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***Tourette syndrome and COVID-19 pandemic - impact of  
obsessive-compulsive symptoms and anxiety on tic worsening***

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## LIST OF INITIALS AND ABBREVIATIONS

ADHDA	Attention-deficit hyperactivity disorder
CHUC	Coimbra Hospital and University Centre
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
DASS-21	Depression Anxiety Stress Scale 21 items
DSM-5	The Diagnostic and Statistical Manual of Mental Disorders
NCS-R	National Comorbidity Survey Replication
NOSI	Non-obscene socially inappropriate symptoms
OC	Obsessive-compulsive
OCD	Obsessive-compulsive disorder
OCI-R	Obsessive-Compulsive Inventory–Revised
OCRD	Obsessive-compulsive-related disorders
OCS	Obsessive-compulsive symptoms
OCTD	Obsessive-compulsive Tic Disorders
$p$	“ $p$ ” value of significance
PUTS	Premonitory Urge for Tics Scale
SARS-CoV-2	Severe acute respiratory syndrome corona virus 2
TD	Tic disorder
TS	Tourette syndrome
WHO	World Health Organization

## ABSTRACT

**Background:** Tourette Syndrome (TS) is a neuropsychiatric disorder with common onset during childhood and clinically characterized by chronic motor and vocal tics, frequently preceded by premonitory urges. At least one neuropsychiatric comorbidity is often associated, typically attention-deficit/hyperactivity disorder and obsessive-compulsive disorder. Coronavirus disease 2019 (COVID-19) pandemic induced marked daily life disruptions and anxiety capable of enhancing tics and other psychiatric conditions. We aimed to: compare differences in premonitory urges, obsessive-compulsive symptoms (OCS) and anxiety between TS patients reporting tic worsening vs. TS patients reporting that their tics remained stable during the COVID-19 pandemic; explore the role of OCS and anxiety on the tics' course during the COVID-19 pandemic.

**Material and methods:** We performed an observational cross-sectional study. Twenty TS patients were invited through the Portuguese Tourette's Syndrome Association social network, during July and December 2021, to perform an online survey, which included: social-demographic questions, a simplified 5-grade scale to evaluate COVID-19-related tic worsening and the Portuguese versions of the: Obsessive-Compulsive Inventory–Revised, Depression Anxiety Stress Scale and Premonitory Urge for Tics Scale. Descriptive, correlational, and mediation analyses were performed using SPSS 26 and PROCESS v3.5.

**Results:** TS patients reporting COVID-19-related tic worsening (50%), also experienced more anxiety and hoarding symptoms. Correlations between hoarding, anxiety and COVID-19-related tic worsening were positive and significant. Mediation analysis revealed that the effect of hoarding on COVID-19-related tic worsening was significant only when mediated by anxiety. On the other hand, anxiety showed a direct effect on COVID-19-related tic worsening.

**Discussion:** Anxiety and hoarding symptoms emerged as a central phenomena in TS patients reporting COVID-19-related tic worsening. Anxiety is a frequent comorbidity in TS but also arose as an epiphenomenon, which may contribute to the strong correlation observed with tic worsening. Mediation analyses showed that hoarding behaviors that are severe enough to generate substantial anxiety, induce, through this pathway, COVID-19-related tic worsening. The effect of anxiety was strong enough to induce tic worsening.

**Conclusion:** During the COVID-19 pandemic, anxiety played a central role in TS, by inducing tic worsening and mediating the impact of hoarding behaviors on tic severity, in our sample of 20 TS patients. Therapeutic strategies for TS patients during the COVID-19 pandemics and similar situations should take into account the effect of the underlying processes (hoarding and anxiety symptoms) on tic severity.

**Keywords:** Tourette Syndrome, Hoarding, Anxiety, Tics, COVID-19 pandemic

## RESUMO

**Introdução:** A síndrome de Tourette (ST) é uma perturbação neuropsiquiátrica com início na infância e caracterizada por tiques motores e fónicos, frequentemente precedidos por sensações premonitórias. Pelo menos uma comorbilidade neuropsiquiátrica está associada, tipicamente a Perturbação de Hiperatividade e Défice de Atenção e a Perturbação Obsessivo-Compulsiva. A doença do coronavírus 2019 (COVID-19) induziu disrupções na rotina diária e ansiedade capazes de exacerbar tiques ou outras condições psiquiátricas. **Objetivos:** comparar níveis de sensações premonitórias, sintomas obsessivo-compulsivos (SOC) e ansiedade entre doentes com ST que agravaram os tiques e os que reportaram estabilidade dos tiques durante a pandemia COVID-19; explorar o papel dos SOC e ansiedade no curso dos tiques durante a pandemia.

**Materias e métodos:** Realizámos um estudo observacional transversal. Vinte doentes com ST, convidados pela Associação Portuguesa de Síndrome de Tourette entre Julho e Dezembro de 2021, preencheram um questionário online que incluiu: questões socio-demográficas, uma escala simplificada de 5 graus relativa ao agravamento dos tiques durante a pandemia COVID-19 e a versão portuguesa das escalas: *Obsessive-Compulsive Inventory–Revised*, *Depression Anxiety Stress Scale* e *Premonitory Urge for Tics Scale*. Realizámos análises descritivas, correlacionais e de mediação através do SPSS 26 e PROCESS v3.5.

