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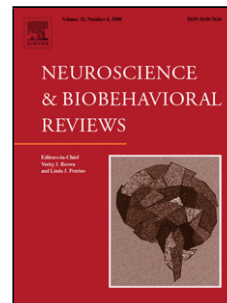
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*Invited Article*

## **Sensory Aspects of Tourette Syndrome**

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### **Highlights**

- Patients with Tourette syndrome (TS) report that their tics have sensory correlates.
- Premonitory urges and multimodal hypersensitivity are common sensory features of TS.
- Both the insula and sensorimotor areas might be involved in the pathophysiology of TS.

**Abstract**

Motor and vocal tics have long been recognised as the core features of Tourette syndrome (TS). However, patients' first-person accounts have consistently reported that these involuntary motor manifestations have specific sensory correlates. These sensory symptoms are often described as feelings of mounting inner tension ("premonitory urges") and are transiently relieved by tic expression. Multimodal hypersensitivity to external stimuli, perceived as triggers and/or exacerbating factors for specific tic symptoms, is also commonly reported by patients with TS. This article focuses on the rapidly expanding literature on the clinical and neurobiological aspects of the premonitory urge and multimodal hypersensitivity in patients with TS, with particular attention to pathophysiological mechanisms and possible treatment implications. These findings suggest that TS is a neurobehavioural condition characterised by intrinsic perceptual abnormalities involving the insula and sensorimotor areas, in addition to basal ganglia dysfunction. Further research will clarify the role of sensory symptoms in TS, as well as the effects of external sensory input on underlying motor abnormalities.

**Keywords:** Tourette syndrome; tics; premonitory urges; insula; sensorimotor areas; multimodal hypersensitivity.

## 1. Motor and non-motor aspects of Tourette syndrome

Tourette syndrome (TS) is a neurodevelopmental condition characterised by repetitive, non-rhythmic, involuntary movements and vocalisations, known as motor and vocal (or phonic) tics (Cavanna and Seri, 2013; Ganos and Martino, 2015; Martino et al., 2013). TS is defined by the presence of at least two motor tics and one vocal tic, with onset before the age of 18 and duration of more than one year (American Psychiatric Association, 2013). Other features of TS can include coprophenomena (inappropriate gestures or verbal expressions) (Eddy and Cavanna, 2013a), echophenomena (imitating gestures or phrases) (Ganos et al., 2012b), and other non-obscene socially inappropriate behaviours (Eddy and Cavanna, 2013b). The worldwide prevalence of TS is estimated between 0.85 and 1% (Scharf et al., 2015). Males are more frequently affected than females, with an approximate ratio of 3:1 (Cavanna and Seri, 2013). Tics typically appear in school-aged children and their severity peaks at around 10-12 years. Motor tics tend to precede the development of vocal tics by one to two years (Leckman et al., 1998). The course of TS typically waxes and wanes, with symptoms improving in many patients as they enter adulthood, at which point approximately one third becomes tic-free (Bloch et al. 2009; Hassan and Cavanna, 2012).

Approximately 90% of the patients with TS receive a co-morbid neuropsychiatric diagnosis, most frequently attention-deficit and hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) (Eddy et al., 2012; Hirschritt et al., 2015), with affective symptoms, anxiety, and impulsivity being also highly prevalent (Frank et al., 2011). Both tic severity and associated behavioural symptoms have been shown to potentially have a significant impact on patients' health-related quality of life (Cavanna et al., 2013; Evans et al., 2016).

The exact pathophysiological mechanisms underlying TS remain elusive. Twin and family studies support a genetic contribution, although no single responsible gene has yet been identified (Paschou, 2013). Its underlying aetiology is thought to involve disruption to neurotransmission within cortico-striato-thalamo-cortical pathways (Serajee and Manhubul Huq, 2015), including dopaminergic, serotonergic, and histaminergic systems (Cox et al., 2015), with possible contributions from cholinergic (Xu et al., 2015) and inhibitory gamma-aminobutyric acid pathways (Puts et al., 2015).

