

Systematic Review The Severity and Neural Correlates of Premonitory Urge in Tourette Syndrome: A Systematic Review and Meta-Analysis

Yanlin Li^{1,†}, Liping Yu^{1,†}, Hua Zhang², Xianbian Wang¹, Yonghua Cui^{1,*}, Ying Li^{1,*}

¹Department of Psychiatry, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, 100101 Beijing, China ²The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, 250061 Jinan, Shandong, China

*Correspondence: cuiyonghua@bch.com.cn (Yonghua Cui); liying@bch.com.cn (Ying Li)

[†]These authors contributed equally.

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Abstract

Introduction: Premonitory urge (PU) is an aversive bodily sensation that signals the onset of tic disorder. To our knowledge, PU typically precedes the appearance of tic symptoms, and both age and tic severity are correlated with PU. However, inconsistent findings have also been reported. Hence, we conducted a meta-analysis to examine the relationship among premonitory symptoms, patient age and the severity of tic symptoms, as well as to summarize the research on the neural underpinnings of PU in Tourette syndrome (TS). **Methods**: We conducted a literature search of relevant studies published between December 2005 and April 2022 using databases such as PubMed, Elsevier, PsycINFO, and Web of Science. Our analysis was carried out using R software with the assistance of the "meta" and "metafor" packages. **Results**: Our meta-analysis included 22 studies with a total of 1236 tic disorder patients. The mean Premonitory Urge for Tics Scale (PUTS) score was 20.17, with a 95% confidence interval of [18.14, 21.68]. Through meta-regression, we found that age and tic severity play important moderating roles in PU severity (p < 0.0001). Neuroimaging studies suggest that PU is related to the insula, prefrontal cortex (PFC), anterior cingulate cortex (ACC), and supplementary motor area (SMA), regardless of the structural or functional level. **Conclusions**: Our meta-analysis confirmed the positive relationship between the severity of tics and PU and identified age as a significant factor influencing PU. The neural mechanisms underlying PU remain largely unknown, but evidence suggests that the insula, PFC, ACC, and SMA are related regions.

Keywords: premonitory urge; age effect; meta-analysis; insula; anterior cingulated cortex

1. Introduction

Tic disorder (TD) is a prevalent neurodevelopmental condition, with Tourette syndrome (TS) being its most severe form. Many patients with chronic TDs and TS report experiencing pressure-like or tickling sensations prior to the occurrence of tics [1,2]. These sensations are well-known symptoms accompanying tics [3]. The term "premonitory urge (PU)" was first used by Leckman *et al.* [4]. The majority of patients describe these pressure, itch, and sore sensations as aversive or unpleasant before the onset of a tic. A prior study found that PU was present in nearly 90% of patients with TS [5]. The most common sites of PU are in the head and neck and are separate from the anatomic region where the tics occur [6].

PU plays a crucial role in the etiology of TD. Many studies have reported that patients can temporarily relieve the sensations associated with PU by producing tic symptoms. In other words, tics are often seen as a motor response aimed at reducing the intensity of PU [7]. For instance, the recognition of an itchy tongue as a PU could lead to tongue biting as a tic symptom, which in turn can alleviate the itchy sensation [1]. Our previous meta-analysis showed a mild to moderate correlation between PU strength and tic severity [8]. Additionally, PU has been shown to play a significant role in behavioral therapy for TS [9]. Awareness of PU before the onset of tics is the first step in habit reversal training, a widely used behavioral psychotherapeutic approach for individuals with TD. This approach highlights the importance of increased insight into PU in helping patients improve their ability to suppress tics. Pertinently, PU is a fundamental component in the formation of tics [10,11]. Despite this, the mechanism underlying PU and its relationship with tic symptoms remains unclear.

The onset of PUs typically occurs around the age of 10 years and may be linked to the patient's increasing awareness and cognitive development [4,12-14]. However, some studies have reported an earlier onset of PU [15]. This may be due to a lack of introspection and the inability of younger children to describe feelings [15,16]. The severity of PU is generally mild in children and adolescents, but it can become more pronounced in adults [7,10,17]. These findings suggest that age is an important factor influencing PU, although the relationship between patient age and PU severity still requires further investigation.

Moreover, the underlying neurobiological mechanism of PU remains unclear. However, several studies have implicated the anterior insula as a potential source of PU [18,19]. One study using functional magnetic resonance



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Fig. 1. Flowchart of the included studies. PU, Premonitory urge.

imaging (fMRI) found that a region in the right insular cortex was associated with PU scores [19]. Other neuroimaging studies, including functional and structural magnetic resonance imaging (MRI), have suggested that PU may be related to activity in the prefrontal cortex (PFC), anterior cingulate cortex (ACC), and supplementary motor area (SMA) [13,20,21]. These findings suggest that the generation of PU may involve multiple brain networks. Further research is needed to explore the relationship between PU and tics, particularly from a network perspective.

The aim of this meta-analysis was to examine the predictors of PU, particularly patient age and tic symptom severity. We conducted a meta-regression analysis to achieve this goal. This study also examined the relationship between PU and tic symptom severity. Additionally, to gain a deeper understanding of PU, we focused on magnetic resonance imaging (MRI) studies and aimed to present an updated summary of the evidence-based neural correlates of PU.

2. Methods

2.1 Protocol and Registration

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO Register CRD42022379230). PRISMA checklist is shown in **Supplementary material**.

2.2 Search Strategy

We conducted a comprehensive literature search for relevant studies published between December 2005 and April 2022 in PubMed, Elsevier, PsycINFO, and Web of Science. Our main search terms included "premonitory urge", "sensory phenomena", and various variants of "tic disorder" or "Tourette syndrome". We also manually checked the reference lists of the included studies to ensure completeness.

To be eligible for inclusion in our meta-analysis, studies had to meet the following criteria: assessment of PU using the Premonitory Urge for Tics Scale (PUTS), assessment of tic severity using the Yale Global Tic Severity Scale (YGTSS), and inclusion of both child and adult subjects. Studies were excluded if they failed to meet any of the following criteria: no mention of PU score, lack of focus on TDs, not original research, and sample size less than 10.