**Resultados:** Doentes com ST com agravamento dos tiques na pandemia COVID-19 (50%), reportaram mais ansiedade e sintomas de acumulação. Correlações entre acumulação, ansiedade e agravamento dos tiques foram positivas e significativas. Análises de mediação revelaram que o efeito da acumulação no agravamento dos tiques só era significativo quando mediado pela a ansiedade. A ansiedade mostrou um efeito direto no agravamento dos tiques durante a pandemia COVID-19.

**Discussão:** Ansiedade e sintomas de acumulação foram um fenómeno central nos doentes com ST que agravaram os tiques na pandemia COVID-19. A ansiedade, comorbilidade frequente na ST, também surgiu como um epifenómeno que pode ter contribuído para a forte correlação com o agravamento dos tiques. Análises de mediação mostraram que sintomas de acumulação suficientemente graves para gerar ansiedade, induziram agravamento dos tiques. O efeito da ansiedade foi forte o suficiente para induzir agravamento dos tiques.

**Conclusão:** Durante a pandemia COVID-19, ansiedade desempenhou um papel central na ST, capaz de provocar agravamento dos tiques e mediar o impacto de sintomas de acumulação na severidade dos tiques, nesta amostra de 20 doentes com ST. Estratégias terapêuticas direcionadas a doentes com ST na pandemia e situações semelhantes devem contemplar o efeito de processos subjacentes (sintomas de acumulação e ansiedade) na severidade dos tiques.

**Palavras-chave:** Síndrome de Tourette, Acumulação, Ansiedade, Tiques, Pandemia COVID-19

## **INTRODUCTION**

### **TS and its main features**

Tourette syndrome (TS) is a neuropsychiatric disorder characterized by chronic motor and vocal tics, with a very common onset in childhood and a maximum severity at 5-7 years of age. The estimated prevalence in childhood is between 0,1 and 1%, where males are the most affected.<sup>1</sup>

DSM-5 criteria require two or more motor tics and at least one vocal tic, occurring for over 12 months, almost every day, with an onset before 18 years.<sup>2</sup> Tics may be simple, involving a single muscular group, or complex, through coordination of movements and vocalizations.<sup>3</sup> Tic execution is frequently preceded by premonitory urges, which are sensory feelings or urges to move that are frequently uncomfortable. Simple motor tics are the first to flourish, followed by vocal tics that typically tend to appear several years later. A rostral-caudal progression of tics is common. As TS patients ages, motor and vocal tics become more complex, following a wax and waning pattern. Focusing attention on motivating tasks may transitorily reduce manifestations of tics. Another feature is that tics may be inducible or exacerbated while seeing someone's tic or talking about tics.<sup>4</sup>

### **TS and its main comorbidities**

The majority of TS patients present at least one neuropsychiatric comorbidity associated, typically attention-deficit/hyperactivity disorder (ADHD) (60%) or OCD (30%-60%).<sup>4</sup> Other less frequent comorbidities are anxiety, mood, elimination, sleep, and social cognition disturbances, as well as disruptive behavior and autism spectrum disorder.<sup>4-6</sup>

Comorbidities negatively affect the quality of life of TS patients in several domains.<sup>7</sup> Individuals with both tics and OCD exhibit worse outcomes with more severe tics, higher levels of anxiety, depressive symptoms and impaired global function. On the other hand, subjects with both tics and ADHD report impaired global functioning, lower impulse control, and higher levels of aggressiveness and irritability behaviors.<sup>8,9</sup> Associations between ADHD, OCD and tics are partially explained by the involvement of overlapping cortico-striato-thalamo-cortical circuits<sup>4,8,10</sup>.

The intricate relationship between tics and OCD, including shared genetic vulnerabilities, supported the inclusion of a "tic-related" subtype in OCD diagnosis in DSM-5.<sup>11</sup> Tic patients with OCD have a higher genetic load.<sup>8,9</sup> Clinically, tics that are preceded by premonitory urges and other related sensory phenomena (eg.: a just-right experience) may be challenging to differentiate from compulsions of obsessive-compulsive disorder (OCD). In some cases of comorbid TS and OCD, repetitive motor actions may become so indistinguishable that they are called compulsive tics or "compultics".<sup>10,12</sup>

OCD is a heterogeneous neuropsychiatric disorder included in a group of related disorders called obsessive-compulsive-related disorders (OCRD).<sup>11</sup> It is characterized by recurrent intrusive and egodystonic thoughts (obsessions) that generate anxiety which is transitorily reduced by the performance of repetitive behaviors (compulsions). The estimated lifetime prevalence of OCD is 2,3%,



and mainly females are affected during adolescence, at approximately 19,5 years. In contrast, males usually have their onset before 10 years of age.<sup>13</sup>

OCD symptoms fall into several dimensions, most frequently pathological doubt (by checking) symmetry (by ordering), hoarding and forbidden thoughts (related to moral, aggressive, sexual and religious issues).<sup>13–16</sup> Otherwise, symmetry, forbidden thoughts, hoarding dimensions, and sensory phenomena are often seen in patients with comorbid TS. Similar to Obsessive-compulsive Tic Disorders (OCTD), symmetry symptoms occur mostly in males, with an early OCD onset.<sup>15,17</sup> Accordingly, investigation suggests that symmetry symptoms without tics are linked to increased TS genetic susceptibility.<sup>18</sup>

### **Impact of COVID-19 on TS symptoms and its comorbidities:**

Similar to the well-described wax and waning pattern of tics, TS comorbidities also oscillate across time. This feature can be induced by daily life disruptions such as the coronavirus disease 2019 (COVID-19) pandemic.<sup>19</sup>