Management of TS symptoms encompasses pharmacological and behavioural strategies. Pharmacotherapy includes both typical and atypical antipsychotics, alpha-2 adrenergic agonists, and selected antiepileptic drugs (Budman, 2014; Cavanna and Nani, 2013; Waldon et al., 2013). Recent research on behavioural and psychological interventions has mainly focused on habit reversal therapy, exposure and response prevention, and psychoeducation (Frank and Cavanna, 2013). Deep brain stimulation (DBS) has also been reported as potentially useful in selected severe and refractory cases (Martinez-Ramirez et al., 2018).

Like other movement disorders, TS has traditionally been considered to be a disorder of impaired motor control resulting predominantly from dysfunction of the basal ganglia. This notion has recently been complemented, largely because of increasing recognition of subjective feelings of mounting inner tension (so-called “premonitory urges”) associated with tic expression, as well as perceptual abnormalities mediating the effects of external sensory input on the motor symptomatology (Patel et al., 2014). In this paper we discuss the rapidly expanding scientific literature on the clinical and neurobiological correlates of altered sensory processing in TS, encompassing tic-related premonitory urges as well as multimodal hypersensitivity to external stimuli.

## **2. Premonitory urges to tic**

### **2.1. Clinical presentation and prevalence of premonitory urges**

The vast majority of patients with TS describe that their tics are preceded by an uncomfortable physical sensation, often referred to as “premonitory urge”. Although difficult to define, premonitory urges have been described as arising internally and precipitating the release of a motor or vocal tic. Two broad types of premonitory urges have been reported; specific feelings such as tension or an itch in a particular area, or more vague feelings that something is “not just right”. Upon expression of the tic, the unpleasant feeling that characterises the urge to tic temporarily resolves. The qualitative features of premonitory urges have been likened to having the need to sneeze or an uncomfortable itch. To individuals with TS, these sensations are considered to be a core symptom of the condition, and have been considered to be even more distressing than the tics themselves in some cases (Kane, 1994).

Premonitory urges are not included within current diagnostic criteria for TS, despite being reported by up to 93% of patients (Leckman et al., 1993). The clinical phenomenology of premonitory urges has been a particular focus in the TS research field, due to their high morbidity and their role as a potential focus for behavioural and psychological therapy. A large study of children with TS showed that the prevalence of premonitory urges increases with age, along with tic severity and ability to suppress tics (Sambrani et al., 2016). In a sample of 1032 children with TS, premonitory urges were reported in 46.7% of those aged less than 10 years, 61.3% of those 10-12 years and 79.9% of those aged above 12 years. The spatial distribution of tics, voluntary tic inhibition, and premonitory urges across different body parts has received relatively little attention, with the results of a recent study showing that the somatotopy of these phenomena can differ (Ganos et al., 2015a).

### **2.2. Clinical assessment of premonitory urges**

The majority of clinical studies use the Premonitory Urge for Tics Scale (PUTS) score as a measure of sensory symptom severity. The PUTS is a self-report questionnaire which includes nine descriptors of premonitory urge symptoms that patients are asked to rate in

term of how they are perceived. This is measured on a Likert-type scale, where a higher score signifies a higher severity of symptoms. This score has been shown to have good internal consistency, and has also shown significant positive correlation with overall tic severity (as measured by Yale Global Tic Severity Scale, or YGTSS, scores), as well as tic number, complexity, and interference (Woods et al., 2005). The PUTS was originally developed and validated in children and young people, but has since been validated for use in adult populations of patients with TS as well (Crossley et al., 2014). In a recently published systematic review of severity scales and screening instruments for tics, the PUTS was recommended in patients older than ten years as the only fully validated instrument to measure tic-related premonitory urges specifically (Martino et al., 2017).

The assessment of premonitory urges has since been revisited, and a more recent study (McGuire et al., 2016) suggested the use of an individualised PUTS score (I-PUTS) to assess urge phenomena in patients with TS, as it provides additional information in comparison to the PUTS score alone. The I-PUTS assesses the presence, frequency, intensity and body location of urges for individual tics over the preceding week. The scores from each domain are then combined to produce values for total urge number (I-PUTS Urge Number), total urge frequency (I-PUTS Frequency) and total urge intensity (I-PUTS intensity). The I-PUTS scoring system was validated on 75 young individuals with tic disorder, 63 of whom had TS; patients experienced an average of three distinct urges, which were mainly located in the head/face, neck/throat, and arm regions. Furthermore, the authors found that in youths whose self-report ratings (measured using the PUTS score) differed from their clinician-rated scores, there was a greater degree of inattention and externalising problems. They have therefore suggested that the I-PUTS may be particularly relevant for youths with attention problems, dysregulated behaviours, or externalising behaviours.

