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Research paper

Exploring circannual rhythms and chronotype effect in patients with Obsessive-Compulsive Tic Disorder (OCTD): A pilot study

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ABSTRACT

Background: The aim of this study was to test, through a chronobiologic approach, the existence of a significant circannual rhythm of tics and obsessive-compulsive symptoms in patients with Obsessive-Compulsive Tic Disorder (OCTD). The chronotype effect on tics and OC symptoms during seasons was also studied.
Methods: Patients with a diagnosis of OCTD (N = 37; mean age = 18.78 ± 8.61) underwent four clinical evaluations: Winter (WIN), Spring (SPR), Summer (SUM) and Autumn (AUT). Tics were evaluated through Yale Global Tic Severity Scale (YGTSS) and OC symptoms through Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Patients' chronotype was assessed by the Horne-Ostberg morningness-eveningness questionnaire (MEQ), which categorizes subjects according to the individuals'chronotype, being morning-type, evening-type, and neither-type.
Results: A statistically significant circannual rhythm was observed for OC symptoms (p = 0.007), with the acrophase occurring between AUT and WIN. Y-BOCS differed along the year (p = 0.0003 and η_p^2 = 0.40) with lower results in SUM compared to WIN ($p < 0.05$) and AUT ($p < 0.01$). Tics displayed no circannual rhythm and YGTSS scores were comparable among seasons. Patients were classified as 15 morning-types (40.5%) 15 neither-types (40.5%) and 7 evening-types (19.0%). YGTSS data were similar for all chronotypes while Y-BOCS results were greater during SUM in evening-types than morning-type patients ($p < 0.05$; 15.7 ± 5.2 vs 3.4 ± 6.0).
Limitations: It is essential to investigate the existence of tics and OC symptoms circannual rhythms over the course of more than one year with a larger sample.
Conclusions: OC symptoms displayed a significant circannual rhythm and were influenced by patients' chronotype. On the contrary, tics resulted similar among seasons and chronotypes.

1. Introduction

Tics are defined as recurrent and nonrhythmic movements or vocalizations that are typical of Tic Disorders (TDs), whereas obsessions and compulsions are thoughts and behaviors that occur over and over again in subjects suffering from Obsessive-Compulsive Disorder (OCD) (APA, 2013). Both tics and OC symptoms are characteristic of the tic-related phenotype of OCD, also referred as to Obsessive-Compulsive Tic Disorder (OCTD) (Dell'Osso et al., 2017; Dell'Osso et al., 2018).

The correct expression of a rhythmicity is crucial for the body homeostasis, with physical and mental performances being better when all biological rhythms are in synch (Haus and Smolensky, 2006, Vitale et al., 2018). Time structure characterizes any biologic entity that exhibit one or more of the following frequencies: 1. Ultradian (period < 20 h), 2. Circadian (period between 20 h and 28 h), and 3. Infradian (period > 28 h) that also includes circannual rhythms (Halberg et al., 1977). The Earth follows an elliptical orbit around the sun and this astronomical characteristic leads to seasonal variations in the duration of daylight and a clear example of the link between chronobiology and clinical manifestations can be observed in seasonal

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affective disorder (Lewy et al., 2006). This circannual rhythm disorder may be caused by a seasonal desynchronization between the light/dark cycle and the human biological clock, with shorter photoperiods (Benedetti et al., 2007). The oscillations between mania and depression may occur with similar regular cycles. Of note, changes in circadian processes are known to be associated with inter-individual differences in morning or evening preferences (Schmidt et al., 2012).