COVID-19 is caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), a single-stranded RNA virus.<sup>20</sup> By 11 March 2021, World Health Organization (WHO) declared COVID-19 as a pandemic.<sup>21</sup> To hold and control the COVID-19 outbreak, lockdown measures were implemented by several nations worldwide. This means sudden social, professional, and economic changes that involve mental health risks for the overall population, mostly the ones with mental health disturbances.<sup>19</sup> Previous research showed that up to 40% of the individuals on isolation or quarantine experienced psychiatric complications, most frequently anxiety and depression.<sup>19</sup>

TS patients may be more vulnerable to the anxiety generated by the pandemic stressors (eg.: quarantine issues, financial worries, routine variations, uncertainties about the future, lack of physical exercise, and parental anxiety).<sup>20,22</sup>

Spending more time at home may also enhance tics, since being less focused on doing tasks may disrupt previous tic-attenuating coping strategies.<sup>19</sup> Routines, like socializing and working, may have a positive effect on tics. *Conte et al.*<sup>19</sup> reported an overall worsening of TS symptoms (over 67% of the individuals), especially motor tics, during COVID-19 lockdown. In a different study, 44% of the participants had their tics stabilized.<sup>22</sup> On the other hand, *Graziola et al.*<sup>23</sup> showed a significant improvement of tic severity, accounted by a decrease in tic impairment.

Non-obscene socially inappropriate symptoms (NOSI) occurring in TS may also lead to life impairment, especially during the COVID-19. Coughing, sneezing, spitting tics, not keeping social distance, or touching other people may generate substantial stigma to TS patients<sup>22</sup> as well as legal repercussions.<sup>20</sup>

Concerning TS comorbidities, *Conte et al.*<sup>19</sup> reported higher levels of OCS. According to *Graziola et al.*<sup>23</sup>, more rituals, checking compulsions, and contamination obsessions were noticed, even though cleaning compulsions had not worsened. Other features such as anxiety, sleep disturbances, and eating disorders were also observed.<sup>19,23</sup>

The extent to which having TS with comorbid OCS was associated with tic's severity and mental health problems during the COVID-19 pandemic is yet to be clarified. Repetitiveness is a core feature shared

across the tic and OC spectrums. Symptoms of TS and OCD also overlap in that anxiety is a common triggering/worsening factor. Additionally, having routines is a key strategy in treating these patients. Considering the high comorbidity between TS and OCD and the effect of COVID-19 pandemics on shared associated factors – anxiety and loss of routines –, we hypothesize that TS patients with OCS would be more vulnerable to the effects of COVID-19-generated anxiety on tic worsening, during the pandemic. This was an exploratory study since, to our knowledge, only one study investigated the association between OC dimensions, in TS patients and the COVID-19 pandemics. The authors found an increase in rituals involving other persons, checking compulsions and contamination obsessions.<sup>23</sup>

We aimed to:

- a) analyze the frequency of TS patients reporting tic's worsening during the COVID-19 pandemics;
- b) compare differences in premonitory urges, obsessive-compulsive symptoms (OCS) and anxiety between TS patients reporting tic worsening vs. TS patients reporting that their tics remained stable during the COVID-19 pandemic;
- c) explore the role of OCS and anxiety on the tics' course during the COVID-19 pandemic.

## MATERIAL AND METHODS

### Procedure

The present work is an observational correlational and transversal study that is part of an ongoing research project approved by the Ethical Committees of the Coimbra Hospital and University Centre (CHUC) – CHUC-022-19.

TS patients (n= 20; mean age  $29.9 \pm 10.5$  years) were invited to participate in this study through the Portuguese Tourette's Syndrome Association social network, during July and December 2021. Only participants who filled in an informed consent were included in the study and were asked to answer an online survey, including sociodemographic questions, validated Portuguese versions of self-reported questionnaires to evaluate OCS, psychological distress and the Portuguese preliminary versions of one questionnaire to evaluate premonitory urges. All participants reported having a TS diagnosis made by a neurologist or a psychiatrist and two of them also have children with TS diagnosis. The majority were Portuguese (75%; n= 15) and all participants were fluent in the Portuguese language.

### Measures

#### ***Premonitory Urge for Tics Scale (PUTS)*** <sup>24–28</sup>

The PUTS is the most used approach to assessing urges in TS. The scale is composed of 10 items answered on a 4-point Likert scale (range = 10–40). PUTS has good to acceptable reliability, in adolescents and adults and good convergent validity. Correlations with tic severity scores are in the low–medium range, indicating that these two phenomena are related but distinct constructs. In this study, we used the Portuguese version of the PUTS, which was translated by a group of researcher specialists in TS. In this study, was used the 9-item PUTS score (PUTS–9) because item 10 ('I am able to stop my tics even if only for a short period of time') is commonly dropped from the overall questionnaire score.

#### ***Obsessive-Compulsive Inventory – Revised (OCI-R)*** <sup>29,30</sup>

The Obsessive-Compulsive Inventory – Revised (OCI-R) is the short 18-item version of the original 42-item self-assessment questionnaire. The OCI-R evaluates the severity of six OC dimensions (hoarding, checking, ordering, neutralization, cleaning and obsessions), during the previous month, on a 5-point Likert scale from 0 (Not at all) to 4 (Extremely). The instrument was designed to be applied in clinical and non-clinical populations. The authors of the original OCI-R found an optimal cut-off score of 21 (sensitivity 65.6%; specificity 63.6%). In our study, we used the validated Portuguese version, which presented good psychometric proprieties (Cronbach alpha .90; Y-BOCS convergent validity analysis showed Pearson's coefficients  $>.70$ ; temporal stability .79).