### **2.3. Premonitory urges and tic suppression**

A recent study reported that tics may be negatively reinforced by the removal of premonitory urges (Capriotti et al., 2014). The results of this study provided support to the “negative reinforcement hypothesis”, suggesting that relief from premonitory urges functions as a negative reinforcer central to tic maintenance (tic expression is associated with relief in premonitory urges, thereby perpetuating ticcing behaviour). A further study showed that premonitory urges increase prior to tics and decrease following tics, within a time window of approximately 10 seconds (Brandt et al., 2016); tic suppression leads to an increase in urge

intensity and a decrease in the size of the correlation between tics and intensity of premonitory urge, suggesting that tic suppression can lead to uncoupling of tics and urge phenomena. However it should be highlighted that this study is based on the assessment of physiological eye blinks and blinking tics, and altogether blinks might be considerably different to tics.

A separate study (Ganos et al., 2012a) measured tic suppressibility in relation to urge sensation, and found no direct relationship between the two, thereby suggesting that at least two distinct neurobiological systems are involved in tic generation and tic suppression. These findings were corroborated by evidence of neither significant increase in urge severity during tic suppression, nor decrease following the period of tic suppression (Specht et al., 2013). In light of this controversial evidence, it appears that the role of tic suppression in urge phenomena is variable and may require further investigation in larger studies to assess the potential role of both urges and tic suppression as a treatment target in behavioural therapy.

#### **2.4. Premonitory urges and obsessive-compulsive symptoms**

Sensory phenomena such as premonitory urges are common in TS and in other neuropsychiatric conditions such as OCD, although their phenomenology typically differs. Prevalence estimates of OCD in patients with TS vary widely between studies, but rates of up to 80% have been reported (Kumar 2016), with obsessive-compulsive symptoms often being assessed using the Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS).

Increased rates of premonitory urges are reported in patients with TS and co-morbid OCD when compared to those with TS alone (Eddy and Cavanna, 2013c; Rajagopal and Cavanna, 2014; Sambrani et al., 2016). A large paediatric study found a strong positive correlation between premonitory urges and “not just right” experiences (Sambrani et al., 2016), which appear to be intrinsic to the phenomenology of TS and commonly associated with co-morbid obsessive-compulsive symptoms (Neal and Cavanna, 2013a).

A recent study (Kano et al., 2015) involving 41 patients with TS showed significant positive correlation between PUTS and DY-BOCS scores, suggesting that patients who experience more obsessive-compulsive symptoms also experience more severe premonitory urges.



There was also a significant negative correlation between PUTS score and Global Assessment of Functioning (GAF) scale, highlighting the adverse effects of premonitory urges on daily life. However the results of a study focusing on interoceptive awareness in TS showed that obsessive-compulsive symptoms have a positive correlation with premonitory urges but this does not reach statistical significance in a regression model where interoceptive awareness is included: this finding raises the possibility that the association between premonitory urges and obsessive-compulsive symptoms occurs via body awareness (Ganos et al. 2015b).

## **2.5. Premonitory urges and anxiety**

Anxiety symptoms are frequently reported by patients with TS, and are associated with increased tic frequency (Conelea and Woods, 2008). A recent study showed that patients with elevated levels of anxiety had higher PUTS scores (Rozenman et al., 2015). In this study, panic and somatic symptoms measured by the SCARED-C panic/somatic subscale (regular and modified versions) were found to independently account for a significant proportion of variance in PUTS scores. The modified subscale includes physiological symptoms such as feeling nauseous, dizzy, and shaky, therefore tapping into sensory aspects which may be relevant to the premonitory urge sensations. There was a weaker correlation between PUTS and cognitive aspects of panic symptoms, suggesting that the relationship between premonitory urges and anxiety may be specific to the increased physiological arousal experienced when feeling anxious.