Study	Year	Male (%)	Age (Year)	AgeG (1/2)	N	PU (Mean)	PU (SD)	YGTSS (Mean)	YGTSS (SD)
Anis et al. 2022 [31]	2022	61.1	30.5	2	18	22.9	5.5	25.3	17.1
Ramsey et al. 2021 [32]	2021	60	10.68	1	75	16.46	6.03	23.53	8.39
Fu et al. 2021 [36]	2021	20	19.7	2	15	21.13	6.749	30.13	8.601
Jackson et al. 2021 [39]	2021	89.3	14.62	1	28	20.21	6.81	22.9	19.25
Bhikram et al. 2020 [34]	2021	80	37.1	2	40	25	4.8	25.6	8.95
Baumung et al. A 2021 [33]	2021	78.5	34.2	2	93	23.84	6.25	20.34	9.18
Baumung et al. B 2021 [33]	2021	83.1	11.8	1	148	21.08	6.32	20.2	9.18
Matsuda et al. A 2020 [40]	2020	N/A	28.5	2	25	22.9	6.9	23.4	7.8
Matsuda et al. B 2020 [40]	2020	N/A	12.9	1	37	21.2	6.9	19.4	7.2
Yi Gu et al. 2020 [37]	2020	81	9.5	1	252	12.96	3.23	19.63	9.2
Sigurdsson et al. A 2020 [41]	2020	89.3	14.6	1	28	20.2	6.8	22.9	19.3
Isaacs et al. 2020 [38]	2020	70.6	33.5	2	34	24.9	4.9	24.9	10.7
Sigurdsson et al. B 2020 [42]	2020	68.8	20.4	2	16	22.94	6.4	21	14.5
Brandt et al. A 2016 [26]	2016	86.4	29.82	2	22	21.05	5.78	17.05	7.7
Brandt et al. B 2016 [26]	2016	77.5	12.05	1	40	17.83	6.38	17.77	8.12
McGuire et al. 2016 [30]	2016	60	10.68	1	75	16.46	6.03	23.53	8.39
Rozenman et al. 2015 [28]	2015	78	11.76	1	134	17.34	6.63	24.65	6.09
Kano et al. 2015 [29]	2015	76	23.1	2	41	18.6	6	20.8	19.1
Capriotti et al. 2014 [35]	2014	86.7	11.4	1	15	18.2	7	22.1	4.7
Sutherland Owens et al. 2011 [17]	2011	72.2	19.35	2	18	25.8	5	24.2	8
Steinberg et al. 2010 [27]	2010	85	11.05	1	40	20.15	5.89	18.15	7.76
Woods et al. 2005 [14]	2005	92.9	10.8	1	42	18.5	6.1	25.9	10.1

Table 1. The included studies.

Note. AgeG1, child group; AgeG2, adult group; PU, premonitory urge; YGTSS, Yale Global Tic Severity Scale; SD, standard deviation.

Additionally, we performed a separate search using the terms "premonitory urge" and "MRI" or "imaging" to identify studies examining the neural correlates of PU.

2.3 Data Extraction

The following data were extracted from each study: first author, publication date, sex and age of participants, sample size, mean value and standard deviation (SD) of PU as assessed by the PUTS, mean value and SD of tic severity as assessed by the YGTSS. In addition, the main findings from included MRI studies examining the neural correlates of PU were documented.

2.4 Assessment of Quality for Included Studies

The quality of each study was evaluated using a modified version of the critical appraisal skills program (CASP) scale [23,24]. This widely used tool assesses the strengths and limitations of qualitative research methodologies and includes 11 items, such as "Item 1: Did the study address a clearly defined issue?" and "Item 4: Were the controls chosen appropriately?" Two authors independently assessed each included trial and reached a consensus. Studies were excluded if they had fewer than 5 'yes' responses on the CASP scale.

2.5 Statistical Methods

We employed the use of a pooled mean with 95% confidence intervals (CIs) to quantify PUs and conducted a meta-regression analysis to examine the predictors of PUs, specifically patient age and the severity of tic symptoms. To assess the heterogeneity of each effect size, we utilized the I^2 statistic, with a value greater than 50% indicating substantial heterogeneity. We sought to identify the source of heterogeneity, including differences within groups, between groups, and in statistical methods, and employed a random effects model in the meta-analysis. Our analysis was performed using R software (version 3.5.3, The University of Auckland, Auckland, New Zealand) with the "meta" and "metaphor" packages for the meta-regression analysis. To detect publication bias, we utilized a funnel plot.

3. Results

3.1 Sample Description

This meta-analysis was conducted in accordance with the PRISMA guidelines and resulted in the inclusion of 22 studies [25] that covered a wide age range of participants between 6 and 50 years old (as shown in Fig. 1). A total of 1236 patients were included in these studies (as outlined in Table 1) [14,17,26–42], and the quality assessment of the included studies can be found in **Supplementary Table 1** (which is also included in the supplementary material as **Supplementary Fig. 1**).

								weight	weight
Study	Total	Mean	SD		Mean	Mean	95%-CI	(common)	(random)
Anis et al. 2022	18	22.90	5.5000			22.90	[20.50; 25.59]	2.0%	4.5%
Ramsey et al. 2021	75	16.46	6.0300	<u> </u>		16.46	[15.15; 17.88]	3.7%	4.7%
Mengmeng Fu et al. 2021	15	21.13	6.7490	-		— 21.13	[17.98; 24.84]	1.0%	4.0%
Jackson et al. 2021	28	20.21	6.8100	_		20.21	[17.84; 22.90]	1.6%	4.4%
Bhikram et al. 2021	40	25.00	4.8000		1	25.00	[23.56; 26.53]	7.1%	4.8%
Baumung et al. A 2021	93	23.84	6.2500			- 23.84	[22.60; 25.14]	8.9%	4.9%
Baumung et al. B 2021	148	21.08	6.3200			21.08	[20.09; 22.12]	10.8%	4.9%
Matsuda et al. A 2020	25	22.90	6.9000			22.90	[20.35; 25.77]	1.8%	4.4%
Matsuda et al. B 2020	37	21.20	6.9000			21.20	[19.09; 23.54]	2.3%	4.5%
Yi Gu et al. 2020	252	12.96	3.2300			12.96	[12.57; 13.36]	26.6%	5.0%
Sigurdsson et al. A 2020	28	20.20	6.8000	_		20.20	[17.83; 22.88]	1.6%	4.4%
Isaacs et al. 2020	34	24.90	4.9000		-	24.90	[23.31; 26.60]	5.7%	4.8%
Sigurdsson et al. B 2020	16	22.94	6.4000		+	22.94	[20.01; 26.30]	1.3%	4.2%
Brandt et al. A 2016	22	21.05	5.7800			- 21.05	[18.77; 23.61]	1.9%	4.4%
Brandt et al. B 2016	40	17.83	6.3800		<u> </u>	17.83	[15.96; 19.92]	2.0%	4.5%
McGuire et al. 2016	75	16.46	6.0300			16.46	[15.15; 17.88]	3.7%	4.7%
Rozenman et al. 2015	134	17.34	6.6300			17.34	[16.25; 18.50]	6.0%	4.8%
kanon et al. 2015	41	18.60	6.0000		<u>.</u>	18.60	[16.85; 20.53]	2.6%	4.6%
Capriotti et al. 2014	15	18.20	7.0000	+		18.20	[14.98; 22.11]	0.7%	3.7%
Sutherland Owens et al. 2011	18	25.80	5.0000			<u> </u>	[23.59; 28.22]	3.1%	4.6%
Steinberg et al. 2010	40	20.15	5.8900			20.15	[18.40; 22.06]	3.1%	4.6%
Woods et al. 2005	42	18.50	6.1000			18.50	[16.74; 20.44]	2.5%	4.6%
Common effect model	1236			<	>	18-52	[18.23: 18.82]	100.0%	
Random effects model					\sim	20.17	[18.76: 21.69]		100.0%
Heterogeneity: $l^2 = 98\%$, $\tau^2 = 0.0$	274. n	< 0.01			Ť		[
	, p			15	20	25			

Fig. 2. The meta-analysis for the mean PU. 95% CI, 95% confidence interval; SD, standard deviation.

