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Article

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Abstract

Accumulating data indicate a common occurrence of tic exacerbations and periods of psychosocial stress. Patients with Tourette's syndrome (TS) also exhibit aberrant markers of hypothalamic-pituitary-adrenal (HPA) axis activation. Based on these findings, a functional relationship between stress and tic disorders has been suggested, but the underlying mechanism of how stress may affect tic pathology remains to be elucidated. We suggest that dopaminergic and noradrenergic neurotransmission as well as immunology play a crucial role in mediating this relationship. Two possibilities of causal direction might be assumed: (a) psychosocial stress might lead to an exacerbation of tics via activation of HPA axis and subsequent changes in neurotransmission or immunology and (b) TS-related abnormalities in neurotransmission or immunology result in a higher vulnerability of affected

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patients to respond to psychosocial stress with a strong activation of the HPA axis. It may also be the case that both assumptions hold true and interact with each other.

Keywords
Tourette's syndrome, stress, tics, HPA axis, cortisol, immunology, dopamine

Introduction

Tourette's syndrome (TS) usually has a waxing and waning course with periods of tic exacerbation and periods of decreased tic severity (Leckman, 2002). Tics arise in bouts over the course of a day, and these episodes change in frequency and severity over weeks and months. The underlying factors of this waxing and waning are unclear. However, these symptom fluctuations might be due not only to internal physiological processes, but may also be influenced by various contextual factors (see Conelea & Woods, 2008, and Hoekstra, Dietrich, Edwards, Elamin, & Martino, 2013, for review). Among the contextual factors suspected to have an influence on tics, the main focus of attention has been on stress. This is reflected by the implication of stress as an influential contextual factor in the majority of reviews on TS (e.g., Du et al., 2010; Leckman, 2002; Leung & Fagan, 1989; Martino & Leckman, 2013; Swain & Leckman, 2005).

To date, there is no uniform consensus definition of "stress." Since Walter Cannon first introduced the term in 1915, many different theories have adopted and subsequently broadened it, by describing somewhat different aspects of the phenomenon. In a narrow biological sense of the word, "stress" describes a condition of the body that includes the activation of the sympathetic nervous system, the release of catecholamine hormones, such as adrenaline or noradrenaline, the acceleration of heart and lung action as well as the dilation of the blood vessels in the muscles. The evolutionary purpose of this state was to prepare animals for fight or flight in the face of danger. The first important stress theory was developed by Hans Selye (1950) who described stress as being a general adaptive reaction to various pleasant or unpleasant stimuli. According to his theory, unspecific stressors elicit an activation of the hypothalamic-pituitary-adrenal (HPA) axis. It is assumed that the physiological stress response of HPA axis activation can be evoked by infections and injuries as well as by psychosocial stress. Psychosocial stress is referred to as the exposure to certain life events (Holmes & Rahe, 1967; Rahe, Biersner, Ryman, & Arthur, 1972; Rahe, Mahan, & Arthur, 1970) or the subjective appraisal of such events considering the individual's resources and abilities to cope with them (Lazarus & Folkman, 1984).

In the following, we will systematically review studies on the relationship between psychosocial stress and (a) the onset of tic disorders, (b) tic exacerbations due to stressful life events, and (c) short-time fluctuations of tic frequency due to experimental manipulations. Subsequently, we will discuss which pathways of the physiological stress response to psychosocial stressors might mediate an exacerbation of tics. We suggest that these pathways include dopaminergic and noradrenergic neurotransmission as well as neuroimmunology.

To identify relevant articles, a literature search was conducted using the databases PsychIINFO, Pubmed, and MEDline. The search terms included *tic* or *Tourette* plus *stress, life events, cortisol*, and *HPA axis*. In addition, the reference lists of the identified articles were scrutinized for further articles of interest. The literature search was limited to empirical research in the English language.

Association Between Psychosocial Stress and Tics

It has been assumed that the onset of tics might frequently be preceded by stressful life events, but this supposition is not supported by the literature. However, accumulating data indicate that tic exacerbations often coincide with periods of psychosocial stress. Other studies report the onset of tics to be frequently preceded by stressful life events. A few other studies also experimentally manipulated stress under controlled conditions, to investigate the effects on short-term fluctuations of tic frequency. In the following, we will refer to "tic frequency" in the context of short-term fluctuation of tics and to "tic severity" or "tic exacerbations" in the context of long-term fluctuation of tics. The terms *tic severity* and, *tic exacerbations* may additionally involve changes in severity, complexity, and interference of tics.

Effect of Psychosocial Stress on the Onset of TS

In a large survey consisting of 763 TS patients, Bornstein, Stefl, and Hammond (1990) identified several events that had commonly occurred within the year before tic onset, including fever, operations requiring general anesthesia and other events that are usually accompanied by emotional tension such as the divorce of parents or moving to a new home.

Horesh, Zimmerman, Steinberg, Yagan, and Apter (2008) investigated the relationship between stressful life events, personality, and onset of TS and Obsessive-Compulsive Disorder (OCD) in 93 patients. Unexpectedly, the TS patients had not experienced a greater number of stressful life events in comparison with the healthy controls, neither during their entire lifetime nor in

the year before tic onset. The authors concluded that the onset of tics is apparently not related to stressful life events, even though the waxing and waning of tics might be.

Overall, the available literature does not support the assumption that psychosocial stress might trigger the first onset of tics. However, the number of studies on this topic is very limited and the stress assessment had been restricted to stressful life events. To comprehensively answer the question about the association between psychosocial stress and tic onset, substantially more research including other measures of stress is needed. Also, prospective studies would be desirable.