## **2.6. Neurobiological mechanisms underlying premonitory urges**

### **2.6.1. Evidence from functional neuroimaging studies**

While the exact pathophysiology of premonitory urges is yet unknown, recent functional and structural neuroimaging studies have significantly contributed to characterise brain networks thought to have a role in the development of these urges. Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Magnetoencephalographic (MEG) findings have converged in identifying limbic brain structures as a key biological substrate (Debes et al., 2017).

The initial neuroimaging data on premonitory urges were extracted from a study on the

neural correlates of tics that involved 6 patients with TS (Stern et al., 2000) and concluded that abnormal activity in sensorimotor, language, executive, and limbic circuits may be involved in motor and vocal tic expression, as well as generation of the urges which often precede them. These findings were confirmed in larger scale studies, which similarly identified the role of limbic and supplementary motor areas in tic generation (reviewed in Rajagopal and Cavanna, 2013; Cavanna et al., 2017).

A functional neuroimaging study by Bohlharter et al. (2006) used functional MRI (fMRI) to demonstrate that limbic structures, including the anterior cingulate and insular cortex, supplementary motor area, and parietal operculum, were activated at the time of the premonitory urge. A number of other functional neuroimaging studies have also supported these findings and provided evidence for the role of the limbic circuitry, as well as the insula, cingulate cortex, and supplementary motor area (Hampson et al., 2009; Lerner et al., 2007; Neuner et al., 2014; Tinaz et al., 2015; Wang et al., 2011;).

### **2.6.2. Evidence from structural neuroimaging studies**

In addition to identifying neuronal circuits involved in the production of tics and their associated premonitory urges, a small number of imaging studies have looked into any structural neurological correlates of premonitory urges. A morphometric study used MRI imaging to assess cortical thickness in 40 adult patients with TS (Draganski et al., 2010). The authors found a significant positive correlation between intensity of premonitory urges (as measured by PUTS scores), grey matter volume and cortical thickness in the left somatosensory and prefrontal cortices. Furthermore, a recent structural imaging study (Draper et al., 2016) demonstrated that TS is associated with decreased grey matter thickness in the insula and sensorimotor areas, and that there is an inverse correlation between grey matter thickness and severity of premonitory urge symptoms, as measured by PUTS scores.

The results of structural neuroimaging studies corroborate the findings of functional neuroimaging studies, suggesting a pivotal role for the insula (**Figure 1**), as well as sensorimotor areas, in tic generation, a mechanism mediated by the subjective perception of the premonitory urge (Cavanna et al., 2017).

*[PLEASE INSERT FIGURE 1 HERE]*

## 2.7. Premonitory urges as a therapeutic target

Behavioural therapy has been shown to be of potential therapeutic benefit in the treatment of TS, with an effect size comparable to that of antipsychotic medication (McGuire et al., 2014). It has been suggested that greatest benefit may be seen in older patients, as well as those with greater therapeutic contact time, whereas beneficial effects might be reduced in patients with co-morbid ADHD.

Habit Reversal Therapy (HRT) is a well-known and validated behavioural therapy used in the management of TS (Dutta and Cavanna, 2013) that has been used as part of a wider treatment package known as Comprehensive Behavioural Intervention for Tics (CBIT) (Woods et al., 2008). CBIT involves a structured behavioural therapy which focuses on training patients in becoming aware of their tics, and using competing responses when they feel the urge to tic. In two large trials from the same group, CBIT has been shown to significantly reduce tic severity in both adults and children (Piacentini et al., 2010, Wilhelm et al., 2012). The improvement in tic severity has been shown to be lower in patients with anxiety and severe premonitory urges (Sukhodolsky et al., 2017).

A recent study has specifically investigated the effect of CBIT on premonitory urges (Houghton et al., 2017). The authors hypothesised that urge severity would be decreased in patients who responded to treatment, suggesting a habituation effect. There was a decrease in premonitory urge severity during treatment in the adult cohort of their study population, however they could not demonstrate that the behavioural therapy specifically caused these changes in urge severity. Overall, there was no significant reduction in premonitory urge severity in the paediatric cohort recruited for this study. These findings suggest that habituation may not underpin the benefits of behavioural therapy in patients with TS, and that there may be some important developmental aspects to premonitory urges which should be further investigated.