### ***Depression Anxiety Stress Scale (DASS-21)***<sup>31,32</sup>

The Depression Anxiety Stress Scale (DASS-21) is a 21-item self-report instrument widely used to measure psychological distress, namely negative emotional states of depression, anxiety and stress among clinical and non-clinical populations. Participants are asked to answer on a Likert scale from 0 (Did not apply to me at all) to 3 (Applied to me very much). The DASS-21 Portuguese psychometric studies resulted in good parameters of reliability, construct, and concurrent validity and its factorial structure overlap with the original. For this study, we only applied the second-order factor “anxiety”.

### ***COVID-19 tic worsening***

To evaluate COVID-19 related tic worsening we asked patients if their tics got worse during the lockdown (in intensity, frequency, or duration), using a simplified 5-grade scale, from “My tics got a lot worse” to “My tics have improved a lot”. Then we joined the answers in two groups: participants who reported tic worsening and the participants who did not report tic worsening (joining the participants who reported either that their tics’ severity remained stable or improved).

## **Statistical analysis**

Descriptive, Spearman correlation and Mann-Whitney U analyses were conducted using the software SPSS, version 26. X<sup>2</sup> analyses were used to examine the dichotomous variables. The mediation analysis was exploratory and was performed using PROCESS macro (Model 4) for SPSS.<sup>33</sup> The effects were estimated with 5000 bias-corrected bootstrap samples. The PROCESS macro uses the bootstrapping method, which is a method of assessing direct and indirect effects of variables in a way that maximizes power and is robust against non-normality. The indirect effect represents the impact of the mediator variable(s) on the original relation (i.e., the relation of the independent variable on the outcome variable).<sup>33</sup> According to the model being analyzed, OCI-R dimensions were the independent variables, anxiety from DASS-21 was the mediator variable, and tic worsening during COVID-19 (dichotomous) was the outcome variable. To further clarify the pathways between OCS, anxiety and COVID-19-related tic worsening we performed a model to analyze the effect of anxiety (independent variable) on COVID-19-related tic worsening (outcome variable) through OCS (from OCI-R). Only the OCI-R dimensions showing significant relationships in previous exploratory analyses (group and correlational analyses) with anxiety (DASS-21) and COVID-19-related tic worsening were expected to be included in our mediational model. The significance level was set at  $p < 0.05$ .

## RESULTS

### ***ST sample characteristics***

The sample was composed of 20 TS patients (30% female;  $n=6$ ), mean aged  $29.9 \pm 10.5$  years. Most (80%;  $n=16$ ) were single and the remaining (20%;  $n=4$ ) were married. Regarding the educational level, half of the participants have concluded secondary school and the other half had academic degrees. Most of our sample reported being working or studying and only 2 (10%) were unemployed or on medical leave. Half of the participants were medicated, mostly ( $n=7$ ; 35%) with antipsychotics and 7 (35%) had current or past psychotherapeutic treatment. Almost all participants ( $n=19$ ; 95%) reported having other psychiatric diagnosis, namely: anxiety ( $n=10$ ; 50%), ADHD and OCD ( $n=6$ ; 30% each), depression ( $n=3$ ; 15%), insomnia ( $n=2$ ; 10%) and addiction. ( $n=1$ ; 5%). The mean and median OCI-R total score was 25, above the Portuguese cut-off of 21.

### ***Comparison of obsessive-compulsive symptoms, premonitory urges and psychological distress between TS subgroups based on tic worsening during COVID-19 (Table 1).***

Compared to TS patients who reported stability or improvement of their tics during the COVID-19 pandemic (COVID-19 TS stable;  $n=9$ ), TS patients who reported tic worsening (COVID-19 TS worsen;  $n=9$ ) during the same period presented significantly higher levels of anxiety ( $Z=-2.928$ ;  $p=.002$ ), hoarding symptoms ( $Z=-2.105$ ;  $p=.004$ ) and more difficulty in stopping their tics ( $Z=-2.029$ ;  $p=0.05$ ).

### ***Correlations between PUTS, hoarding, anxiety and COVID-19-related tic worsening (Table2).***

Since differences in OCS between “COVID-19 ST stable” vs. “COVID-19 ST worsen” were only significant for hoarding (group analysis), we included this OC dimension in our correlational analysis. Correlations between hoarding and anxiety ( $r=0.479$ ;  $p=0.033$ ) and between hoarding and COVID-19 worsening ( $r=0.510$ ;  $p=0.030$ ) were positive, significant and of moderate magnitude (Table 3). Anxiety from DASS-21 correlated positively, significantly, and with high magnitude with COVID-19 tic worsening ( $r=0.710$ ;  $p=0.001$ ).

**Table 1:** Sample's demographic and clinical features: medication, obsessive-compulsive symptoms, premonitory urges and psychological distress.

