating conditions may lead to stereotypies or PPI deficits in TS models.

4.4. Fatigue and sleep loss

Fatigue may be defined as exhaustion due to physical or mental exertion. Ample evidence has shown that fatigue and sleep loss (a key correlate of fatigue) increase tic severity in patients (Bornstein et al., 1990; Silva et al., 1995; Cohrs et al., 2001; Robertson et al., 2002; Eapen et al., 2004). In keeping with this possibility, several clinical reports have documented sleep abnormalities in TS patients (Kostanecka-Endress et al., 2003; Ghosh et al., 2014; Modafferi et al., 2016). While the mechanism linking sleep disturbances (and fatigue) to tics is still largely unclear, total sleep deprivation has been shown to disrupt PPI in both humans and rats (Frau et al., 2008; Petrovsky et al., 2014), and to increase repetitive responses induced by dopamine agonists in comparison with controls (Ferguson and Dement, 1969; Tufik et al., 1978). The main effect of fatigue on tics may be related to a reduced tolerance for some of the other contextual/emotional triggers. Accordingly, fatigue has been shown to reduce tolerance to frustration (Anitei et al., 2013).

The neurobiological bases of the exacerbation of PSP and tics in sleep-deprived patients likely reflects the disinhibition/enhancement of cortical excitability and alterations of thalamic feedback mechanisms (Gorgoni et al., 2014; Killgore et al., 2015), as well as the enhanced expression, binding and activity of dopamine receptors in the dorsal striatum (Tufik et al., 1978; Demontis et al., 1990; Nunes-Junior et al., 1994).

Taken together, clinical and animal findings support that urges and tics are increased by a number of specific stressors through different, yet inter-related mechanisms. Irrespective of the specific process, however, all these modalities lead to alterations of sensory processing in the cortex and greater likelihood of information overload, by either increasing the degree of stimulation or reducing the ability to filter sensory input. Emotional responses to certain types of anxiety, frustration and perhaps boredom also appear to increase the activation of specific areas in the CSTC circuitry, and ultimately facilitate the stimulation of the striatum. This mechanism may be specifically facilitated by dopamine release; the enhanced efflux of this neurotransmitter, which can be also contributed by acute stress, may help reduce the discomfort of the urges and facilitate the formation of maladaptive habits (Fig. 1). In the next section, we will discuss how neuroendocrine mechanisms of stress response may play a direct role in this process, and outline potential future directions to research this link and develop therapies that may reduce the impact of stress in TS pathophysiology.

5. Conclusions: neurobiological mechanisms and therapeutic perspectives

The physiological response to acute stress is largely mediated by the hypothalamic-pituitary-adrenal (HPA) axis, which enables the utilization of additional cognitive and energetic resources to mount an adaptive response to the stressor and regain homeostasis (McEwen, 2002; McEwen, 2007). The neuroendocrine effects of the HPA axis are initiated with the secretion of corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus, which in turn promotes the concatenated release of adrenocorticotropic hormone (ACTH) from the pituitary gland, and cortisol from the adrenal cortex. The rapid surge of these hormones is essential for stress coping; one of the mechanisms that mediate this action may be the increase in dopamine release following acute release of CRH and cortisol (Lemos et al., 2012; Vaessen et al., 2015). This increased dopamine efflux has been primarily documented in key regions of the mesocorticolimbic system, including the prefrontal cortex, nucleus accumbens and dorsal striatum (Abercrombie et al., 1989; Lavicky and Dunn, 1993; Hermans et al., 2014), and appears to be essential for stress resilience and coping (Cabib and Puglisi-Allegra, 2012; Pfau and Russo, 2015).

Once the stressor is no longer present, a fast recovery to baseline activity is ensured by feedback inhibition of CRH release from cortisol. Other endocrine factors are involved in the modulation of stress response, including neuropeptides (such as endogenous opioids, vasopressin and neuropeptide Y), neurosteroids and endocannabinoids. These neuromediators help balance the effects of the HPA axis to help counteract negative emotional consequences of negative emotional consequences that may be triggered by excess or chronic stress. For opioids, the interactions between CRH with enkephalins and certain neurosteroids (such as allopregnanolone or tetrahydrocorticosterone) are critical for the modulation of stress response (Gunn et al., 2011; Valentino and van Bockstaele, 2015).