### 3. Multimodal hypersensitivity

Premonitory urges are not the only sensory phenomena reported by patients with TS. There is increasing evidence that patients with TS display a heightened level of sensitivity to external stimuli. It has been widely recognised that some tics occur as a response to external stimuli. For example, patients with echophenomena report complex tic behaviours that involve mirroring movements (echopraxia) or sounds made by others (echolalia) (Ganos et al., 2012b). As well as mirroring external stimuli, certain tic behaviours appear to be related to other, seemingly unrelated stimuli. An early study found that 70% of patients with TS reported heightened sensitivity to tactile, auditory, and/or visual stimuli (Cohen and Leckman, 1992). In particular, the possible association between selective sound sensitivity and tic disorders has been the focus of a fruitful line of research in recent years (Neal and Cavanna, 2013b; Cavanna, 2014; Cavanna and Seri, 2015).

The role of multimodal hypersensitivity in TS has been specifically addressed in a study assessing the prevalence of sensory symptoms in patients with TS compared with healthy controls (Belluscio et al., 2011). Eighty percent of the TS cohort described heightened sensitivity to external stimuli, compared to 35% of healthy controls. This finding was consistently significant across the modalities of sound, light, smell, and touch (but not taste). Furthermore, the authors found that patients with TS were more affected by faint stimuli as compared to intense stimuli. This study also assessed whether the increase in sensitivity was due to increase in peripheral perception of faint stimuli, or whether it was due to alterations in central sensory processing. The authors compared detection threshold for olfactory and tactile stimuli in both patients with TS and healthy controls. No significant difference between modalities was found, suggesting that the increase in sensitivity seen in the TS group is more likely to be related to altered central processing.

The role of abnormal central sensorimotor processing has also been suggested by the findings of a recent study, in which the Quantitative Sensory Testing (QST) battery was used in 14 adult patients with TS and 14 controls (Schunke et al., 2016). The authors reported no significant difference in the threshold for detection of externally applied sensory stimuli between patients with TS and controls. There was also no particular pattern demonstrated in patients with TS and no correlation between QST and PUTS score. The authors therefore

suggested that central perceptual mechanisms such as abnormal central sensorimotor processing or aberrant interoceptive awareness may underpin sensory symptoms in TS.

In addition to heightened response to external stimuli, it has been experimentally shown that patients with TS have lower (or, if corrected for gender, similar) interoceptive awareness to non-TS subjects: this is in line with the observation that exteroception thresholds of patients with TS are in fact unchanged compared to non-TS subjects, although the former appear to be more sensitive to external stimuli (Ganos et al., 2015b). Moreover, these findings suggest that the association between premonitory urges and tics might occur within the filter-spectrum of interoceptive awareness: patients with higher interoceptive awareness will perceive more urges for the same amount of tics (Ganos, 2016). Indeed, patients' beliefs or subjective reports might be that they perceive their bodily states stronger than others, although objectively they do not. In a clinical study, adults with TS report increased awareness of their internal state in comparison to healthy controls (Eddy et al., 2014), and this appears to correlate with number of tics (Woods et al., 1996). Interoceptive awareness has also been evaluated in patients with TS using the University of Sao Paulo Sensory Phenomena Scale (USP-SPS), which assesses abnormal sensory experiences (Sutherland Owens et al., 2011). The main categories of assessed symptoms include uncomfortable physical sensations, "just right" feelings triggered by external stimuli, feelings of incompleteness, the feeling of built up energy which needs to be released, and more simple urges. USP-SPS scores were found to be positively correlated with PUTS scores, suggesting that patients with stronger premonitory urges also had a greater degree of abnormal sensory experience. The findings of a recent study on sensory dysregulation in children with tic disorders were consistent with the hypothesis that somatosensory dysregulation, as measured by subjective measures but not by objective, is probably more associated with central processing rather than peripheral perception (Weisman et al., 2018).