	M (SD) / Md (IqR) COVID-19 ST stable (n=9)	M (SD) / Md (IqR) COVID-19 ST worsen (n=9)	Mann-Whitney U test / Chi Square test	<i>p</i>
Sex (%)	Males = 89%	Males= 83%	$\chi^2 = 0.599$	NS
Age	30.11 (6.53) / 27.00 (10.00)	29.67 (11.24) / 25.00 (15.00)	Z = -0,488	NS
Medication	Yes= 4	Yes= 6	$\chi^2 = 0.900$	NS
OCD diagnosis	Yes= 2	Yes = 4	$\chi^2= 1,000$	NS
Anxiety diagnosis	Yes=4	Yes= 5	$\chi^2=0,222$	NS
OCI-R (total)	22.33 (5.69) / 18.00 (33.50)	27.11 (5.36) / 25.00 (31.50)	Z = -0.884	NS
<b>OCI-R (hoarding)</b>	<b>1.67 (0.75) / 0.00 (3.50)</b>	<b>4.33 (0.99) / 5.00 (4.50)</b>	<b>Z = -2.105</b>	<b>&lt;0,04</b>
OCI-R (checking)	4.22 (1.48) / 3.00 (7.50)	4.11 (0,73) / 3.00 (4.00)	Z = -0,541	NS
OCI-R (ordering)	4.67 (1.53) / 5.00 (9.50)	4.33 (1.12) / 5.00 (4.50)	Z = -0.089	NS
OCI-R (neutralization)	2.44 (1.19) / 1.00 (5.50)	2.89 (1.06) / 3.00 (5.00)	Z = -0.324	NS
OCI-R (cleaning)	2.67 (0,90) / 2.00 (5.50)	4.55 (1.19) / 4.00 (7.00)	Z = -1.259	NS
OCI-R (obsessions)	6.67 (1.51) / 7.00 (9.00)	6.89 (1.18) / 6.00 (6.50)	Z = -0.133	NS
PUTS-9*	23.89 (2.54) / 26.00 (12.00)	25.11 (2.38) / 24.00 (14.00)	Z = -0.044	NS
<b>PUTS-item10</b>	<b>1.67 (0,33) / 1.00 (1.00)</b>	<b>2.56 (0.29) / 3.00 (1.00)</b>	<b>Z = -2.029</b>	<b>&lt;0,050</b>
<b>DASS (anxiety)</b>	<b>3.67 (1.17) / 3.00 (7.00)</b>	<b>9.89 (1.17) / 10.00 (4.50)</b>	<b>Z = -2.928</b>	<b>&lt; .002</b>

M, Mean; SD, Standard Deviation; Md, Median; IqR, Interquartile Range; OCI-R: Obsessive-Compulsive Inventory – Revised; PUTS, Premonitory Urge for Tics Scale; DASS, Depression, Anxiety and Stress Scale; NS, non significant.

\* PUTS-9 includes all items except item 10 from PUTS.

**Table 2:** Spearman Correlations between PUTS, hoarding, anxiety and COVID-19-related tic worsening

	<b>PUTS-9</b>	<b>PUTS-item10</b>	<b>COVID-19 worse</b>	<b>ANX</b>
<b>HOARD</b>	NS	NS	<b>.510*</b> p= .030	<b>.479*</b> p= .033
<b>ANX</b>	NS	NS	<b>.710**</b> p=.001	

\* p <.05; \*\* p<.01; ANX, Anxiety; HOARD, Hoarding; PUTS-9, all items except item number 10 from PUTS; NS, non significant.

### ***Serial multiple mediation analyses***

Mediational analysis with the dichotomous outcome variable (Y) was informed by the results of our group and correlational analyses.

Table 3 presents the summary of the results of the serial mediation analysis, with an indication of the direct (c') and indirect (a1b1) effects that were estimated for all mediations.

The first serial multiple mediation model was performed to test the mediation role of anxiety (M) in the relationship between OCS, specifically hoarding (X) and COVID-19-related tic worsening (Y). Hoarding was hypothesized to have an enhancing effect on anxiety leading to COVID-19-related tic worsening. Results indicated that the direct effect of hoarding on COVID-19-related tic worsening was not significant, but the indirect effect of hoarding on COVID-19-related tic worsening through anxiety was 0,4499 and statistically different from zero (95% CI: 0.0440 to 26.6546). This model explained 31.58% of COVID-19-related tic worsening variance (F = 7.3844, p=.0152) (Fig.1).

To further examine the role of anxiety in TS and to clarify the direction of the pathway between hoarding, anxiety and COVID-19-related tic worsening, we performed a second mediation model to analyze if hoarding symptoms (M) were a necessary condition for the relationship between anxiety (X) and COVID-19-related tic worsening (Y). The model being tested showed that the indirect effect of anxiety on COVID-19-related tic worsening, through hoarding, was not statistically different from zero, but the direct effect of anxiety on COVID-19-related tic worsening was 0.4952 and statistically different from zero (95% CI: 0,0000 to 0,9904). This model explained 31,58% of COVID-19-related tic worsening variance (F=7,3844, p=.0152) (Fig.2)