Daily peaks of tics are well recognized and referred to as "burstlike" in nature, with interbout periods that can last from minutes to hours and brief intertic intervals of 0.5-1.0 seconds (Peterson et al., 1998). Other than the existence of short-term bouts, the occurrence of tics may also be fractal, which means that the temporal patterning remains self-similar regardless of the time scale considered (e.g. a sequence of tics in a few seconds may be similar in complexity to a sequence of more than one hundred tics during hours) (Peterson et al., 1998), with significant dependence upon age, mental stress, and even body temperature (Scahill et al., 2001; Leckman et al., 2006). The relationship between clinical symptoms and stress-related activity may suggest a role of the hypothalamic-pituitary-adrenocortical (HPA) axis in the neuropathology of the syndrome (Lombroso et al., 1991). An altered cortisol rhythmicity was measured in children with TD together with higher cortisol levels being found in response to stressors (Corbett et al., 2008), thus possibly suggesting a greater sensitivity to environmental stimuli, such as light, temperature, or even food (Belluscio et al., 2011), in these patients. Furthermore, dopamine, which is known to be a modulator of circadian rhythm (Korshunov et al., 2017), showed periodic features in the striatum that were associated with motor excitability in a TD rat model (Xiaoyi, 2016).

Concerning OC symptoms, sparse data literature focus on circannual rhythms of symptoms, possibly because of the requirement of long medical history with respect to seasonality (Sinha et al., 2014). Ultradian rhythms are far more visible, and are mainly supported by evidences concerning cortisol and melatonin dysregulations, which again suggest the involvement of the HPA (Nota et al., 2015). The efficacy of the add-on treatment with the melatonergic agonist antidepressant Agomelatine in OCD patients may further support the HPA hypothesis in OC pathophysiology (Lange et al., 2012). Of note, the regulation of the HPA axis is important for the maintaining of a diurnal rhythmicity and the restoration of a basal activity via negative feedback mechanisms. Other than tics, OC symptoms were reported to show fractal fluctuations with month-to-month synchronous variations and a high degree of intra-subject variability (Lin et al., 2002; Rocha et al., 2011). Of note, the period of worst-ever OC symptoms was reported to occur on average 2 years after the worst-ever tics, usually around 10-11 years old (Pappert et al., 2003; Bloch et al., 2006).

Other than a seasonal pattern, the expression of a biological rhythmicity may be defined as categories of ultradian chronotypes, which differ among individuals and can be influenced by both personal (e.g., age or gender) and/or environmental (e.g., photoperiod at birth or latitude) factors (Adan et al., 2012). Based on validated scales or questionnaires (Montaruli et al., 2017; Roveda et al., 2017), three categories of chronotype are identified: morning-types (i.e. M-types, preference for going to bed and waking up early), evening-types (i.e. E-types, preference for later wake up and bed times), and neither-types (i.e. N-types) (Adan et al., 2012). A large body of the literature already showed many differences between M-types and E-types in the circadian rhythms of different biological, physiological and psychological variables (Vitale et al., 2017). The morningness and eveningness types share some behavioral dimensions with psychiatric disorders, such as alterations of the sleep/wake cycle and cognition, which often lead to social impairment.

To the best of our knowledge, no previous study used valid methods to evaluate rhythmometric characteristics of tics and OC symptoms. Therefore, we first investigated the seasonal variations of tics and OC symptoms in patients with OCTD, specifically adopting a rhythmometric approach to test the existence of a significant seasonal rhythm for these two variables. Secondly, we aimed to evaluate the chronotype distribution in OCTD patients and to test the chronotype effect on tics and OC symptoms during the seasons.

2. Methods

2.1. Study design and population

In this pilot study, patients with a diagnosis of OCTD (Yale-Brown Obsessive Compulsive Scale [Y-BOCS] $\geq$ 15) who had their first assessment at Tourette's Syndrome and Movement Disorders Centre (Milan, Italy), were screened by the clinical psychologist. Eligibility criteria comprised both male and female genders with no age restrictions. Those patients who matched eligibility criteria signed the informed consent and were instructed about benefits and potential risks of the study. All patients underwent four consecutive clinical evaluations, one in each of the four seasons of the year; specifically in Winter [WIN] = January–February, Spring [SPR] = April–May, Summer [SUM] = July–August, and Autumn [AUT] = September–October of the years 2017 and 2018. The San Raffaele Ethics Committee of Milan (Italy) approved and authorized the protocol (37/INT/2018, NCT04076852) in compliance with current national and International laws and regulations governing the use of human subjects in clinical trials (Declaration of Helsinki II).