Effect of Psychosocial Stress on Tic Exacerbations

In a large survey by Bornstein and colleagues (1990), worsening of tics due to psychosocial stress or anxiety was reported by 96.8% of the patients. In a study on the influence of 29 environmental factors on tic expression in 14 TS patients, the most commonly reported situations related to tic exacerbation were those associated with psychosocial stress, such as starting a new school year, waiting for test results, moving to a new location, and family arguments (Silva, Munoz, Barickman, & Friedhoff, 1995). An evaluation of global measures for the assessment of psychosocial stress in children and adolescents with TS determined that there was no correlation between tic severity and global stress level, but tic severity was correlated with daily life stressors. Also, the number of stressful life events and the level of perceived stress were higher in patients with TS compared with unaffected controls (Findley et al., 2003). In a 12-week study by Hoekstra, Steenhuis, Kallenberg, and Minderaa (2004), 25 children with TS and 32 TS-affected adults were asked to rate the severity of their tics on a weekly basis and to indicate how often an undesirable life event had occurred during the preceding week. Only a small minority of patients (21% in the pediatric and 18% in the adult TS sample) showed a significant association between tic severity and psychosocial stress due to small life events in the same or in the preceding week, although a weak but significant correlation between tic severity and negative small life events during the same week was found in the adult sample. Both minor and major life events and their effect on tic severity were investigated in a recent study including a sample of 60 children and adolescents with TS. The Yale Global Tic Severity Scale (YGTSS) motor tics score was associated with the quantity of positive and negative major life events. In addition, the YGTSS motor tics score and the YGTSS total score were significantly correlated with the quantity of negative minor life events (Steinberg, Shmuel-Baruch, Horesh, & Apter, 2012).

A longitudinal study by Lin et al. (2007) assessed stress levels and tic severity in 45 children with TS and/or OCD and 41 healthy controls over 2 years. Overall, levels of psychosocial stress were elevated in TS patients compared with controls and current levels of psychosocial stress were found to be a significant predictor for future tic, OCD, and depressive symptom severity 4 months in the future. In other words, those who had higher levels of psychosocial stress were more prone to having a more severe and complicated course.

In addition to the systematic studies on the role of stress in TS, there are also several case reports describing the onset of tics or worsening of the symptoms due to stressful life events (Hayes, Weber, Gallagher, & Drouillard, 2009; Surwillo, Shafii, & Barrett, 1978; Tijssen, Brown, Morris, & Lees, 1999; Witzum, Bar-On, Dolberg, & Kotler, 1996).

Maternal psychosocial stress during pregnancy has also been considered as an influencing factor for the occurrence of TS. In a study on 31 pediatric patients, it was one of three significant predictors of current tic severity (Leckman et al., 1990). In line with this finding, another study reported higher rates of psychosocial stress during pregnancy in mothers of TS patients with comorbid ADHD compared with mothers of healthy children (Motlagh et al., 2010).

In summary, the existing literature on the influence of stress on tic exacerbations is much larger than the body of research concerning the association between psychosocial stress and the onset of tics. Most of the available studies, including several retrospective and one prospective study, support the assumption that stressful life events are associated with the exacerbation of tics.

Effect of Psychosocial Stress on Short-Time Fluctuations of Tic Frequency

Only little experimental work has been done on the topic of tic fluctuations over the course of the day, although many tic patients report that the frequency of their tics is highly situation-specific. One case study by Lombroso, Mack, Scahill, King, and Leckman (1991) showed a marked situational increase in the frequency of tics in response to a physiological stressor, namely, thermal stress. This study prompted the conduct of a larger study involving 78 adults with TS of which 24% reported an increase in tic frequency on exposure to heat (Scahill et al., 2001). Ten subjects of the total sample were subjected to a thermal challenge under well-controlled circumstances (i.e., their core body temperature was increased either passively or through physical exercise). Fifty percent of them displayed a strong positive

correlation between tic frequency and their local sweat rate that is thought to be mediated by dopaminergic inputs into the hypothalamus.

O'Connor and colleagues (O'Connor, Brisebois, Brault, Robillard, & Loiselle, 2003; O'Connor, Gareau, & Blowers, 1993; 1994) identified situations in which tics or habits were likely to appear and situations in which tics were weak or even absent by using Kelly's repertory grid technique. Socializing was the most frequently named high-risk activity, while studying was most frequently named as low-risk activity. High-risk activities were commonly appraised as creating feelings of tension. That is, tense states were associated with an enhanced frequency of tics (O'Connor et al., 2003).

Another experimental study on short-term fluctuation of tic frequency included four TS patients who watched emotional scenes from a movie including scenes eliciting fear, anger, sadness, and happiness as well as a separation scene and a family scene. At baseline, patients were videotaped while waiting for the movie to begin and while actually watching the movie, to allow for an objective rating of tic frequency. Tic frequency was lowest during happy and anger scenes and moderate during scenes provoking sadness and fear. Tic severity was highest during periods of anticipation, resolution of emotional changes, and lower levels of concentration. Interestingly, when later asked about emotional triggers for their tics, the patients reported that being happy was the only emotion which resulted in the improvement of the tics (Wood et al., 2003). A disparity to the objective ratings of tic severity confirms the assumption that self-reports are not comprehensive and underlines the need for experimental studies using objective measures for tic frequency as well as stress (i.e., physiological stress parameters).

Situational psychosocial stress might influence tic frequency by reducing the ability to suppress tics. Ten TS patients underwent four different experimental conditions: a free-to-tic baseline, a reinforced tic suppression condition, a stress induction (mental math) task, and a condition combining the reinforced tic suppression condition and the stress induction task. Tic frequency was ascertained from video recordings and in covert observation through a one-way observation mirror. Interestingly, tic frequency did not differ between the baseline and the stress induction condition. However, stress was found to disrupt tic suppression, as indicated by higher tic frequencies in the combined stress and tic suppression condition, in comparison with the only tic suppression condition (Conelea, Woods, & Brandt, 2011).