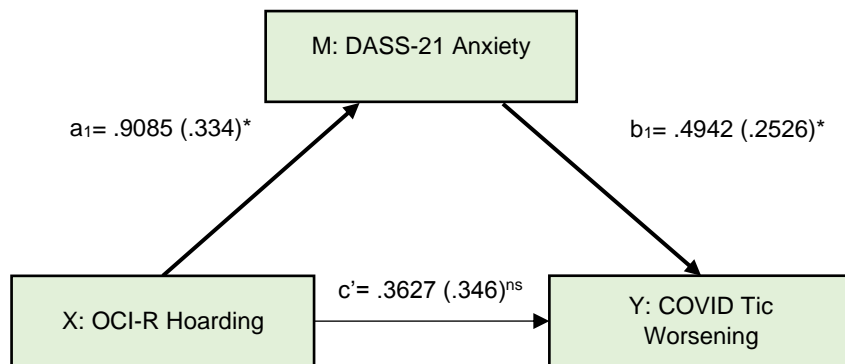


**Table 3:** Serial mediation analysis

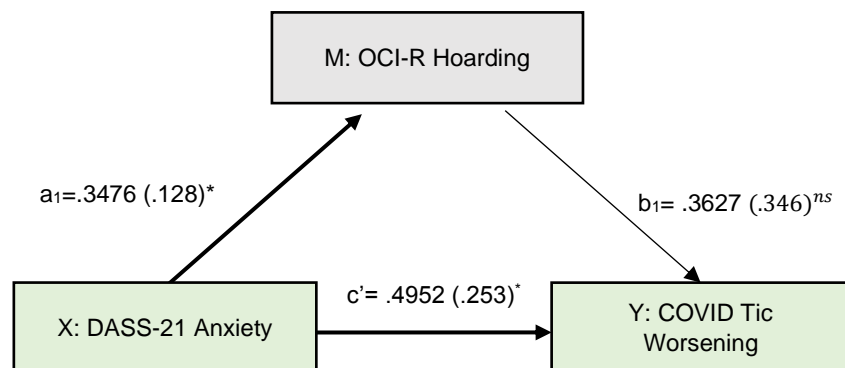
Effects	Coefficient	SE	p	Bootstrapping 95% CI	
				Lower	Upper
<b>X: Hoarding, Y: COVID-19 Tic Worsening, M: Anxiety</b>					
Direct effect c'	0.3627	0.3462	0.2948	-.3158	1.0412
Indirect effect a1b1	0.4499	7.6707		0.0440	26.6546
<b>X: Anxiety, Y: COVID-19 Tic Worsening, M: Hoarding</b>					
Direct effect c'	.4952	.2526	0.0500	.0000	.9904
Indirect effects a1b1	0.1261	3.0937		-1.8980	8.8411

SE, standard error, CI, confidence interval

Note: Direct and indirect effects of the serial mediation models with COVID-19-related tic worsening as the outcome.



**Figure 1.** Serial multiple mediation model with hoarding as the predictor and self-reported tic worsening during the COVID-19 pandemic as the outcome. Numbers in parentheses represent standard errors. \* $p < .05$ ; NS, non significant



**Figure 2.** Serial multiple mediation model with anxiety as the predictor and self-reported tic worsening during the COVID-19 pandemic as the outcome. Numbers in parentheses represent standard errors. \* $p < .05$ ; NS, non significant.

## DISCUSSION

COVID-19 pandemic is not only a socio-political and public health matter but also a mental health issue, especially for those with pre-existing psychiatric disorders. Through a cross-sectional assessment of 20 TS patients, this study investigates the impact of having comorbid OCS and anxiety symptoms on tics' course during the COVID-19 pandemic.

Using an online survey during the post lockdown period in Portugal (from July to December 2021), we found that 50% of the TS patients of our sample reported that their tics have worsened during the COVID-19 pandemics. This feature is in line with previous research, where the authors showed a tic worsening in over 67% of the 239 individuals with TS included.<sup>19</sup> More time spent at home, without the usual work and social settings, provoked by the lockdown, may explain exacerbation of tic symptoms, during that period.

TS individuals who reported tic worsening during COVID-19 lockdown, compared to the ones who got their tics stable, did not report significant exacerbation of premonitory urges. According to previous research, the correlation between tic severity and premonitory urges is moderate to weak. This led to the assumption that tics and premonitory urges were distinct phenomena, determined by different neuropsychological pathways.<sup>34</sup> While tics consist of motor actions, premonitory urges are more related to sensory dysregulation. Regarding item 10 from PUTS, which is usually analyzed separately, TS patients with tic worsening were more prone to have less control over their tics. This is in line with other studies that suggest that item 10 does not reflect the main construct of the scale, i.e., premonitory urges.<sup>34,35</sup> Thus, our results indicate that TS patients with tic exacerbation during the COVID-19 do not have more distressful sensory experiences (premonitory urges) but they report a feeling of lack of control over their tics. Importantly, a feeling of lack of control is also present in OCD.

Previous research in TS reported an increase of OCS<sup>19</sup>, such as contamination obsessions and checking compulsions,<sup>23</sup> during the lockdown. Our study was not designed to answer whether and which OCS have worsened during the pandemics. We found that TS patients whose tics worsened during the lockdown reported in overall more hoarding symptoms. Accordingly, OCS were previously shown to predict tic severity.<sup>36</sup>

Worries and fear about COVID-19 pandemic may drive individuals to stockpile need-based items, such as toilet paper, canned goods or even masks, hand sanitizers and medication. This feature can be socially relevant, as it can lead to a shortage of supplies.<sup>37</sup> Probably, hoarding behaviors can be a strategy to deal with situations where individuals perceive they are devoid of control.<sup>38</sup> Due to psychopathological features of OCD and TS, those patients are more vulnerable to perceived lack of control as harmful and may, subsequently, engage into OC behaviors, such as hoarding, in threatful situations such as the lockdown.

Besides hoarding symptoms, neither of the other OC dimensions nor an OCD diagnosis were reported by our "COVID-19 ST worsen" subgroup. This may be a result of our analysis being underpowered. On

the other hand, differences between hoarding and other OC dimensions found in our study are according to hoarding gaining its statute in DSM-5 as hoarding disorder and being independent of OCD.<sup>2</sup>

Symmetry is an OCD dimension frequently associated with tic disorders and genetically related to TS susceptibility.<sup>18</sup> In our study, having symmetry features was not associated with tic worsening during COVID-19. Despite the neurobiological and genetic relationship between OC symmetry dimensions, psychiatry social context is also crucial. The unique context of lockdown may have reduced exposure to triggering stimuli of symmetry obsessions and ordering rituals. The lack of association between OCS of cleaning and COVID-19 tic worsening was previously reported.<sup>23</sup> Considering that COVID-19 hygiene guidelines could enhance cleaning obsessions, this topic deserves further investigation. One explanation could be that COVID-19 hygiene guidelines would normalize perceptions of severity, interference and inadequacy of contamination/cleaning symptoms. This was sure encountered in OC clinical settings.