2.2. Clinical evaluations

Tics were evaluated through Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989) and OC symptoms through Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989; Goodman et al., 1989). For what concerns YGTSS score (total tic severity score + impairment), it ranges from 0 to 100, with the highest score being the worst severity. The Y-BOCS score ranges from 0 to 40 points, with five different intervals of OC severity: 0-7 points (subclinical), 8-15 points (mild), 16-23 points (moderate), 24-31 points (severe), and 32-40 points (extremely severe).

2.3. Analysis of circannual rhythmicity

Scores from YGTSS and Y-BOCS were processed with the single cosinor and population-mean cosinor tests to evaluate the presence of a circannual rhythm. These methods are widely used to evaluate the rhythmometric characteristics of both the single individual and whole population (Halberg et al., 1977; Nelson et al., 1979). These methods calculate a cosine function by means of the amplitude (**A**), the acrophase (Φ), and the Midline Estimating Statistic Of Rhythm (MESOR). The **A** is the measure of one half the extent of the rhythmic variation in a cycle, the MESOR is the rhythm-adjusted mean, the Φ indicates the time interval within which the highest values of the variable are expected. These three parameters are always reported with the relevant 95% confidence intervals (CI). The statistical analysis was carried out using the Time Series Analysis Seriel Cosinor 6.3 (Expert Soft Technology, Richelieu, France) and took into account four evaluations per patient, corresponding to different seasonal visits.

2.4. Assessment of chronotype

Participants' circadian typology was assessed once by the Horne-Ostberg morningness-eveningness questionnaire (MEQ) (Horne et al., 1976) which is the most cited and used questionnaire to assess individuals'chronotype. According to the MEQ-score, participants were categorized as M-type (scoring $\geq$ 59), E-type (scoring $\leq$ 41), and N-type (scoring 42–58). Individual chronotype scores and categories were communicated to the participants only after the completion of the experimentation.

2.5. Statistical analysis

2.5.1. Seasonal difference

YGTSS and Y-BOCS for each season were checked for normality with the Shapiro–Wilk test. To detect possible differences among WIN, SPR, SUM, and AUT a Repeated-Measures ANalysis Of VAriance (RM-ANOVA) followed by the Bonferroni *post hoc* test was performed for YGTSS, while the non-parametric Friedman test followed by the Dunn's procedure was performed for Y-BOCS. Partial eta-squared (η_p^2) was used to determine the magnitude of the effect for significant outcomes ($\alpha = .05$). A value of $p \leq 0.05$ was considered statistically significant. In tables, data were reported as mean ± standard deviation (SD).

2.5.2. Chronotype effect

To test the chronotype effect on tics and OC symptoms during the seasons, YGTSS and Y-BOCS scores were calculated four times (WIN, SPR, SUM, AUT) for the three chronotype categories (M-types, N-types and E-types). The normal distribution was then checked twelve times (four seasons * three chronotypes) with the Shapiro–Wilk test. Those data that showed normal distribution were tested using parametric methods; on the contrary, non-normal data were analyzed with the equivalent non-parametric tests. The Mixed ANOVA procedure was applied for both YGTSS and Y-BOCS. First, it was established if there was an interaction between the two factors, within-subjects factor (time) and between-subjects factor (chronotype). Second, the simple main effects of chronotype and time were evaluated. In details, the effect of time was evaluated with three separate one-way ANOVA (one for each chronotype categories) for differences in the questionnaire scores among WIN, SPR, SUM, AUT. The effect of chronotype was determined by evaluating the differences among M-, N-, and E-types for each season of the year (four separate one-way ANOVA, one for each season). A p value ≤ 0.05 was considered statistically significant. The data are presented as mean ± SD.