These results indicate that psychosocial stress does not influence tic frequency per se, but that stress mainly reduces the ability to suppress tics. Therefore, stress particularly influences tic frequency in situations in which TS patients usually try not to tic. Conceivably, stressful situations (like the mental math task used to induce stress in the study by Conelea et al., 2011)

require attentional resources which are thus not available for tic suppression. In addition, cortex excitability might be increased by stressful events (Rollnik, Schubert, & Dengler, 2000), whereby motor control—required for tic suppression—is compromised (Conelea & Woods, 2008).

In summary, a few experimental studies showed that psychosocial stress does not only influence long-term tic exacerbations but might also increase short-term tic frequency. Interestingly, there is also evidence that stress might influence tic frequency by reducing the ability to suppress tics.

Limitations of Existing Research and Future Perspectives

There is only very little evidence supporting the assumption that stressful life events might trigger the first onset of tics. Nonetheless, many of the studies examining the influence of psychosocial stress on tic fluctuations support the assumption that stressful life events as well as experimentally induced stress are associated with the exacerbation of tics. These findings, however, are not uniform and most likely depend on the study design and the means of subject selection, as well as how tic severity and stress levels were assessed. Most of these studies use a cross-sectional retrospective self-report design, which is susceptible to recall bias, and only include small numbers of patients. More compelling data could be derived from prospective, multisite, longitudinal studies.

Another weakness of the available studies can be found in the inclusion of only clinically referred cases. Especially when discussing psychosocial stress as a potential trigger for the onset of tics, population-based studies using epidemiological samples would be ideal and birth cohort and registry studies would be the way forward. Discordance between the results from different studies may also derive from dissimilar sample characteristics, such as age, co-morbidities, and treatment history. In addition, a lot of variance might stem from the different measures used to assess stress and tic exacerbations. As pointed out above, there is not one definition of "stress" and the findings on stress and TS may well vary depending on the method used to assess stress.

In the case of assessing psychosocial stress in patients with TS, a major limitation of most stress self-reports might be that they have been developed to assess psychosocial stress or exposure to stressful life events in the general population. They might, therefore, not be specific enough for the assessment of tic-related stress in TS. To overcome this shortcoming, a rating scale has been designed especially to measure psychosocial stress in children with TS: the Stress Index for Children and Adolescents With Tourette's Syndrome (SICATS). The questionnaire was developed and can be obtained from Chao

et al. (2010). The SICATS is a self-administered tool including subscales to assess psychosocial stress directly related to TS: (a) unfairly treated stress (punishment by teachers or parents and unfair treatment by classmates), (b) psychological stress (difficulties in interacting with other people), (c) symptom control stress (interference of tics with daily life), and (d) future concern stress (worries about academic achievement or finding a job in the future). In our opinion, it will be very beneficial to include this measure of symptom-related stress in future studies on stress in TS.

One major problem regarding the assessment of tic exacerbations can be found in the fact that the measures differ with regard to their degree of objectivity—(a) self- or parental report, (b) expert ratings, and (c) observed number of tics—and also in respect to the covered time span (minutes, hours, weeks, and month). Self- or parental ratings are frequently employed. They are, however, susceptible to retrospective bias. The studies by Wood et al. (2003) and Scahill et al. (2001) demonstrate that there can be some discordance between objective ratings of stress-associated increase of tic frequency (i.e., tic counts from videotape) and self-reports. In addition, in light of the study by Conelea et al. (2011), it is questionable whether tic exacerbations, as described by the patients, result from an increased urge to tic or if they derive from increased difficulties in suppressing the tics.

In summary, some caution is warranted when interpreting studies based only on findings acquired through self-report measurements. Future studies should overcome these limitations by additionally including assessments of physiological stress parameters, for example, cortisol concentrations and electrodermal activity. Most of those measures are well suited for assessing physiological stress responsivity by means of short-time fluctuations of skin conductance or cortisol secretion determined from blood, salivary, or urinary samples. For a long-term assessment of physiological stress, the measurement of cortisol concentration in a hair sample offers a promising approach (Meyer & Novak, 2012; Stalder & Kirschbaum, 2012; Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2013). Hair cortisol concentrations are assumed to provide a retrospective assessment of integrated cortisol secretion over periods of several months. With this method, aberrant hair cortisol concentrations have been found in patients with different psychiatric disorders and under socially or physically demanding conditions (Dettenborn et al., 2012; Dettenborn, Tietze, Bruckner, & Kirschbaum, 2010; Kirschbaum, Tietze, Skoluda, & Dettenborn, 2009; Manenschijn, van Kruysbergen, de Jong, Koper, & van Rossum, 2011; Skoluda, Dettenborn, Stalder, & Kirschbaum, 2012; Stalder et al., 2010; Steudte et al., 2013; Van Uum et al., 2008). To the best of our knowledge, there is still a lack of studies on patients with TS assessing hair cortisol concentration to determine long-term

physiological stress. Studies on physiological stress responsivity of patients with TS measuring cortisol concentration in blood, saliva, urine, or cerebrospinal fluid, will be reviewed in the next section.

In summary, although several studies were able to show that long- and short-term fluctuation of tics is associated with psychosocial stress, the available body of research suffers from some methodological limitations. To investigate the issue more comprehensively, prospective studies are needed which should apply biological measures of stress (i.e., cortisol concentration in hair or saliva) and include self- and expert-rated stress scales specifically designed to assess stress in patients with tics (Table 1).