5.1. What mechanisms may underpin the role of stress in tic fluctuations?

A number of studies have shown that TS patients exhibit greater HPA axis activation in response to acute stressors, with higher levels of CRH, ACTH and cortisol (Chappell et al., 1994; Chappell et al., 1996; Corbett et al., 2008). Notably, however, a strong, *negative* correlation was found between evening cortisol levels and tic severity (Corbett et al., 2008), leading to the possible interpretation that tics may have anxiolytic properties in TS patients. To contextualize these findings, it is worth noting that, particularly in adolescent and adult patients, tics are regarded as a response aimed at mitigating the discomfort associated with premonitory urges (Kwak et al., 2003).

Applying these concepts to our knowledge of the neurobiological machinery serving acute stress response and TS pathophysiology, the release of CRH and dopamine is likely to be transiently enacted with the goal of mitigating the stressful sensations associated with PSP. The discomforting effect of PSP appears to be compounded by specific contextual factors that could either increase their psychological burden (with a greater degree of cortical and amygdalar activation, such as in the case of overstimulation or high anxiety) or reduce the subjective ability to tolerate urges (as in the case of fatigue). Irrespective of the cause, the increase in cortical output and dopamine release in the striatum may lead to the activation of ectopic foci and the production of tics. From this perspective, tics may first occur as a by-

product of these mechanisms, and then be progressively consolidated as a maladaptive coping response throughout the developmental trajectory of the disorder. This plastic adaptation would be enabled by negative-reinforcement mechanisms facilitated by D_1 receptor stimulation in corticostriatal areas.

The involvement of CRH and dopamine in the enactment of defensive reactions may be also the distinguishing feature that may link only certain anxiogenic stimuli with tic exacerbation (see above). Indeed, dopamine has been shown to be instrumental for the enactment of defensive responses to acute stress (Cabib and Puglisi-Allegra, 2012). From a psychological standpoint, these premises suggest that anxiety and other negative emotional states may either aggravate or reduce tic severity in TS patients, depending on their coping style. Building on this notion, different subtypes of TS may lead to different reactions to contextual triggers, contingent on their profile of comorbid neuropsychiatric entities. For example, it is likely that patients with high levels of reactive aggression and impulsivity may exhibit a greater proclivity to display tic exacerbations in response to anxiogenic and frustrating stimuli; conversely, concurrent depressive/dysthymic symptoms (in which CRH and dopamine responses are blunted) may lead to tic reduction in the presence of certain contextual factors. Future studies will be necessary to verify how different coping modalities may predict for different fluctuations of tic severity in response to various contextual triggers. Furthermore, further research is warranted to ascertain how tic-like responses and information-processing impairments (including PPI deficits) in animal models of TS may be modified by environmental manipulations that increase either defensive reactivity (such as exposure to predator cues) or depression-like responses (such as chronic mild stress).

5.2. How can the role of stress in TS inform the development of novel therapies?

Another highly intriguing corollary of this conceptual framework is that, if tics are a component of stress-coping mechanisms in TS, these manifestations should be attenuated by therapies that *reduce*, rather than increase, the resilience to acute stress. In line with this concept, the main pharmacological strategy in TS therapy consists of dopaminergic antagonists, which are also known to suppress active defensive responses aimed at countering stress (Cabib and Puglisi-Allegra, 2012). Along the same lines, opioid antagonists have been generally shown to reduce the severity of tics (Sandyk and Awerbuch, 1989; Kurlan et al., 1991; van Wattum et al., 2000; but see Erenberg and Lederman, 1992 for contrasting findings). Finally, our group has shown that inhibition of neurosteroid synthesis by the 5α-reductase inhibitor finasteride leads to a marked reduction of tic severity in TS patients (Bortolato et al., 2007; Muroni et al., 2011); these findings were paralleled by the discovery that finasteride reduces PPI deficits and stereotypies induced by dopaminergic agonists in rats and mice, likely through the attenuation of D_1 receptor signaling (Bortolato et al., 2008; Frau et al., 2013; 2016).