3.2 Mean PUTS Scores and Publication Bias

The results of our meta-analysis showed that the average PUTS score was 20.17, with a 95% CI of [18.76, 21.69] and I² of 98%. Significant heterogeneity was confirmed by a Q test, with a value of 934.86 and 21 degrees of freedom (df = 21, p < 0.0001, as shown in Fig. 2). There was no evidence of publication bias, as indicated by the funnel plot (as shown in **Supplementary Fig. 1** in the supplementary material).

3.3 Subgroup Analysis of the Pooled Mean PUTS Scores

The source of heterogeneity was explored through subgroup analysis, which showed a significant difference between adult and child participants. The mean PUTS score in the adult group was 22.98 (95% CI [21.58, 24.47], $I^2 =$ 77%), and in the child group, it was 18.15 (95% CI [16.67, 19.76], $I^2 = 97\%$). The heterogeneity between the adult and child groups was determined to be significant by the Q test (Q = 19.12, df = 1, *p* < 0.0001) (More details see Fig. 3).

3.4 Meta-Regression Analysis

The results showed that age was a significant predictor of PU, with tau² = 0.0137, tau = 0.117, I² = 89.16%, H² = 9.23, R² = 50.07%, QM (the statistic of the test of predictors) = 19.95, and p < 0.05. However, the results indicated that tic severity was not a significant predictor of PU, with tau² = 0.0273, tau = 0.1651, I² = 94.4%, H² = 17.85, R² =

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0.50%, QM = 0.9881, and p = 0.3202. These results suggest that as patient age increases and tic symptoms become more severe, PU scores also increase (See Fig. 4).

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3.5 Neural Correlates of PU

Both MRI and magnetic resonance spectroscopy (MRS) were employed to investigate the neural basis of PU at both functional and structural levels. Our analysis identified 12 relevant studies (refer to Fig. 2). In terms of functional aspects, the results showed that PU severity as measured by PUTS scores and the inhibition of PU were correlated with decreased connectivity between the cortex and insula seeds, as revealed by resting-state functional MRI [19,34]. On the other hand, functional connectivity between the right dorsal anterior insula and bilateral SMA was found to positively correlate with PU severity [18]. At the structural level, structural MRI showed an inverse association between PU and gray matter volume in the insula and sensorimotor cortex [13]. Additionally, increased activity in other regions, such as the ACC and right temporoparietal junction, was observed during the inhibition of PU [43,44]. Furthermore, gray matter volume in the cerebellar lobule was implicated in sensorimotor processing, which is related to PU [41,45]. Finally, Gamma-aminobutyric acid (GABAergic) processing was found to be crucial in sensorimotor processing [46]. Gamma-aminobutyric acid (GABA)-edited MRS studies revealed lower levels of GABA in the primary sensorimo-



Study	Total	Mean	SD	Mean	Mean	95%–CI	Weight (common)	Weight (random)
AgeG = 2								
Anis et al. 2022	18	22.90	5.5000		22.90	[20.50; 25.59]	2.0%	4.5%
Mengmeng Fu et al. 2021	15	21.13	6.7490	<u>+</u>	21.13	[17.98; 24.84]	1.0%	4.0%
Bhikram et al. 2021	40	25.00	4.8000		25.00	[23.56; 26.53]	7.1%	4.8%
Baumung et al. A 2021	93	23.84	6.2500		23.84	[22.60; 25.14]	8.9%	4.9%
Matsuda et al. A 2020	25	22.90	6.9000		22.90	[20.35; 25.77]	1.8%	4.4%
Isaacs et al. 2020	34	24.90	4.9000		24.90	[23.31; 26.60]	5.7%	4.8%
Sigurdsson et al. B 2020	16	22.94	6.4000		22.94	[20.01; 26.30]	1.3%	4.2%
Brandt et al. A 2016	22	21.05	5.7800		21.05	[18.77; 23.61]	1.9%	4.4%
kanon et al. 2015	41	18.60	6.0000		18.60	[16.85; 20.53]	2.6%	4.6%
Sutherland Owens et al. 2011	18	25.80	5.0000		- 25.80	[23.59; 28.22]	3.1%	4.6%
Common effect model	322			\diamond	23.60	[22.98; 24.23]	35.5%	
Random effects model Heterogeneity: $I^2 = 77\%$, $\tau^2 = 0.0$)076, p	< 0.01			22.98	[21.58; 24.47]		45.3%
Bamsey et al. 2021	75	16 46	6.0300		16 46	[15 15: 17 88]	3.7%	4 7%
Jackson et al. 2021	28	20.21	6 8100		20.21	[17 84: 22 90]	1.6%	4 4%
Baumung et al. B 2021	148	21.08	6.3200	-	21.08	[20.09; 22.12]	10.8%	4.9%
Matsuda et al. B 2020	37	21.20	6,9000		21.20	[19.09; 23.54]	2.3%	4.5%
Yi Gu et al. 2020	252	12.96	3.2300		12.96	[12.57: 13.36]	26.6%	5.0%
Sigurdsson et al. A 2020	28	20.20	6.8000		20.20	[17.83: 22.88]	1.6%	4.4%
Brandt et al. B 2016	40	17.83	6.3800		17.83	[15.96: 19.92]	2.0%	4.5%
McGuire et al. 2016	75	16.46	6.0300		16.46	[15.15; 17.88]	3.7%	4.7%
Rozenman et al. 2015	134	17.34	6.6300	- <u></u>	17.34	[16.25: 18.50]	6.0%	4.8%
Capriotti et al. 2014	15	18.20	7.0000		18.20	[14.98: 22.11]	0.7%	3.7%
Steinberg et al. 2010	40	20.15	5.8900	1 1	20.15	[18.40; 22.06]	3.1%	4.6%
Woods et al. 2005	42	18.50	6.1000		18.50	[16.74; 20.44]	2.5%	4.6%
Common effect model	914			\$	16.21	[15.89: 16.53]	64.5%	
Random effects model					18.15	[16.67; 19.76]		54.7%
Heterogeneity: $I^2 = 97\%$, $\tau^2 = 0.0$	0199, p	< 0.01						
Common effect model	1236			\$	18.52	[18.23; 18.82]	100.0%	
Random effects model					20.17	[18.76; 21.69]		100.0%
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 0.0$)274, p	< 0.01		1 1 1				
Test for subgroup differences (fix	ed effe	ct): χ ₁ ² =	492.74, df =	15 (<i>p</i> < 0.01)20 25				

Test for subgroup differences (random effects): $\chi_1^2 = 19.12$, df = 1 (p < 0.01)





Fig. 4. Meta-regression analysis for PUs by age and tic severity. PU, Premonitory urge; PUTS, Premonitory Urge for Tics Scale.

tor cortex (SM1) in children with TS and a correlation between more severe and frequent PUs with lower levels of SMA GABA+ [47]. A summary of these findings can be found in Table 2 (Ref. [13,18,21,34,43,48–55]).