Anxiety occurs in TS, either as a comorbidity<sup>1,4</sup> and/or as an epiphenomenon of the central pathology. Although our “COVID-19 ST worsen” subgroup reported more anxiety symptoms, they have not been significantly more often diagnosed with an anxiety disorder. This indicates that anxiety was, more frequently, generated by the tics or other primary phenomena (eg.: OCS). Another hypothesis is that our analyses were underpowered and we also have to be mindful of possible underdiagnosis. Anxiety may also result from COVID-19 pandemic circumstances. For instance, confinement and quarantine involve lack of physical exercise, fewer distractions, altered/lack of routine, financial worries, which, in addition to media coverage, can lead to substantial anxiety. Our results show that high levels of anxiety were related to hoarding symptoms and with the perception of tic worsening during the pandemic.

Through mediation models informed by previous analyses, we understood that hoarding behaviors and tic worsening were fully mediated by anxiety. This indicates that only when hoarding behaviors generate substantial anxiety, this relationship induced tic exacerbation during COVID-19. We may hypothesize that COVID-19-related tic worsening only arises when hoarding behaviours are severe enough to interfere with the individuals’ functioning (eg.: maintaining a safe environment), ultimately generating anxiety. Importantly, change in symptoms during the pandemic do not necessarily mean a progression of TS disorder and may be a result of the unique circumstances.<sup>20</sup>

Our second mediation model showed that even when controlling the effect of hoarding symptoms, the anxiety burden was strong enough to induce tic worsening during the COVID-19. This indicates that anxiety does not only emerge from the tics’ distress but also anxiety, per se, is capable of exacerbating TS manifestations. A reciprocal relationship between generalized anxiety and tic severity was previously reported leading the authors to suggest that this relationship should be taken into consideration when establishing therapeutic targets.<sup>39</sup>

## LIMITATIONS

Our study has several limitations that should be highlighted. The impact of the small sample size on the statistical strength of the assessment has already been discussed. Regarding our mediational analysis and assuming that the effects remain stable, a sample of at least 107 participants would be necessary to reach 80% power.<sup>40</sup>

Thus, our models are exploratory and preliminary and should be replicated in larger samples. However, challenges of data collection from a clinical sample should be considered. Some features of TS (low prevalence, being a high stigmatizing disorder and under/misdiagnosis) hamper the recruitment of TS patients in clinical studies. Our opinion is that those features should not preclude TS investigation. Instead, the current panorama should encourage more investigation into the field, as TS is a life-long neurodevelopmental disorder. Another limiting aspect is the cross-sectional nature of this study. Future longitudinal cohorts can better evaluate the impact of COVID-19 on mental health of TS patients.

Limitations associated with the use of self-assessment scales should also be regarded. Although self-report protocols are based on subjective and sometimes retrospective, evaluations of one's traits and behaviours, most of the questionnaires used in the present study have been extensively applied and are validated for the Portuguese population. Even though PUTS is not validated for the Portuguese population, the questionnaire was translated by a group of researcher specialists in TS.<sup>41</sup> The assumption of a TS diagnosis based on one question ("Do you have Tourette Syndrome diagnosis, done by a professional health worker") is another limitation of the present study.

## SUGESTIONS FOR FUTURE RESEARCH

Future investigation should include larger samples and investigate other COVID-19-related phenomena, namely functional tics. Functional tic – like behaviors emerged substantially among female teenagers, due to massive growth in online content, such as TikTok™ videos<sup>42</sup>, which was also intensified during the lockdown. Since tic and functional tics may coexist, to what extent tic-like behaviors are a relevant underlying cause of tic worsening during the lockdown, is not clarified.

Additionally, it would be relevant to investigate therapeutic compliance in patients reporting tic worsening during the COVID-19.

Finally, despite the well-described effect of neurotropism of SARS-CoV-2 little is known about its potential neurological effects. Importantly, there is a relationship between other viral infections occurring during childhood and the subsequent development of neurodevelopmental symptoms. Thus, future studies should investigate if SARS-CoV-2 neurotrophic effects could lead to central nervous system sequelae specific to TS.<sup>43</sup>

## **CONCLUSION**

Findings in our study suggest that anxiety plays a central role in TS symptoms, as it can lead to increased tic severity and mediated the impact of hoarding behaviors on tic worsening during the COVID-19 pandemic. Therefore, anxiety clinical management should embrace the patient's background, such as the presence of comorbidities (tics, ADHD, OCD, ...). We found a pathway in which hoarding symptoms enhanced the deleterious effect of anxiety leading to COVID-19-related tic worsening. Additionally, it is important to explore other anxiety-generating sources among TS patients, especially during the pandemic or in altered routine situations such as unemployment.