The development of pharmacological agents that target the interface between stressors and their neurobiological targets may be critical for the improvement of life quality in TS patients. The employment of animal models of TS may prove essential to enable the pursuit of this goal. In this respect, a particularly attractive direction may be to test the response of these models to behavioral paradigms based on relevant triggers, such as sleep deprivation,

frustration of expected rewards, and sensory over- or understimulation. The refinement of these paradigms and experimental protocols may enable us to study the behavioral and neurobiological impact of key neuromodulators, as well as its relevance to multiple components of tic phenomenology. This approach may ultimately help tailor different pharmacological and behavioral therapeutic strategies for specific subtypes of TS patients.

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Highlights

- Tourette syndrome (TS) patients exhibit stress-response abnormalities
- Tics and premonitory sensory phenomena are worsened by several contextual trigger
- Animal models can be employed to study the impact of stress on TS symptoms
- The main categories of triggers in TS and their preclinical models are reviewed
- Tics may be maladaptive coping responses to reduce the negative effects of stress

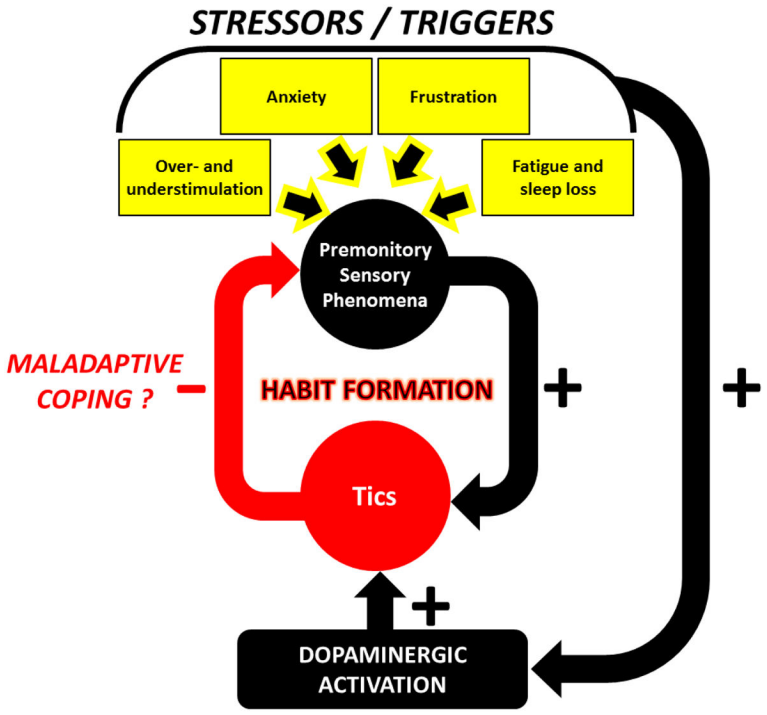

Figure 1. Synoptic diagram of the hypothesized link between premonitory sensory phenomena and tics

Stressors and contextual triggers increase the intensity of premonitory sensory phenomena and dopaminergic activity, ultimately leading to tic exacerbation. In turn, tic execution mitigates the intensity of premonitory sensory phenomena; this hypothetical coping process may potentially result in the formation of a maladaptive habit. See text for details.

Table 1

Synoptic table of the major hypothesized contextual triggers activating the key areas of the functional circuit responsible for Tourette Syndrome.

Primary neuroanatomical substrate	Major hypothesized contextual triggers
Sensorimotor cortex/SMA	Overstimulation/Understimulation/Fatigue (?)
Prefrontal cortex and insula	Anxiety Fatigue/Sleep loss/Frustration
Amygdala	Fear/Anxiety
Striatum	Frustration/Sleep loss/Overstimulation (?)
Thalamus	Overstimulation/Understimulation (?)/Sleep loss