Physiological Approaches to the Interaction of Stress and TS—The Modulating Role of Dopamine and Noradrenaline

Physiological stress is basically manifested in an activation of the HPA axis. Within this multi-step biochemical pathway, several brain regions, including the prefrontal cortex and the amygdala, pass information about environmental stressors on to the paraventricular nucleus of the hypothalamus, which, in turn, releases the corticotropin-releasing hormone (CRH) which interacts with receptors of corticotropic cells in the pituitary gland. Subsequently, adrenocorticotropic hormone (ACTH) is secreted into the blood. ACTH binds to the cortex of the adrenal glands and causes the secretion of the steroid hormone cortisol, the final key messenger in the cascade. Glucocorticoids (cortisol in humans and corticosterone in rodents) can permeate the cellular membranes and interact with neurons via binding to steroid hormone receptors. Thereby glucocorticoids are able to influence the regulation of signaling pathways and the long-term remodeling of dendrites and synapses particularly in the prefrontal cortex, the amygdala, and the hippocampus (McEwen, 2007, 2010). In this way, glucocorticoids can also affect the transcription of multiple genes (de Kloet, Fitzsimons, Datson, Meijer, & Vreugdenhil, 2009; Zalachoras, Houtman, & Meijer, 2013) and—depending on the nature of the target cell—take influence on the metabolism, the immune system, and cognitive processes such as attention and memory (Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Vedhara, Hyde, Gilchrist, Tytherleigh, & Plummer, 2000; Wolf, 2009).

There is compelling evidence that TS patients exhibit stronger activation of the HPA axis, leading to enhanced levels of cortisol secretion when exposed to psychosocial stress.

When exposed to the magnetic resonance imaging (MRI) environment during a mock scan session, children with TS showed higher levels

Table 1. Overview of Studies on the Association of Stress With TS.

Author	Study design	Number of subjects	Age of subjects in years	Main findings
Surwillo, Shafii, and Barrett (1978)	CR	1 TS	10	Stressful life events have an impact on tic severity
Bornstein, Stefl, and Hammond (1990)	C-S,	763 TS	4-76	Exacerbation of tics due to stress or anxiety reported by 96.8%
Leckman et al. (1990)	C-S,	31 mothers of TS patients	7-17	Tic severity could partly be predicted by prenatal stress
Lombroso, Mack, Scahill, King, and Leckman (1991)	CR	1 TS	Not available	Marked increase in the frequency of tics in response to thermal stress
Chappell et al. (1994)	C-S	13 TS 10 healthy	17-41	Plasma ACTH level significantly higher in TS patients than in controls
Leckman et al. (1995)	C-S	33 TS 39 OCD 44 controls	31.1-63.1	TS patients exhibit higher level of cerebrospinal norepinephrine than controls
Silva, Munoz, Barickman, and Friedhoff (1995)	C-S	14 TS	6.6-14.5	Exacerbation of tics in situations making the patient upset or anxious
Chappell et al. (1996)	C-S	21 TS 20 OCD 29 controls	13-61	TS patients exhibit enhanced levels of CRF in the cerebrospinal fluid
Witzum, Bar-On, Dolberg, and Kotler (1996)	CR	1 TS		Mild TS that became severe after intense traumatic war experience
Tijssen, Brown, Morris, and Lees (1999)	CR	3 TS	25-33	Tics developed after physical trauma and emotional stress

(continued)

Table 1. (continued)

Author	Study design	Number of subjects	Age of subjects in years	Main findings
Scahill et al. (2001)	C-S	Study 1: 78 TS Study 2: 10 TS	Study 1: 18-60 Study 2: 20-39	Study 1: 24% of TS patients report increased tic on exposure to heat Study 2: Increased tics on exposure to thermal stress in 50% of patients
Findley et al. (2003)	P-L	33 TS and/or OCD 25 controls	7-17	TS and OCD patients experience higher levels of psychosocial stress and report more major life events and daily life stress
O'Connor, Brisebois, Brault, Robillard, and Loiselle (2003)	P-L	76 tic or habit disorder	18-62	Tense states, like socialization were associated with the worsening of tics
Wood et al. (2003)	C-S	4 TS	8-14	Tic severity consistently lower during happy and anger video scenes
Hoekstra, Steenhuis, et al. (2004)	P-L	25 children with TS 32 adults with TS	Children: 7-16 Adults: 18-64	Only a small minority of patients showed a significant association between tic severity and frequency of small life events
Lin et al. (2007)	P-L	45 TS and OCD 41 controls	7-17	Current stress levels are a powerful predictor of future tic, OCD and depressive symptom severity
Corbett, Mendoza, Baym, Bunge, and Levine (2008)	P-L	20 TS 16 controls	7-13	TS patients exhibited higher levels of salivary cortisol when exposed to the MRI environment
Horesh, Zimmerman, Steinberg, Yagan, and Apter (2008)	C-S	41 TS 28 OCD 24 controls	7-18	TS patients had not experienced more stressful life events than healthy controls, neither in lifetime nor in the last year before tic onset.

Table 1. (continued)

Author	Study design	Number of subjects	Age of subjects in years	Main findings
Hayes, Weber, Gallagher, and Drouillard (2009)	CR	1	22	Correlation between occurrence of tics and symptoms of PTSD
Lin et al. (2010)	P-L	45 TS and OCD 41 controls	7-17	Especially the combined influence of psychosocial stress and infection with beta-hemolytic streptococcus leads to an exacerbation of tics
Motlagh et al. (2010)	C-S	157 mothers of patients with 52 ADHD 60 TS + ADHD 45 TS 65 controls	7-18	Mothers of patients exhibited higher psychosocial stress than mothers of control children
Conelea, Woods, and Brandt (2011)	C-S	10 TS	9-10	Tic frequency significantly higher in the condition with combined tic suppression and stress induction as compared with the stress induction condition alone → stress might reduce the ability to suppress tics
Steinberg, Shmuel-Baruch, Horesh, and Apter (2012)	C-S	60 TS	7-17	Correlation between tic severity and negative minor life events

Note. TS = Tourette's Syndrome; OCD = Obsessive-Compulsive Syndrome; C-S = cross-sectional study; P-L = prospective longitudinal study; CR = case report; ACTH = adrenocorticotropic hormone; CRF = corticotrophin-releasing factor; PTSD = Posttraumatic Stress Disorder.

of salivary cortisol compared with healthy controls, while both groups of children exhibited the normal diurnal cortisol rhythm, with the physiological sharp rise of the cortisol levels in the morning (cortisol awakening response) and lower levels in the evening. However, there was a trend toward lower evening cortisol levels in the TS group, which might be the result of chronic daily stress (Corbett, Mendoza, Baym, Bunge, & Levine, 2008).