4. Discussion

To our knowledge, this was the first study to conduct a meta-analysis investigating the relationship between PU and patient age. Our findings indicated that younger individuals tended to have a lower level of PU, while older individuals tended to experience a higher level. This could be because with age, children develop greater self-awareness and the ability to describe their sensory experiences [12,28]. As a result, the reporting of PU increases [4,12]. By age 10, children are better able to describe the sensations they experience and report more awareness of PU [4,5,56]. On the

Table 2. Neuroimaging studies of PUs.									
Study	Sex (M/F)	Age	Imaging method	Measurement	Main findings				
Cavanna et al. (2008) [48]	TS: 30/10	TS: 32.4 ± 11	VBM analysis	VGTSS: PUTS	Premonitory urges had an impact on the integrity of tracts corres-				
	HC: 25/15	HC: 34.4 ± 9	v Divi unurysis	10105,1015	ponding to cortico-cortical and cortico-subcortical connections.				
Hampson <i>et al.</i> (2009) [49]	_	TS: 30.0 ± 9.7	Coactivating analysis	_	The SMA showed a significantly broader profile of cross-correlation				
	_	HC: 30.0 ± 9.0	Coactivating analysis	_	with the motor cortex during tics than during intentional movements.				
We get r_{1} (2011) [50]	TS: 8/5	$\text{TS:}~33.5\pm13.3$	Activity and connectivity analysis	VGTSS: V-BOCS: ADHS	Tics are caused by the combined effects of excessive activity in motor				
Wallg et ul. (2011) [50]	HC: 12/9	HC: 32.5 ± 11.1	Territy and connectivity analysis	10105, 1 2005, 12115	pathways and reduced activation in control portions of				
					cortico-striato-thalamo-cortical circuits.				
Ganos et al. (2014) [51] TS: 13/1		TS: 30.6 ± 8.8	ReHo analysis	YGTSS; MRVS; PUTS; Y-BOCS;	ReHo of the left inferior frontal gyrus was increased dur-				
				ADHS; BDI	ing voluntary tic inhibition compared to that during free				
					ticcing.				
Timez at $al (2015) [19]$	TS: 10/3	TS: 18–46 years	Theory-based neural network analysis	YGTSS: PUTS	The right dorsal anterior insula is part of the urge-tic network and could				
111112 <i>ct ut</i> . (2015) [10]	HC: 10/3	HC: 22-56 years	Theory based neural network analysis	10105,1015	influence the urge- and tic-related cortico-striato-thalamic regions even				
					during rest in TS.				
Draper et al. (2016) [13]	TS: 26/3	TS: 14 ± 3.1	Grav matter thickness analysis	YGTSS: PUTS: WASI	Premonitory sensory phenomena are inversely associated with gray mat-				
	HC: 26/3	HC: 14 ± 3.1	Gray matter thereis analysis	10100,1010, 0401	ter thickness measurements within the insula and sensorimotor cortex.				
Eddy et al. (2016) [43]	TS: 19/6	TS: 31.48 ± 11.50	Task-fMRI (theory of mind)	YGTSS; PUTS; Y-BOCS; ASRS;	Activity within the right temporo-parietal junction and amygdala as				
	HC: 19/6	HC: 29.88 ± 10.12	rusk hvirti (theory of hilling)	HADS; MIDI	localized by this task covaried with PUs.				
Kanaan <i>et al.</i> (2017) [52]	TS: 31/6	TS: 38.3 ± 11.1	MRS	YGTSS; RVTRS; PUTS; Y-BOCS;	The lamic Glu and PUs had a significant negative correlation				
	HC: 29/7	HC: 38.4 ± 11.1	WIKS	OCI-R; BDI-II					
Simulation of $al (2018)$ [52]	TS: 32/3	TS: 14.0 ± 3.3	DTI tract-based spatial statistics and	YGTSS; PUTS; CY-BOCS; Conners-3	The frequency of PU was associated with increased connectivity between				
Sigurdsson <i>et ut</i> . (2010) [55]	HC: 32/3	HC: 13.9 ± 3.3	probabilistic tractography	self-report; SCQ; WASI	M1 and the caudate nucleus, and increased information transfer between				
					M1 and the insula, respectively.				
Botteron at al. (2010) [54]	TS: 6/9	$TS:28.0\pm3.8$	Task-fMRI (urge to blink)	VGTSS: DCI: PUTS: V.BOCS: ASRS	Combining this approach with observed eye closure during fMRI blink				
Dotteron <i>et ut</i> . (2017) [34]	HC: 6/9	HC: 26.0 ± 2.2	rusk hvirt (urge to offick)	10100, Del, 1010, 1 Doeb, Abro	suppression trials should extract brain signals more tightly linked to the				
					urge to blink.				
Repeat al. (2020) [21]	TS: 13/8	$\text{TS: } 33.0 \pm 10.0$	Task-fMRI (go/no-go task)	YGTSS: PUTS: Y-BOCS: ASRS	SMA connectivity varied in proportion to premonitory sensations				
Tale et al. (2020) [21]	HC: 11/10	HC: 34.0 ± 14.0		10100,1010,10000,1010					
Bhikram et al. (2020) [34]	TS: 32/8	TS: 37.1 ± 13.1	Seed-based EC analysis	VGTSS: V-BOCS: PUTS: ASPS	PU severity was associated with less connectivity between the orbitofr-				
	HC: 16/4	HC: 36.9 ± 17.2	Seed-based i C anarysis	10105, 1-0005, 1015, ASK5	ontal cortex and sensorimotor cortex and among the inferior frontal gyrus,				
					the putamen and insula seeds.				
Bhikram <i>et al.</i> (2021) [55]	TS: 31/8	TS: 37.1 ± 13.1	Task-fMRI (blink inhibition and	YGTSS; Y-BOCS; WBSI; USP-SPS;	Greater premonitory urge severity was associated with greater activity				
	HC: 16/4	HC: 36.9 ± 17.2	free blinking)	PUTS	in the hippocampus, middle temporal gyrus and subcortex.				

 Bhikram et al. (2021) [55]
 TS: 31/8
 TS: 37.1 ± 13.1
 Task-fMRI (blink inhibition and YGTSS; Y-BOCS; WBSI; USP-SPS; Greater premonitory urge severity was associated with greater activity in the hippocampus, middle temporal gyrus and subcortex.