Lastly, it is relevant to highlight the vulnerability of these patients during the pandemic. During the lockdown, non-essential medical services were suspended, which could have led to a lack of medical follow-up or the discontinuation of psychotherapy. This ultimately could have been a propitious moment to tic worsening.<sup>37</sup>

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## SUPPLEMENTARY MATERIAL

### I - ESCALA DE SENSações PREMONITÓRIAS ASSOCIADAS A TIQUES\*

	Nada verdadeiro	Um pouco verdadeiro	Verdadeiro	Muito verdadeiro
Imediatamente antes de fazer um tique, sinto uma espécie de comichão dentro de mim.				
Imediatamente antes de fazer um tique, sinto uma pressão dentro do meu cérebro ou corpo.				
Imediatamente antes de fazer um tique, sinto-me “nervoso(a)” ou tenso interiormente.				
Imediatamente antes de fazer um tique, sinto que alguma coisa não está exatamente “certa”.				
Imediatamente antes de fazer um tique, sinto que alguma coisa não está completa.				
Imediatamente antes de fazer um tique, sinto que há energia no meu corpo que precisa de sair.				
Tenho estas sensações quase sempre antes de fazer um tique.				
Estas sensações ocorrem para todos os tiques que tenho.				
Depois de fazer o tique, a comichão, energia, pressão, sensação de tensão, ou sensação de que alguma coisa não está exatamente certa ou não está completa, desaparecem, pelo menos durante um bocadinho.				
Consigo parar os meus tiques, mesmo que seja por apenas um curto período de tempo.				

\* Translated from “Premonitory Urge for Tics Scale” de Woods, D., Piacentini, J., Himle, M. B., & Chang, S. (2005), *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, Vol. 26, No. 6, pp. 397-403. Translation performed on May, 2015 by Prof. Dr. Tiago V. Maia's laboratory (with participation of Prof. Dr. Tiago V. Maia and Dr.ª Andreia Leitão), in collaboration with Dr.as Fátima Nunes and Soraia Nobre.*

## II - OCI-R

	0	1	2	3	4
	Nada	Pouco	Moderadamente	Muito	Extremamente
1	Eu tenho acumulado tantas coisas que elas já me estão a atrapalhar.				0 1 2 3 4
2	Eu verifico as coisas mais vezes do que é necessário.				0 1 2 3 4
3	Eu fico incomodado(a) se os objetos não estão arrumados corretamente.				0 1 2 3 4
4	Eu sinto vontade de contar enquanto estou a fazer coisas.				0 1 2 3 4
5	Eu sinto dificuldade em tocar num objeto se sei que este já foi tocado por estranhos ou por certas pessoas.				0 1 2 3 4
6	Eu tenho dificuldades em controlar os meus próprios pensamentos.				0 1 2 3 4
7	Eu coleciono coisas que não preciso.				0 1 2 3 4
8	Eu verifico repetidamente as portas, janelas, gavetas, etc.				0 1 2 3 4
9	Eu fico incomodado(a) se outras pessoas mudam as coisas que arrumei.				0 1 2 3 4
10	Eu sinto necessidade de repetir certos números.				0 1 2 3 4
11	Às vezes tenho que me lavar simplesmente porque me sinto contaminado(a).				0 1 2 3 4
12	Fico perturbado(a) com pensamentos desagradáveis que invadem a minha mente contra a minha vontade.				0 1 2 3 4
13	Evito deitar coisas fora, pois tenho medo de precisar delas mais tarde.				0 1 2 3 4
14	Eu verifico repetidamente o gás, as torneiras e os interruptores de luz depois de os desligar.				0 1 2 3 4
15	Eu preciso de que as coisas estejam arrumadas numa determinada ordem.				0 1 2 3 4
16	Eu acredito que há números bons e maus.				0 1 2 3 4
17	Eu lavo as minhas mãos mais vezes que o necessário.				0 1 2 3 4
18	Eu tenho pensamentos impróprios com frequência e tenho dificuldade em me livrar deles.				0 1 2 3 4

### III - DASS-21

0	1	2	3
Não se aplicou nada a mim	Aplicou-se a mim algumas vezes	Aplicou-se a mim muitas vezes	Aplicou-se a mim a maior parte das vezes

1. Tive dificuldades em me acalmar.	0	1	2	3
2. Senti a minha boca seca.	0	1	2	3
3. Não consegui sentir nenhum sentimento positivo.	0	1	2	3
4. Senti dificuldades em respirar.	0	1	2	3
5. Tive dificuldade em tomar iniciativa para fazer coisas.	0	1	2	3
6. Tive tendência a reagir em demasia em determinadas situações.	0	1	2	3
7. Senti tremores (por ex., nas mãos).	0	1	2	3
8. Senti que estava a utilizar muita energia nervosa.	0	1	2	3
9. Preocupei-me com situações em que podia entrar em pânico e fazer figura ridícula.	0	1	2	3
10. Senti que não tinha nada a esperar do futuro.	0	1	2	3
11. Dei por mim a ficar agitado(a).	0	1	2	3
12. Senti dificuldade em me relaxar.	0	1	2	3
13. Senti-me desanimado(a) e melancólico(a).	0	1	2	3
14. Estive intolerante em relação a qualquer coisa que me impedisse de terminar aquilo que estava a fazer.	0	1	2	3
15. Senti-me quase a entrar em pânico.	0	1	2	3
16. Não fui capaz de ter entusiasmo por nada.	0	1	2	3
17. Senti que não tinha muito valor como pessoa.	0	1	2	3
18. Senti que por vezes estava sensível.	0	1	2	3
19. Senti alterações no meu coração sem fazer exercício físico.	0	1	2	3
20. Senti-me assustado(a) sem ter tido uma boa razão para isso.	0	1	2	3
21. Senti que a vida não tinha sentido.	0	1	2	3