Chappell and colleagues (1994) obtained blood samples to measure the level of plasma ACTH, plasma cortisol, and urinary catecholamines in medication-free TS patients and healthy controls at several points in time before and after lumbar puncture. The ACTH level was significantly higher in TS patients compared with controls, before as well as after the procedure, indicating a stronger responsivity of the HPA axis in TS patients, which is in line with the findings reported by Corbett and colleagues (2008). Inconsistent with the findings on the plasma ACTH levels was the result regarding the plasma cortisol levels, which were similar in both groups. The authors, however, considered it possible that the difference between both groups might have been masked by the circadian rise of plasma cortisol levels, as the study took place rather early in the day. In another study, in which blood samples were taken during the morning, there were also no differences between patients with tic disorders and healthy subjects in regard to plasma cortisol concentration (Hoekstra, Anderson, Troost, Kallenberg, & Minderaa, 2007). In a subsequent study, Chappell et al. (1996) measured the levels of CRH in the cerebrospinal fluid of the same patient groups. Compared with both healthy controls and OCD patients, the mean levels of CRH were enhanced in TS patients by about 28% (TS vs. controls) and 31% (TS vs. OCD), respectively.

In summary, the reported findings suggest that patients with TS exhibit higher levels of cortisol, ACTH, and CRH, indicating that TS is associated with a stronger responsivity of the HPA axis.

The complex neurochemical pathways by which biochemical stress responses might influence tic expression are still unclear, but there is a lot of evidence suggesting that activation of the HPA axis may have a negative impact on the normal physiology of the dopaminergic system (Pani, Porcella, & Gessa, 2000), which plays a pivotal role in the pathophysiology of TS (Buse, Schoenefeld, Münchau, & Roessner, 2012; Leckman, Bloch, Smith, Larabi, & Hampson, 2010; Singer, 2013).

There is broad evidence supporting the influence of the stress response on the dopaminergic system. As early as 1989, Thind and Goldsmith found that CRH neuronal efferents synaptically activate A14 dopamine neurons in the primate periventricular nucleus and parvocellular paraventricular nucleus. Studies on rodents have shown that exposure to stressors effects the

extracellular dopamine concentration in many regions of the brain (Mora, Segovia, Del Arco, de Blas, & Garrido, 2012), namely, the prefrontal cortex (Del Arco & Mora, 2001; Del Arco, Segovia, Garrido, de Blas, & Mora, 2007; Del Arco, Segovia, & Mora, 2001; Feenstra, Botterblom, & Mastenbroek, 2000; Segovia, Del Arco, de Blas, Garrido, & Mora, 2008), the amygdala (Inglis & Moghaddam, 1999), the hippocampus (Yamato et al., 2002), and the nucleus accumbens (Feenstra, Botterblom, & van Uum, 1998; Imperato, Angelucci, Casolini, Zocchi, & Puglisi-Allegra, 1992). Administering ovine CRH to rats had stimulatory effects on dopaminergic neuron terminals in the nucleus accumbens, hypothalamic periventricular nucleus and the paraventricular nucleus and intermediate pituitary lobe, as measured by means of 3,4-Dihydroxyphenylacetic acid (DOPAC), a major metabolite of dopamine (Pan, Lookingland, & Moore, 1995). The relationship between stress and dopamine release has also been demonstrated in humans. In a Positron emission tomography (PET) study on healthy students, psychosocial stressors were found to cause dopamine release in the ventral striatum (Pruessner, Champagne, Meaney, & Dagher, 2004).

Dopaminergic neurotransmission in the cortico-striato-thalamocortical circuits has an important influence on the etiology and course of tic disorders (Ganos, Roessner, & Münchau, 2013; Leckman et al., 2010). The firing rate of the GABAergic projection neurons in the striatum is modulated by dopamine receptors. The D1-dominant cells predominantly send inhibitory projections to the substantia nigra pars reticulate (SNr) (direct pathway), while the D2-dominant cells of the striatum send inhibitory projections to the globus pallidus (indirect pathway), which in turn send inhibitory projections to the subthalamic nucleus and the SNr. These GABAergic cells in turn send tonic inhibitory output to their targets in the thalamus and brainstem (DeLong & Wichmann, 2007). The selection of movement takes place across the direct pathway, while the inhibition of ongoing movement is regulated across the indirect pathway via disinhibition of the SNr (Humphries, Stewart, & Gurney, 2006). Both pathways play an essential role in the etiology and course of tic disorders. The balance between direct and indirect pathways is regulated by the differential actions of dopamine on striatal neurons (DeLong & Wichmann, 2007). Taking the above into consideration, it becomes clear how enhanced dopamine activity, for example, through stress, can lead to a dysbalance in the motor circuit, which in turn potentially might result in motor disorders, such as tics.

Stress-induced enhancement of dopamine release in the human prefrontal cortex has also been observed and was associated with the subjectively rated experiences of psychosocial stress (Lataster et al., 2011). Finlay and Zigmond (1997) noted, that the response of dopamine neurons is highly heterogeneous

with the largest increase of extracellular dopamine in response to acute stress being observed in the prefrontal cortex. Stress-induced abnormalities in prefrontal areas are especially interesting in light of the observation that stress might challenge the ability to control or suppress tics instead of enhancing the urge to tic.