 Note: TS, Tourette syndrome; HC, healthy control; N, number; M, male; F, female; VBM, voxel-based morphometry; ReHo, regional homogeneity; fMRI, functional magnetic resonance imaging; MRS, magnetic resonance spectrum; DTI, diffusion tensor imaging; FC, functional connectivity; YGTSS, Yale Global Tic Severity Scale; PUTS, Premonitory Urge for Tics Scale; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; ADHS, ADHD self-assessment scale; MRVS, Modified Rush Video Scale; BDI, Beck Depression Inventory; WASI, Wechsler's Abbreviated Scale of Intelligence; ASRS, ADHD Self-Report Scale; HADS, Hospital Anxiety and Depression Scale; MIDI, Minnesota Impulsive Disorders Interview; RVTRS, Rush Video-based Tic Rating Scale; OCI-R, Revised Obsessive-Compulsive Inventory; SCQ, Social Communication Questionnaire; DCI, Diagnostic Confidence Index; WBSI, White Bear Suppression Inventory; USP-SPS, University of São Paulo Sensory; SMA, supplementary motor area; M1, motor cortex; CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale.

other hand, while the tic symptoms of some patients start to subside at approximately 17 years of age, approximately 23% of severe tic cases become intractable [57–59]. Additionally, the PUTS tool for PU assessment is self-reported, and its diagnostic validity in young patients is limited, making it challenging to use in this population [26]. Therefore, developing a structured interview to assess PU in young patients may be a valuable direction for future research. Traditionally, PUs have often been observed to present three years after the onset of tics [60]. In addition, a recent study found that associations between reported urge levels and instantaneous tic intensity tended to be less pronounced in children and adolescents than in adult TS patients, which also supports the age effect in PU [61].

Furthermore, tics can be voluntarily suppressed for a brief period [62]. Thus, PU is a valuable cue for tic suppression. Behavioral treatments, such as habit reversal therapy (HRT), are considered a promising therapy for tics [8,63]. HRT, which is widely used to treat TS, has been confirmed by numerous studies to be effective [64–66]. For instance, a meta-analysis of HRT showed that PU is closely related to tic symptoms [8,67]. Detecting PU is the first step in HRT [68]. The therapy aims to increase awareness of urges and to help patients develop coping behaviors to replace tic symptoms [69]. This implies that greater awareness of PU leads to improved HRT efficacy. Furthermore, several studies have reported that PUs may play a crucial role in maintaining TD and have confirmed that PUs have a strong association with tic symptoms [11,60].

The widely accepted neurobiological basis for TS is dysfunction of the cortico-striatal-thalamo-cortical (CSTC) circuit, as supported by numerous neuroimaging studies [13,39,45,70]. These studies have shown that aberrant activity in the striatum may be linked to PUs. Structural MRI data, such as gray matter volume, cortical thickness, and connectivity matrices obtained from resting/task-state fMRI data, provide valuable morphological insights into PUs. Decreased gray matter thickness in the insula and sensorimotor cortex has been linked to PUs in young people with TS [13]. Whole-brain analysis of cortical (gray matter) thickness demonstrated that in young adults with TS, a reduction in cortical thickness within the insula, sensorimotor cortex, anterior cingulate, and insula was associated with higher ratings of PU severity and was significantly lower than that in a group of typically developing controls [13].

At the neurochemical level, dopaminergic modulation of glutamatergic corticostriatal afferents has been linked to the expression of diverse motor and nonmotor symptoms, including those seen in TS [71]. This anatomical substrate is reflected in the lower functional connectivity between the orbitofrontal cortex and sensorimotor cortex, between the inferior frontal gyrus and the putamen, and between the inferior frontal gyrus and insula as PU severity increases [34,43]. The SMA shows a broader profile of crosscorrelation with the motor cortex during tics compared to that during intentional movements, with its proportion varying with premonitory sensations [18]. Increased PU frequency was found to be associated with greater connectivity between the primary motor cortex (M1) and the caudate nuclei and increased transfer of information between M1 and the insula [72]. Moreover, greater PU severity was associated with greater activity in the hippocampus, middle temporal gyrus and subcortex [55].

The insula has been indicated to play a critical role in PU, suggesting that it is associated with the urge-to-tic [19]. The brain network involving the insula, ACC, and SMA is associated not only with the neural mechanism of PU but also with tic symptoms [73,74]. Further imaging studies are needed to better understand the relationship between PU and tic symptoms in the future.

Overall, the current neuroimaging research suggests that PUs may be an early component of a network that includes the insula, ACC, and SMA. The insula appears to play a key role in the generation of PUs, connecting the sensory and emotional aspects of PUs. Moreover, the ACC and SMA may be involved in the urge-to-tic. These areas are recognized as important nodes of the salience network, suggesting that this network may play a role in both urge generation and the urge-to-tic. Further studies are required to fully understand PUs at the network level.

In addition to the generation of PUs, PU inhibition is also an important aspect to consider. Evidence from multiple studies has indicated that TS patients exhibit dysfunction in the inhibition of PUs [75–77]. This evidence highlights the need to investigate the role of inhibition in the development of PUs. Of note, impaired automatic inhibition has been reported [78]. We speculate that the generation and inhibition of PUs appear to be interrelated processes, and an imbalance between them may contribute to an increased urge-to-tic. Whether PUs translate into tics may depend on the balance between these two processes.

To advance PU research, a reliable and validated measure of sensory symptom severity is crucial. One widely used instrument is the PUTS, which was developed by Woods and his team [14]. The PUTS was optimized to nine items and has been widely used in clinical practice [78–80]. Multiple studies have provided evidence for the reliability and validity of PUTS [21,26,81]. However, new assessment tools have also been developed, including the Individualized Premonitory Urge for Tics Scale (I-PUTS) [30] and the Rumination and Awareness Scale for Tic-associated Sensations (RASTS) [40]. While these tools provide new insights into PUs, they also have limitations, and further development is necessary. The inclusion of multiple dimensions, such as location, severity, frequency, and intensity, is important for future advancements in PU assessment.

This meta-analysis supports the correlation between PUs and tic symptoms, reinforcing the significance of PUs in the treatment of TDs. The findings indicated that patient age is a crucial moderator affecting PU severity, implying that the impact of age should be considered during PU assessments. Considering these results, future research should be directed toward further understanding the nature of PUs. However, several challenges need to be addressed in future studies. First, current PU assessment tools are subjective and lack objectivity. New tools such as the I-PUTS and the RASTS require further validation across different countries and languages. Second, neuroimaging studies face difficulties in separating the processing of PUs and tic symptoms. Thus, future studies should aim to explore PUs at the neural circuitry level. Third, while computational psychiatry approach holds potential in understanding PUs, it requires further development to align with clinical practices. Finally, considering dopaminergic hyperinnervation in TS, investigating PUs based on this aspect may also be worthwhile.