It has been hypothesised that the symptoms characterising TS occur as a result of the failure of sensory gating, a concept which describes the prevention of sensory overload by filtering out irrelevant stimuli. Sensory gating deficits have been shown to have a role in the phenomenology of schizophrenia, and can be assessed using the Sensory Gating Inventory (SGI) and Structured Interview for Assessing Perceptual Anomalies (SIAPA). A number of the items included in the SGI are relevant to the sensory symptoms experienced by patients with TS, and a clinical study found significantly elevated SGI scores in patients with TS compared to healthy controls (Sutherland Owens et al., 2011). The authors of this study did

not find any significant relationship between SGI scores and tic severity (measured by YGTSS scores) or premonitory urges (measured by PUTS scores). This suggests that although not directly related to tic severity or premonitory urges, a failure of sensory gating may play a significant role in TS, and the use of the SGI may identify clinical aspects of TS not previously assessed by other scales. Indeed, the results of a functional neuroimaging study assessing pre-pulse inhibition of the startle reflex, a marker of sensorimotor gating, showed several regions where brain activity during pre-pulse inhibition differed significantly between patients with TS and healthy subjects. These included the caudate nucleus, a key region within cortico-striato-thalamo-cortical pathways that appears to be involved in the modulation of tic severity.

Overall, possible alterations in both external and internal awareness of sensory stimuli are likely to play an important role in tic generation, however our understanding of perceptual alterations in patients with TS is largely incomplete. **Table 1** summarises the results of the main studies to date focusing on exteroception and interoception in patients with tic disorders.

*[PLEASE INSERT TABLE 1 HERE]*

#### 4. Conclusions

Although TS is a neurodevelopmental disorder primarily characterised by motor and vocal tics, sensory phenomena have been shown to play a central role in TS pathophysiology. Premonitory urges are the most widely studied sensory symptoms, and have been shown to be prevalent in the vast majority of patients with TS, especially in adulthood. Premonitory urges have been shown to be related to tic severity, anxiety, obsessive-compulsive symptoms, and “not just right experiences”. There is mixed evidence surrounding the relationship between premonitory urges and tic suppression, as well as their role in behavioural therapy. Evidence from recent neuroimaging studies implicates the insula and the somatosensory cortices in premonitory urges, in addition to the known role of the cortico-striato-thalamo-cortical loop in tic expression. It has recently been proposed that the insula plays an important role as a nexus linking the sensory and emotional features of premonitory urges with their translation into actual tics (Conceição et al., 2017). Finally, both neuroanatomical and neurophysiological data suggest that the influence of sympathetic autonomic arousal on tics might also be mediated by the insula (Nagai et al., 2009; Hawksley et al., 2015).

Multimodal hypersensitivity is another facet of TS which has not yet been widely investigated. The results of preliminary small scale studies have indicated that patients with TS have heightened sensitivity to external stimuli when compared to healthy controls, but the exact cause or implications of this has not been widely studied. There could be a link between both exteroceptive and interoceptive awareness and premonitory urges that plays an important role in the pathophysiology of tics (**Figure 2**).

*[PLEASE INSERT FIGURE 2 HERE]*

Further research is acutely needed to elucidate the pathophysiological mechanisms underlying multimodal hypersensitivity in TS. Adaptation of behavioural and cognitive therapy approaches to target sensory symptoms is likely to play a significant contribution to the improvement of health-related quality of life in patients with tics (Crossley and Cavanna, 2013).

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TABLE

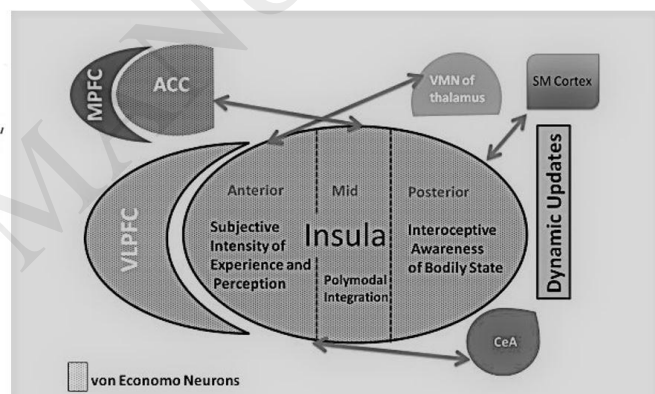
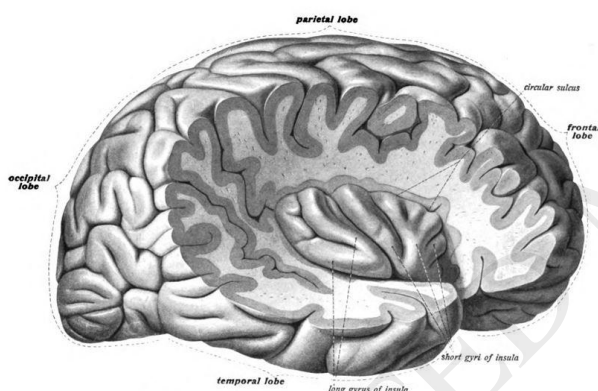
**Table 1.** Summary of studies focusing on sensory function (exteroception and interoception) in patients with Tourette syndrome (TS).