The previous paragraphs have aimed to provide an explanation of how the biochemical stress response might influence dopaminergic neurotransmission which might, in turn, cause an exacerbation of tics. In general, the stress-induced exacerbation of tics might be understood to be the result of additional demands placed on an already compromised population of dopamine neurons (Finlay & Zigmond, 1997). However, the interaction between physiological stress response and the dopaminergic system can also be looked on from another perspective. That is, TS pathology, for example, altered dopaminergic neurotransmission, might also influence the physiological stress response. This assumption derives from the findings that patients with TS exhibit enhanced physiological responses to stress-inducing stimuli (Chappell et al., 1996; Chappell et al., 1994; Corbett et al., 2008), but because studies which directly assess the neurobiological relationship between altered dopamine levels and stress responsivity in patients with TS are still missing, this assumption has to remain unproved.

However, there are some animal studies showing that dopaminergic neurotransmission influences the secretion of biological stress parameter (Borowsky & Kuhn, 1992; Cheung, Ballew, Moore, & Lookingland, 1998; Eaton, Cheung, Moore, & Lookingland, 1996; Liposits & Paull, 1989; Wagner, Eaton, Moore, & Lookingland, 1995).

In summary, the physiological mechanisms of stress seem to be closely related to changes in dopaminergic neurotransmission which plays a major role in TS. Although the exact interplay among stress, DA, and tics is still unclear, two causal models can be proposed: (a) psychosocial stress activates dopaminergic neurotransmission which then initiates or exacerbates tics and (b) an overactive or imbalanced dopaminergic neurotransmission underlying TS leads to an elevated physiological stress response. It may also be the case that both assumptions hold true and interact with each other, with increased baseline dopamine levels resulting in TS patients being susceptible to an enhanced physiological stress response which again enhances dopamine release even more, in turn exacerbating tics.

In addition to ACTH, CRH, and cortisol, levels of norepinephrine in the urine (Chappell et al., 1994) and in the cerebrospinal fluid (Leckman et al., 1995) were found to be enhanced in TS patients. This finding is of particular interest as noradrenaline is not only part of the acute stress response but also plays an important role in the pathophysiology of TS (Leckman et al., 2010).

Alpha-2 agonists, such as clonidine and guanfacine, have proven to be efficient in reducing tics (Bloch, Panza, Landeros-Weisenberger, & Leckman, 2009; Pringsheim et al., 2012). These agents reduce the firing rate and the release of noradrenaline from noradrenergic neurons via negative feedback through binding to receptors on presynaptic sites. In this regard, the noradrenergic pathway might also be a mechanism by which stressors may influence tic severity (Leckman et al., 2010). It might be speculated that part of the benefits of alpha-2 agonists in the treatment of tics derives from their modulating influence on the physiological stress response.

Immunopathogenic Mechanisms in TS and the Modulating Role of Stress

It has been suggested that the influence of stress on tic expression is entangled with the influence of immunology on tic expression. One possible means of interaction of both mechanisms might be the modulation of dopaminergic neurotransmission.

There is ample evidence pointing toward immunopathogenic mechanisms playing a role in TS (Elamin, Edwards, & Martino, 2013; Hoekstra, Anderson, et al., 2004; Hoekstra, Kallenberg, Korf, & Minderaa, 2002; Hoekstra et al., 2007; Murphy, Kurlan, & Leckman, 2010, for review, see Hoekstra et al., 2013). Various alterations of the immune response have been observed in TS patients, for instance, overexpression of D8/17B lymphocyte surface marker (Hoekstra, Anderson, et al., 2004; Murphy et al., 1997), increased levels of tumor necrosis factor alpha (Leckman et al., 2005), reduced percentages of regulatory T-cells (Kawikova et al., 2007), elevated levels of IL-12 plasma cytokines (Gabbay et al., 2009), elevated levels of memory T-cells (Hsieh et al., 2010), decreased levels of lgA (Kawikova et al., 2010), pathological oligoclonal bands in the corticotrophin-releasing factor (CRF) (Wenzel, Wurster, & Müller-Vahl, 2011), decreased serum lg3 (Bos-Veneman et al., 2011), elevated anti-streptolysin O (ASO) titers (Martino et al., 2011), altered autoantibody positivity, antistreptolysin, and several plasma cytokines (Cheng et al., 2012).

Altered immune response regulation in TS has been intensively discussed, especially in the context with Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS; Kurlan, 1998; Kurlan & Kaplan, 2004; Leslie et al., 2008; Martino et al., 2011; Martino, Dale, Gilbert, Giovannoni, & Leckman, 2009; Singer, Gause, Morris, Lopez, & Tourette's Syndrome Study Group, 2008; Swedo et al., 1998). PANDAS refers to the onset of tic or OCD symptoms after an infection with Group A streptococcus (GAS; Swedo et al., 1998). In children with

PANDAS, a positive correlation between antineuronal antibodies and severity of tics was found (Pavone et al., 2004). However, the PANDAS hypothesis remains a very controversial issue (Hoekstra et al., 2013), especially because two recent studies of high methodological quality reported negative results (Kurlan, Johnson, & Kaplan, 2008; Leckman et al., 2011).