There were two limitations to this study. First, the sample size of the included studies was small, which may have affected the accuracy of the results. Second, most of the included studies were from clinical samples with different inclusion and exclusion criteria, which might increase the heterogeneity of the meta-analysis.

5. Conclusions

The present meta-regression study confirmed the positive correlation between the severity of tics and PUs. Moreover, patient age appears to be a significant influencing factor for PU, as evidenced by the increasing PUTS score with age and tic severity. Neural correlates of PUs were associated with the insula, ACC and SMA, as well as the network associated with these regions. To further support these findings, future studies with larger sample sizes are necessary.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

YLL and LPY were responsible for the extraction and drafting of the manuscript, as well as the analysis of data. HZ and XBW assisted with the search for relevant articles and creation of figures. YL and YHC were involved in the design and revision of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have read and approved the final manuscript, and have contributed significantly to the work. All authors have agreed to take responsibility for all aspects of the study.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10. 31083/j.jin2206159.

References

- Li Y, Zhang JS, Wen F, Lu XY, Yan CM, Wang F, *et al.* Premonitory urges located in the tongue for tic disorder: Two case reports and review of literature. World Journal of Clinical Cases. 2019; 7: 1508–1514.
- [2] Rajagopal S, Seri And S, Cavanna AE. Premonitory urges and sensorimotor processing in Tourette syndrome. Behavioural Neurology. 2013; 27: 65–73.
- [3] Nam SH, Park J, Park TW. Clinical Aspects of Premonitory Urges in Patients with Tourette's Disorder. Journal of Child & Adolescent Psychiatry. 2019; 30: 50–56.
- [4] Leckman JF, Walker DE, Cohen DJ. Premonitory urges in Tourette's syndrome. The American Journal of Psychiatry. 1993; 150: 98–102.
- [5] Gulisano M, Calì P, Palermo F, Robertson M, Rizzo R. Premonitory Urges in Patients with Gilles de la Tourette Syndrome: An Italian Translation and a 7-Year Follow-up. Journal of Child and Adolescent Psychopharmacology. 2015; 25: 810–816.
- [6] Essing J, Jakubovski E, Psathakis N, Cevirme SN, Leckman JF, Müller-Vahl KR. Premonitory Urges Reconsidered: Urge Location Corresponds to Tic Location in Patients With Primary Tic Disorders. Journal of Movement Disorders. 2022; 15: 43–52.
- [7] Kyriazi M, Kalyva E, Vargiami E, Krikonis K, Zafeiriou D. Premonitory Urges and Their Link With Tic Severity in Children and Adolescents With Tic Disorders. Frontiers in Psychiatry. 2019; 10: 569.
- [8] Li Y, Wang F, Liu J, Wen F, Yan C, Zhang J, et al. The Correlation Between the Severity of Premonitory Urges and Tic Symptoms: A Meta-Analysis. Journal of Child and Adolescent Psychopharmacology. 2019; 29: 652–658.
- [9] Liu S, Li Y, Cui Y. Review of habit reversal training for tic disorders. Pediatric Investigation. 2020; 4: 127–132.
- [10] Brandt VC, Beck C, Sajin V, Baaske MK, Bäumer T, Beste C, et al. Temporal relationship between premonitory urges and tics in Gilles de la Tourette syndrome. Cortex. 2016; 77: 24–37.
- [11] Reese HE, Scahill L, Peterson AL, Crowe K, Woods DW, Piacentini J, *et al.* The premonitory urge to tic: measurement, characteristics, and correlates in older adolescents and adults. Behavior Therapy. 2014; 45: 177–186.
- [12] Banaschewski T, Woerner W, Rothenberger A. Premonitory sensory phenomena and suppressibility of tics in Tourette syndrome: developmental aspects in children and adolescents. Developmental Medicine and Child Neurology. 2003; 45: 700– 703.
- [13] Draper A, Jackson GM, Morgan PS, Jackson SR. Premonitory urges are associated with decreased grey matter thickness within

the insula and sensorimotor cortex in young people with Tourette syndrome. Journal of Neuropsychology. 2016; 10: 143–153.

- [14] Woods DW, Piacentini J, Himle MB, Chang S. Premonitory Urge for Tics Scale (PUTS): initial psychometric results and examination of the premonitory urge phenomenon in youths with Tic disorders. Journal of Developmental and Behavioral Pediatrics. 2005; 26: 397–403.
- [15] Openneer TJC, Tárnok Z, Bognar E, Benaroya-Milshtein N, Garcia-Delgar B, Morer A, *et al.* The Premonitory Urge for Tics Scale in a large sample of children and adolescents: psychometric properties in a developmental context. An EMTICS study. European Child & Adolescent Psychiatry. 2020; 29: 1411–1424.
- [16] Sambrani T, Jakubovski E, Müller-Vahl KR. New Insights into Clinical Characteristics of Gilles de la Tourette Syndrome: Findings in 1032 Patients from a Single German Center. Frontiers in Neuroscience. 2016; 10: 415.
- [17] Sutherland Owens AN, Miguel EC, Swerdlow NR. Sensory gating scales and premonitory urges in Tourette syndrome. The Scientific World Journal. 2011; 11: 736–741.
- [18] Tinaz S, Malone P, Hallett M, Horovitz SG. Role of the right dorsal anterior insula in the urge to tic in Tourette syndrome. Movement Disorders. 2015; 30: 1190–1197.
- [19] Jackson SR, Loayza J, Crighton M, Sigurdsson HP, Dyke K, Jackson GM. The role of the insula in the generation of motor tics and the experience of the premonitory urge-to-tic in Tourette syndrome. Cortex. 2020; 126: 119–133.
- [20] Cavanna AE, Black KJ, Hallett M, Voon V. Neurobiology of the Premonitory Urge in Tourette's Syndrome: Pathophysiology and Treatment Implications. The Journal of Neuropsychiatry and Clinical Neurosciences. 2017; 29: 95–104.
- [21] Rae CL, Parkinson J, Betka S, Gouldvan Praag CD, Bouyagoub S, Polyanska L, *et al.* Amplified engagement of prefrontal cortex during control of voluntary action in Tourette syndrome. Brain Communications. 2020; 2: fcaa199.
- [22] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015; 4: 1.
- [23] Quigley JM, Thompson JC, Halfpenny NJ, Scott DA. Critical appraisal of nonrandomized studies-A review of recommended and commonly used tools. Journal of Evaluation in Clinical Practice. 2019; 25: 44–52.
- [24] Williams V, Boylan AM, Nunan D. Critical appraisal of qualitative research: necessity, partialities and the issue of bias. BMJ Evidence-Based Medicine. 2020; 25: 9–11.
- [25] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. International Journal of Surgery. 2010; 8: 336–341.
- [26] Brandt VC, Beck C, Sajin V, Anders S, Münchau A. Convergent Validity of the PUTS. Frontiers in Psychiatry. 2016; 7: 51.
- [27] Steinberg T, Shmuel Baruch S, Harush A, Dar R, Woods D, Piacentini J, *et al*. Tic disorders and the premonitory urge. Journal of Neural Transmission. 2010; 117: 277–284.
- [28] Rozenman M, Johnson OE, Chang SW, Woods DW, Walkup JT, Wilhelm S, *et al.* Relationships between Premonitory Urge and Anxiety in Youth with Chronic Tic Disorders. Children's Health Care. 2015; 44: 235–248.
- [29] Kano Y, Matsuda N, Nonaka M, Fujio M, Kuwabara H, Kono T. Sensory phenomena related to tics, obsessive-compulsive symptoms, and global functioning in Tourette syndrome. Comprehensive Psychiatry. 2015; 62: 141–146.
- [30] McGuire JF, McBride N, Piacentini J, Johnco C, Lewin AB, Murphy TK, *et al.* The premonitory urge revisited: An individualized premonitory urge for tics scale. Journal of Psychiatric Research. 2016; 83: 176–183.
- [31] Anis S, Zalomek C, Korczyn AD, Rosenberg A, Giladi N, Gurevich T. Medical Cannabis for Gilles de la Tourette Syn-