| Authors                 | Year | Focus on exteroception / interoception | Clinical / experimental protocol | Participants  | Measure(s)   | Finding(s)  |
|-------------------------|------|--|----------------------------------|---|--|---|
| Cohen and Leckman       | 1992 | Exteroception                          | Clinical                         | 28 patients with TS (24 males; age range 9-60 years)                        | Specific interview questions   | Of 20 patients questioned about site sensitization, 14 (70%) had heightened sensitivity to tactile, auditory, and/or visual stimuli   |
| Belluscio et al.        | 2011 | Exteroception                          | Clinical + Experimental          | 19 patients with TS (16 males; age range 23-50 years) + 19 matched controls | Adapted version of the Adult Sensory Profile; VonFrey filament test; <i>n</i> -butanol sticks  | 80% of patients described heightened sensitivity to external stimuli, with examples among all sensory modalities. Bothersome stimuli were characterised as faint, repetitive or constant, and non-salient, whereas intense stimuli were well tolerated. Patients' perceived sensitivity derives from altered central processing rather than enhanced peripheral detection                             |
| Sutherland Owens et al. | 2011 | Exteroception + Interoception          | Clinical                         | 20 patients with TS (15 males; age range 10-41 years) + 22 matched controls | University of Sao Paulo Sensory Phenomena Scale (USP-SPS); Sensory Gating Inventory (SGI); Structured Interview for Assessing Perceptual Anomalies (SIAPA)   | SGI (but not SIAPA) scores were significantly higher in patients with TS. USP-SPS scores correlated significantly with premonitory urge scores, but not with the SGI or SIAPA; sensory gating scales did not correlate significantly with symptom severity. Patients with TS endorsed difficulties in sensory gating and the SGI may be valuable for studying these clinical phenomena                |
| Eddy et al.             | 2014 | Interoception                          | Clinical                         | 18 patients with TS (13 males; age range 16-61 years) + 18 matched controls | Private Body Consciousness (PBC) scale   | Patients with TS reported significantly higher PBC scores, which were not correlated with premonitory sensations or tic severity. Inhibitory functioning was negatively related to PBC scores and premonitory sensations. Patients with TS reported increased PBC in addition to inhibitory deficits. Aspects of inhibitory functioning were related to PBC, premonitory sensations, and tic severity |
| Ganos et al.            | 2015 | Interoception                          | Experimental                     | 19 patients with TS (13 males; mean age 39 years) + 25 matched controls     | 'Mental tracking' method   | Patients with TS reported lower interoceptive awareness compared to controls. Interoceptive awareness was the strongest predictor of premonitory urges in patients with TS, with greater interoceptive awareness being associated with more urges   |
| Schunke et al.          | 2016 | Exteroception                          | Experimental                     | 14 patients with TS (12 males; mean age 32 years) + 14 matched controls     | Quantitative Sensory Testing (13 parameters: cold and warm detection thresholds, thermal sensory limen, paradoxical heat sensations, cold and heat pain thresholds, mechanical detection and pain thresholds, mechanical pain sensitivity, pressure pain threshold, vibration detection thresholds, mechanical allodynia, and wind-up ratio) | There were no relevant group differences in any of the 13 QST parameters and no specific QST pattern in patients with TS. There was no correlation between QST parameters and premonitory urge scores. The perceptual threshold detection of externally applied sensory stimuli was normal in adults with TS  |
| Weisman et al.          | 2018 | Exteroception                          | Clinical + Experimental          | 92 patients with TS or other chronic tic disorders (78                      | Caregiver-reported Short sensory profile (SSP); VonFrey filament test; Fabric prickliness test (FPT)   | Almost 50% of the cohort had no somatosensory dysregulation. Of the remainder, 14 (15%) had suspected somatosensory dysregulation and 32 (35%) had somatosensory dysregulation. Somatosensory dysregulation was significantly more common and severe when there were co-  |

|  |  |  |  |                              |  |   |
|--|--|--|--|------------------------------|--|---|
|  |  |  |  | males; age range 7-14 years) |  | morbidities. The presence of somatosensory dysregulation was associated with more severe impairment in quality of life and less participation in daily activities |
|--|--|--|--|------------------------------|--|---|