Martino et al. (2009) developed a pathophysiological model describing how an enhanced autoimmune response (i.e., to GAS infection) might contribute to the onset or worsening of tics via dopaminergic neurotransmission. According to this model, antineuronal antibodies in the central nervous system (CNS) increase calcium-calmodulin-dependent (CaM) kinase II and tyrosine hydroxylase (TH) activity which in turn increase dopamine release in central synapses. In the periphery, the infections elicit inflammatory responses by up-regulating natural killer cells, cytotoxic T-lymphocytes, and the synthesis of cytokines. This, in turn, enhances dopamine release from sympathetic nervous system fibers, resulting in high levels of dopamine in the periphery. Dopamine modulates immunology by activating D1/D5 dopamine receptors on the lymphocyte cell surface (Ferrari et al., 2008). The stimulation of the dopamine receptors modifies the differentiation of t-cells in favor of autoimmunology (Pacheco, Prado, Barrientos, & Bernales, 2009). An enhanced autoimmune response might, in turn, contribute to the onset and/or worsening of tics via the CNS pathway described above (Martino et al., 2009). According to Martino's pathophysiological model (Martino et al., 2009), psychosocial stress may contribute to the increase of dopamine release from the sympathetic nervous system leading to an enhanced autoimmune response. Consistent with this, several studies reported that the level of plasma DA, the primary source of dopamine for t-cells, is increased in the pathophysiological state of stress (for a review, see Pacheco et al., 2009).

The relevance of the interplay between stress and immunology in TS is underpinned by a longitudinal study on 45 children with TS and/or OCD and 41 healthy controls. Structural equation modeling indicated that these newly diagnosed GAS infections were predictive of modest increases in future tic and OCD symptom severity. The inclusion of GAS infections in the model also greatly enhanced the predictive power of psychosocial stress. Thus, the prediction of future tic and OCD symptoms was most accurate when both GAS infections as well as psychosocial stress were included in the model (Lin et al., 2010).

It is a well-known fact that the activation of the HPA axis has a powerful effect on the immune system, in terms of cortisol suppressing the inflammatory response to avoid deleterious effects (Pittman, 2011). The complex HPA axis response to inflammation is mediated my cytokines, including IL-1, IL-6, and leukemia inhibitory factor (LIF) . During inflammation, these

cytokines stimulate the HPA axis and thereby antagonize their own peripheral pro-inflammatory action (Chesnokova & Melmed, 2002). Thus, concurrent with the pro-inflammatory response, an anti-inflammatory response is activated (Pittman, 2011). With regard to this mechanism, the increased activation of HPA axis observed in TS patients might possibly also be considered to be a consequence of elevated inflammatory response, for example, to GAS infection.

Stress Reduction in the Treatment of TS

With regard to the outlined relevance of psychosocial stress and the pathophysiological stress response for tics, stress reduction might be an important component in the treatment of TS. It might be particularly beneficial for those patients, who report suffering from stress-related tic exacerbations.

Various stress reduction techniques are available that produce common, general as well as specific positive effects (Lehrer, Carr, Sargunaraj, & Woolfolk, 1994). In TS, where muscular activity is abnormal, "muscle-oriented" methods such as muscle relaxation and/or electromyography (EMG) biofeedback might be most promising. A review showed that progressive muscle relaxation had moderate overall effects when used as an intervention for psychophysiological and stress-related disorders (Carlson & Hoyle, 1993). There is evidence that progressive muscle relaxation training also reduces saliva cortisol and enhances levels of immunoglobulin A (Jasnoski & Kugler, 1987; Pawlow & Jones, 2002, 2005). To the best of our knowledge, there is only one study on the effects of progressive muscle relaxation training in the treatment of tics, reporting a tic reduction by 32% (Peterson & Azrin, 1992). A study on the effectiveness of a relaxation therapy comprised of awareness training, diaphragmatic breathing, behavioral relaxation training, and biofeedback failed to show significant improvement of tics (Bergin, Waranch, Brown, Carson, & Singer, 1998). However, in both studies only a small number of patients were included in the relaxation training group (6 and 7), therefore reducing the validity of these results.

The European clinical guidelines for TS and tic disorders suggest relaxation training as a second-line behavioral treatment or add-on treatment to other behavioral techniques (Verdellen, van de Griendt, Hartmann, Murphy, & ESSTS Guidelines Group, 2011), while habit reversal training, which is also the most extensively researched behavioral treatment for tics, is considered to be first choice (Frank & Cavanna, 2013; Piacentini et al., 2010; Scahill et al., 2013; Verdellen et al., 2011; Wile & Pringsheim, 2013; Wilhelm et al., 2012).

Many programs for habit reversal include a relaxation component (O'Connor et al., 2001; O'Connor et al., 2009; Rowe, Yuen, & Dure, 2013; Verdellen et al., 2011), such as the comprehensive behavioral intervention for tics (CBIT) program that has proven to be very efficient in reducing the number of tic expressions, tic severity, and level of distress associated with tics (Rowe et al., 2013). Habit reversal training usually includes awareness exercises that comprise the identification of high-risk situations associated with enhanced tic activity, for example, situations in which a person experiences mainly psychosocial stress (O'Connor et al., 2001; O'Connor et al., 2003). It is important to be able to foresee such high-risk situations, if habit reversal shall be applied successfully by the patients in their daily life. It is also an important component of the habit reversal training to identify cognitive factors (e.g., catastrophic anticipations/unrealistic expectations) associated with the stressful situations and to modify them to reduce stress (O'Connor et al., 2001).

Furthermore, biofeedback has been used as a method for stress management, for example, in the treatment of heart disease (Moravec & McKee, 2011). One study determined that relaxation biofeedback on galvanic skin response was successful in reducing tic frequency (Nagai, Cavanna, & Critchley, 2009).