drome: An Open-Label Prospective Study. Behavioural Neurology. 2022; 2022: 5141773.

- [32] Ramsey KA, Essoe JKY, Storch EA, Lewin AB, Murphy TK, McGuire JF. Urge Intolerance and Impairment Among Youth with Tourette's and Chronic Tic Disorders. Child Psychiatry and Human Development. 2021; 52: 761–771.
- [33] Baumung L, Müller-Vahl K, Dyke K, Jackson G, Jackson S, Golm D, *et al.* Developing the Premonitory Urges for Tic Disorders Scale-Revised (PUTS-R). Journal of Neuropsychology. 2021; 15: 129–142.
- [34] Bhikram T, Arnold P, Crawley A, Abi-Jaoude E, Sandor P. The functional connectivity profile of tics and obsessive-compulsive symptoms in Tourette Syndrome. Journal of Psychiatric Research. 2020; 123: 128–135.
- [35] Capriotti MR, Brandt BC, Turkel JE, Lee HJ, Woods DW. Negative Reinforcement and Premonitory Urges in Youth With Tourette Syndrome: An Experimental Evaluation. Behavior Modification. 2014; 38: 276–296.
- [36] Fu M, Wei H, Meng X, Chen H, Shang B, Chen F, et al. Effects of Low-Frequency Repetitive Transcranial Magnetic Stimulation of the Bilateral Parietal Cortex in Patients With Tourette Syndrome. Frontiers in Neurology. 2021; 12: 602830.
- [37] Gu Y, Li Y, Cui Y. Correlation between premonitory urges and tic symptoms in a Chinese population with tic disorders. Pediatric Investigation. 2020; 4: 86–90.
- [38] Isaacs D, Key AP, Cascio CJ, Conley AC, Walker HC, Wallace MT, et al. Sensory Hypersensitivity Severity and Association with Obsessive-Compulsive Symptoms in Adults with Tic Disorder. Neuropsychiatric Disease and Treatment. 2020; 16: 2591–2601.
- [39] Jackson SR, Sigurdsson HP, Dyke K, Condon M, Jackson GM. The role of the cingulate cortex in the generation of motor tics and the experience of the premonitory urge-to-tic in Tourette syndrome. Journal of Neuropsychology. 2021; 15: 340–362.
- [40] Matsuda N, Nonaka M, Kono T, Fujio M, Nobuyoshi M, Kano Y. Premonitory Awareness Facilitates Tic Suppression: Subscales of the Premonitory Urge for Tics Scale and a New Self-Report Questionnaire for Tic-Associated Sensations. Frontiers in Psychiatry. 2020; 11: 592.
- [41] Sigurdsson HP, Jackson SR, Jolley L, Mitchell E, Jackson GM. Alterations in cerebellar grey matter structure and covariance networks in young people with Tourette syndrome. Cortex. 2020; 126: 1–15.
- [42] Sigurdsson HP, Jackson SR, Kim S, Dyke K, Jackson GM. A feasibility study for somatomotor cortical mapping in Tourette syndrome using neuronavigated transcranial magnetic stimulation. Cortex. 2020; 129: 175–187.
- [43] Eddy CM, Cavanna AE, Rickards HE, Hansen PC. Temporoparietal dysfunction in Tourette syndrome: Insights from an fMRI study of Theory of Mind. Journal of Psychiatric Research. 2016; 81: 102–111.
- [44] Buse J, Beste C, Roessner V. Neural correlates of prediction violations in boys with Tourette syndrome: Evidence from harmonic expectancy. The World Journal of Biological Psychiatry. 2018; 19: 130–141.
- [45] Ramkiran S, Heidemeyer L, Gaebler A, Shah NJ, Neuner I. Alterations in basal ganglia-cerebello-thalamo-cortical connectivity and whole brain functional network topology in Tourette's syndrome. NeuroImage. Clinical. 2019; 24: 101998.
- [46] Puts NAJ, Harris AD, Crocetti D, Nettles C, Singer HS, Tommerdahl M, *et al.* Reduced GABAergic inhibition and abnormal sensory symptoms in children with Tourette syndrome. Journal of Neurophysiology. 2015; 114: 808–817.
- [47] He JL, Mikkelsen M, Huddleston DA, Crocetti D, Cecil KM, Singer HS, et al. Frequency and Intensity of Premonitory Urgesto-Tic in Tourette Syndrome Is Associated With Supplementary Motor Area GABA+ Levels. Movement Disorders. 2022; 37:

563-573.