## FIGURES

**Figure 1.** Anatomy of the insula (*left*) and its widespread connectivity with both sensorimotor and limbic structures (*right*). The posterior insula is connected with the sensorimotor (SM) cortex; the anterior insula is connected with both the central nucleus of the amygdala (CeA) and the ventromedial nucleus (VMN) of the thalamus; the mid-insula is connected to the thalamus and is intermediary in translating the somatosensory stimuli to the anterior region where they are perceived and further evaluated in conjunction with the anterior cingulate cortex (ACC) and the medial prefrontal cortex (MPF). The insula has cytoarchitectural similarities (von Economo neurons) with both the ACC and the ventrolateral prefrontal cortex (VLPFC).

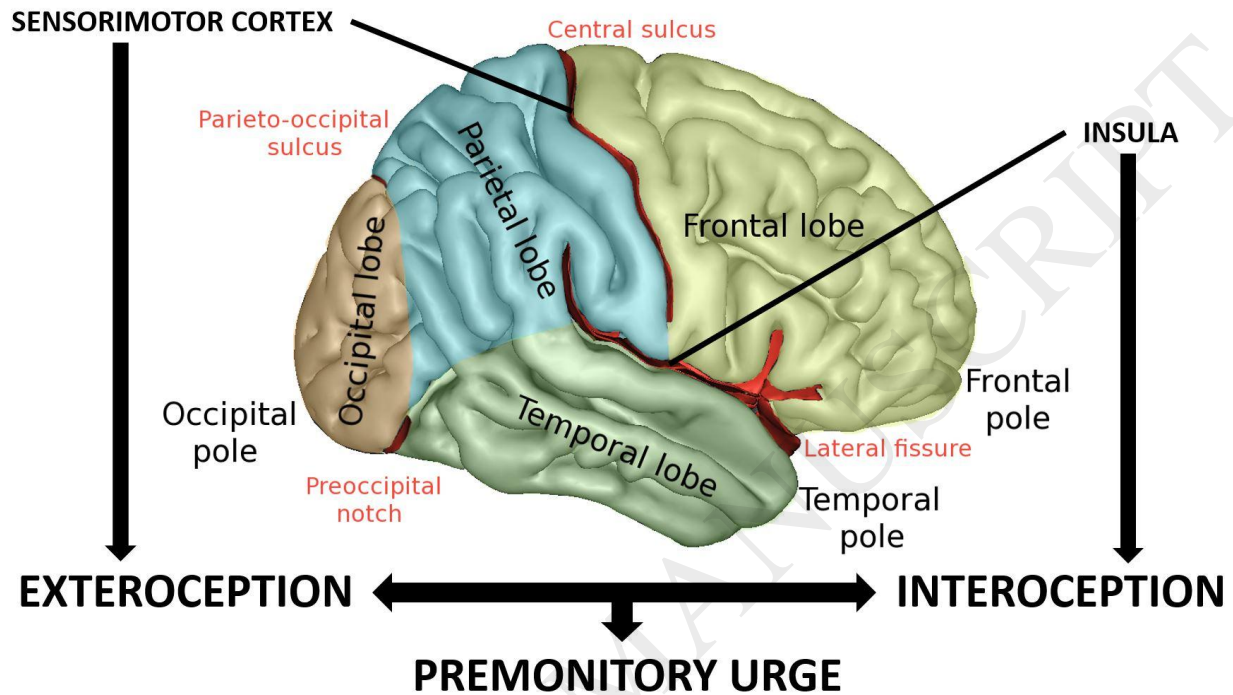


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**Figure 2.** Possible link between exteroceptive/interoceptive awareness and the premonitory urge to tic in patients with Tourette syndrome.



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