There are also various alternative therapies that might help in reducing stress. For instance, yoga has been found to be a beneficial intervention for stress. However, the evidence is not entirely clear because controlled trials of high methodological quality are missing (Li & Goldsmith, 2012; McCall, Ward, Roberts, & Heneghan, 2013). There is one report about self-hypnosis techniques helping children with TS to reduce the frequency of their tics (Kohen, 1995). In addition, mindfulness-based stress reduction (MBSR) programs have received a substantial amount of attention in recent years. These programs aim at enhancing awareness of moment-to-moment experiences in which thoughts, feelings, and/or sensations that arise in the attentional field are to be acknowledged and accepted non-judgmentally. A meta-analysis including 20 studies of acceptable quality on both clinical and non-clinical samples supports the positive effect of MBSR (Grossman, Niemann, Schmidt, & Walach, 2004). There is also accumulating evidence indicating that activation of the HPA axis, indicated by cortisol levels, decreased after participation in an MBSR program (Matousek, Dobkin, & Pruessner, 2010). To the best of our knowledge, there are no reports about MBSR in TS patients so far, but a trial testing a modified form of MBSR in combination with habit reversal training for the treatment of TS, that was founded by the international TS association, was initiated in 2011 (http://tsa-usa.org/aResearch/gran/2011_rees.html).

Pharmacological treatment with D2 dopamine receptor blockers has shown to be very effective in treating tic disorders. In particular, the blockade of striatal D2 dopamine receptors is thought to lead to a reduction of tics (Roessner et al., 2011). As stress effects the dopamine neurotransmission, for example, in the ventral striatum (Pruessner et al., 2004), D2 receptor antagonists might not only be successful because they regulate a substantial tic-related dysfunction of the dopamine system but also because they might regulate stress-induced increase of dopamine.

In addition, alpha-2 agonists, such as clonidine and guanfacine, which reduce the release of noradrenaline, have proven to be efficient in reducing tics (Bloch et al., 2009; Pringsheim et al., 2012). Because the release of noradrenaline is a core part of the physiological stress response and stress is associated with an increase of tics, it might be speculated, that one part of the benefits of alpha-2 agonists in the treatment of tics derives from their ability to reduce the effects of stress. In light of the finding that the ability to suppress tics may be reduced under the condition of psychosocial stress (Conelea et al., 2011), it is interesting to note that stress-related noradrenaline release effects functioning of the prefrontal cortex (Arnsten, 2009), which is in turn involved in the voluntary suppression of tics. It has been found that stress-induced cognitive deficits can be prevented by administration of α1-receptor antagonists in the prefrontal cortex and that stimulation of postsynaptic α2A-receptors in the prefrontal cortex improves working memory performance (Arnsten, 2009). In light of this, it might be assumed that administration of alpha-2 agonists could improve the ability to suppress tics even when experiencing psychosocial stress.

Summary

Based on clinical experience, stress has been assumed to play a role in the onset and course of TS for a long time. In recent years, a number of studies have pointed toward the association between psychosocial stress and fluctuations in tic severity. Initial studies of the physiological stress response in terms of the activation of the HPA axis suggest that it may be dysregulated in TS. We suggest that dopaminergic and noradrenergic neurotransmission as well as immunology play a crucial role in mediating the relationship between stress and tic exacerbations. Stress can have an impact on dopamine activity in the cortico-striato-thalamocortical circuits, which play a crucial role in the selection and inhibition of movements and are dysfunctional in patients with tic disorders. By influencing dopamine activity in the striatum, stress might also impact tic expression.

An enhanced autoimmune response (e.g., to GAS infection) might also contribute to the onset or worsening of tics via dopaminergic

neurotransmission. With growing awareness concerning the important role of stress on the course of TS, stress reduction techniques might become an important component in its treatment. Well-established programs for habit reversal training in patients with TS, such as the CBIT, already include a relaxation component, but detailed research on specific stress reduction techniques, like progressive muscle relaxation training or MBSR, is still lacking.

Future Research Directions

The review emphasizes the need for more research on the relationship between stress and TS. On one hand, further studies with longitudinal designs are needed that are not susceptible to retrospective bias and able to capture both long-term fluctuations in psychosocial stress level as well as tic severity. On the other hand, more studies using experimentally controlled stress paradigms are needed to investigate the relation between situational stress and short-term changes in tic frequency. To overcome limitations associated with the use of patients or parents' self-reports, future studies should include more objective measures of tic exacerbation and researchers in this field might want to work toward a common definition of tic exacerbations. In addition, we assume that the inclusion of different physiological measures of stress would add a lot to our understanding of the precise mechanisms underlying the relationship between stress and tic exacerbations.

The ongoing European Multicentre Tics Study (EMTICS) project, which comprises 27 centers in 11 European countries, is a promising opportunity to further investigate the functional relationship among stress, immunological processes, and tics. EMTICS continuously records immunological parameters, psychosocial stress and exacerbation or onset of tics in a total of 500 children with a high risk to develop tics and 700 children already exhibiting tics over a time span of 3 years. All of these children will be assessed with the same measures of stress, including self- and parent reports as well as biological parameters (i.e., cortisol concentration in hair). Tic severity will be rated by clinicians, who had received the identical kind of training, and tic exacerbations will be classified on the basis of a joint definition. Because—parallel to the assessment of tics and stress—many immunological parameters will be determined from regularly taken blood samples, the project will be of particular value in elucidating the modulating role of the immune system.

We assume that stress might impact tic expression via influencing dopamine activity in the striatum. However, this assumption is derived from the aggregated knowledge of three different kinds of studies: (a) studies assessing the relationship between stress and tic disorders, (b) studies assessing the

relationship between stress and the dopamine neurotransmission, and (c) studies assessing the relationship between the dopamine system and tic disorders. To get a deeper understanding of the precise underlying biological mechanisms, studies are needed that integrate all three approaches in one. Conceivably mouse models mimicking tic disorders might offer a good opportunity for broadening the knowledge in this field. One question that is still unresolved is whether stress-related fluctuations in tic expression that occur on a long-term basis have the same underlying biological mechanism as stress-related fluctuations in tic expression that occur on a short-term basis. Both may perhaps differ with respect to the impact they have on tonic versus phasic dopamine neurotransmission. However, so far, this is subject of speculation, and would rather be an interesting question in future studies.

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