- [48] Cavanna AE, Draganski B, Martino D, Robertson MM, Defazio G, Monaco F, *et al.* Premonitory urges in tourette syndrome: A voxel based morphometry and diffusion tensor imaging MRI study. Journal of Neurology Neurosurgery and Psychiatry. 2008; 79: 972–972.
- [49] Hampson M, Tokoglu F, King RA, Constable RT, Leckman JF. Brain areas coactivating with motor cortex during chronic motor tics and intentional movements. Biological Psychiatry. 2009; 65: 594–599.
- [50] Wang Z, Maia TV, Marsh R, Colibazzi T, Gerber A, Peterson BS. The neural circuits that generate tics in Tourette's syndrome. The American Journal of Psychiatry. 2011; 168: 1326–1337.
- [51] Ganos C, Kahl U, Brandt V, Schunke O, Bäumer T, Thomalla G, *et al.* The neural correlates of tic inhibition in Gilles de la Tourette syndrome. Neuropsychologia. 2014; 65: 297–301.
- [52] Kanaan AS, Gerasch S, García-García I, Lampe L, Pampel A, Anwander A, *et al.* Pathological glutamatergic neurotransmission in Gilles de la Tourette syndrome. Brain. 2017; 140: 218– 234.
- [53] Sigurdsson HP, Pépés SE, Jackson GM, Draper A, Morgan PS, Jackson SR. Alterations in the microstructure of white matter in children and adolescents with Tourette syndrome measured using tract-based spatial statistics and probabilistic tractography. Cortex. 2018; 104: 75–89.
- [54] Botteron HE, Richards CA, Nishino T, Ueda K, Acevedo HK, Koller JM, *et al.* The urge to blink in Tourette syndrome. Cortex. 2019; 120: 556–566.
- [55] Bhikram T, Crawley A, Arnold P, Abi-Jaoude E, Sandor P. Neuroimaging the emotional modulation of urge inhibition in Tourette Syndrome. Cortex. 2021; 135: 341–351.
- [56] Leckman JF, Peterson BS, King RA, Scahill L, Cohen DJ. Phenomenology of tics and natural history of tic disorders. Advances in Neurology. 2001; 85: 1–14.
- [57] Coffey BJ, Biederman J, Spencer T, Geller DA, Faraone SV, Bellordre CA. Informativeness of structured diagnostic interviews in the identification of Tourette's disorder in referred youth. The Journal of Nervous and Mental Disease. 2000; 188: 583–588.
- [58] Fahim C, Yoon U, Das S, Lyttelton O, Chen J, Arnaoutelis R, et al. Somatosensory-motor bodily representation cortical thinning in Tourette: effects of tic severity, age and gender. Cortex. 2010; 46: 750–760.
- [59] Pappert EJ, Goetz CG, Louis ED, Blasucci L, Leurgans S. Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. Neurology. 2003; 61: 936–940.
- [60] Houghton DC, Capriotti MR, Conelea CA, Woods DW. Sensory Phenomena in Tourette Syndrome: Their Role in Symptom Formation and Treatment. Current Developmental Disorders Reports. 2014; 1: 245–251.
- [61] Langelage J, Verrel J, Friedrich J, Siekmann A, Schappert R, Bluschke A, *et al*. Urge-tic associations in children and adolescents with Tourette syndrome. Scientific Reports. 2022; 12: 16008.
- [62] Jankovic J. Tourette syndrome. Phenomenology and classification of tics. Neurologic Clinics. 1997; 15: 267–275.
- [63] Pringsheim T, Okun MS, Müller-Vahl K, Martino D, Jankovic J, Cavanna AE, *et al.* Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. Neurology. 2019; 92: 896–906.
- [64] Fründt O, Woods D, Ganos C. Behavioral therapy for Tourette syndrome and chronic tic disorders. Neurology. Clinical Prac-

tice. 2017; 7: 148-156.

- [65] McGuire JF, Ricketts EJ, Scahill L, Wilhelm S, Woods DW, Piacentini J, et al. Effect of behavior therapy for Tourette's disorder on psychiatric symptoms and functioning in adults. Psychological Medicine. 2020; 50: 2046–2056.
- [66] Nissen JB, Parner ET, Thomsen PH. Predictors of therapeutic treatment outcome in adolescent chronic tic disorders. BJPsych Open. 2019; 5: e74.
- [67] McGuire JF, Piacentini J, Brennan EA, Lewin AB, Murphy TK, Small BJ, et al. A meta-analysis of behavior therapy for Tourette Syndrome. Journal of Psychiatric Research. 2014; 50: 106–112.
- [68] Wile DJ, Pringsheim TM. Behavior Therapy for Tourette Syndrome: A Systematic Review and Meta-analysis. Current Treatment Options in Neurology. 2013; 15: 385–395.
- [69] Viefhaus P, Döpfner M, Dachs L, Goletz H, Görtz-Dorten A, Kinnen C, et al. Treatment satisfaction following routine outpatient cognitive-behavioral therapy of adolescents with mental disorders: a triple perspective of patients, parents and therapists. European Child & Adolescent Psychiatry. 2019; 28: 543–556.
- [70] Cui Y, Jin Z, Chen X, He Y, Liang X, Zheng Y. Abnormal baseline brain activity in drug-naïve patients with Tourette syndrome: a resting-state fMRI study. Frontiers in Human Neuroscience. 2014; 7: 913.
- [71] Maia TV, Conceição VA. The Roles of Phasic and Tonic Dopamine in Tic Learning and Expression. Biological Psychiatry. 2017; 82: 401–412.
- [72] Wu SW, Maloney T, Gilbert DL, Dixon SG, Horn PS, Huddleston DA, *et al.* Functional MRI-navigated repetitive transcranial magnetic stimulation over supplementary motor area in chronic tic disorders. Brain Stimulation. 2014; 7: 212–218.
- [73] Jackson SR, Parkinson A, Jung J, Ryan SE, Morgan PS, Hollis C, et al. Compensatory neural reorganization in Tourette syndrome. Current Biology. 2011; 21: 580–585.
- [74] Rae CL, Larsson DEO, Eccles JA, Ward J, Critchley HD. Subjective embodiment during the rubber hand illusion predicts severity of premonitory sensations and tics in Tourette Syndrome. Consciousness and Cognition. 2018; 65: 368–377.
- [75] Brandt VC, Moczydlowski A, Jonas M, Boelmans K, Bäumer T, Brass M, *et al.* Imitation inhibition in children with Tourette syndrome. Journal of Neuropsychology. 2019; 13: 82–95.
- [76] Fan S, Cath DC, van der Werf YD, de Wit S, Veltman DJ, van den Heuvel OA. Trans-diagnostic comparison of response inhibition in Tourette's disorder and obsessive-compulsive disorder. The World Journal of Biological Psychiatry. 2018; 19: 527–537.
- [77] Isaacs D, Riordan H. Sensory hypersensitivity in Tourette syndrome: A review. Brain & Development. 2020; 42: 627–638.
- [78] Rawji V, Modi S, Latorre A, Rocchi L, Hockey L, Bhatia K, et al. Impaired automatic but intact volitional inhibition in primary tic disorders. Brain. 2020; 143: 906–919.
- [79] Forcadell E, Garcia-Delgar B, Nicolau R, Pérez-Vigil A, Cordovilla C, Lázaro L, *et al.* Tic disorders and premonitory urges: validation of the Spanish-language version of the Premonitory Urge for Tics Scale in children and adolescents. Neurologia. 2020. (online ahead of print)
- [80] Kim M, Chung SK, Yang JC, Park JI, Nam SH, Park TW. Development of the Korean Form of the Premonitory Urge for Tics Scale: A Reliability and Validity Study. Journal of Child & Adolescent Psychiatry. 2020; 31: 146–153.
- [81] Li Y, Woods DW, Gu Y, Yu L, Yan J, Wen F, *et al.* Psychometric Properties of the Chinese Version of the Premonitory Urge for Tics Scale: A Preliminary Report. Frontiers in Psychology. 2021; 12: 573803.