3. Results

Seventy-eight patients were screened and a sub-sample of 37 subjects met the inclusion criteria, specifically 9 females and 28 males with a mean age of 18.78 ± 8.61 years old (minimum and maximum age range: 7-39 years old).

3.1. Circannual rhythmicity

The single cosinor test of YGTSS revealed the presence of a statistically significant rhythm in 6 of the 37 subjects (16.2 %), but the population-mean cosinor analysis detect no circannual rhythm. Concerning Y-BOCS, the single cosinor showed the presence of a rhythm in 6 of the 37 subjects (16.2 %) and the population-mean cosinor revealed instead a statistically significant circannual rhythm ($p = 0.007$) for OC symptoms, with the Φ occurring between AUT and WIN. We reported in Table 1 the rhythmometric parameters of YGTSS and Y-BOCS and in Fig. 1 the associated schematics for circannual rhythms.

3.2. Seasonal differences

YGTSS data showed a normal distribution while results of Y-BOCS deviated from normality. The results from RM-ANOVA used to compare the results of Y-BOCS and YGTSS among the four seasons were reported in Table 2. YGTSS data did not vary among seasons, while Y-BOCS results significantly differed along the year ($p = 0.0003$ and $\eta_p^2 = 0.40$). In particular, lower results were registered in SUM (7.0 ± 11.0) compared to both WIN (12.3 ± 10.1; $p < 0.05$) and AUT (15.2 ± 10.4; $p < 0.01$). Fig. 2 shows the raw data, with means ± SDs of Y-BOCS (panel A) and Y-GTSS (panel b) in the four seasons of the year.

3.3. Chronotype effect

A total of 37 subjects were classified in 15 M-types (40.5 %, 4 females and 11 males), 15 N-types (40.5 %, 3 females and 12 males) and 7 E-types (19.0 %, 2 females and 5 males). YGTSS scales gave similar scores for all seasons and chronotype categories, while Y-BOCS results showed to be influenced by the chronotype. The mixed ANOVA highlighted no interactions ($p = 0.12$) and no group effect ($p = 0.90$), but time effect was significant ($p < 0.001$). In particular, the *post hoc* analysis revealed a significant difference between M-types and E-types during SUM ($p < 0.05$), with E-type subjects having greater Y-BOCS scores than M-type subjects, 15.7 ± 5.2 vs 3.4 ± 6.0, respectively. Fig. 3 shows the distribution of Y-BOCS (panel A) and YGTSS (panel B) scores according to the four seasons and the three chronotypes. Globally, the E-types reported significant higher Y-BOCS scores than M-types ($p < 0.01$).

4. Discussion

This is the first study that evaluated the seasonal differences of tics and OC symptoms and that tested the existence of a circannual rhythm of these variables in OCTD patients. Two different complementary approaches were used: (1) a rhythmometric approach, based on the single and population mean cosinor, has been adopted to describe the circannual rhythm's characteristics of tics and OC symptoms and (2) the conventional statistical approach with the use of RM-ANOVA, in order to test differences between Summer, Autumn, Winter, and Spring for both clinical variables. In addition, we investigated if the subjects' chronotype could possibly influence tics and OC symptoms during the four seasons of the year.

Both tics and OC are defined as repetitive signs in nature even if tics have being specifically defined as nonrhythmic (APA, 2013). We observed that OC symptoms, evaluated through the Y-BOCS, showed a significant circannual rhythm with an acrophase that occurred between Autumn and winter while the lowest values were registered in Summer. Contrarily, tics, which were evaluated through the YGTSS, displayed no significant circannual pattern in our OCTD patients. Our results about OC symptoms are partially in line with previous evidences since the acknowledgement of annual variations in psychiatric symptoms and the existence of seasonal affective disorders (Magnusson et al., 2005). In particular, panic and anxiety disorders were showed to be more

Table 1
Rhythmometric analysis (population mean cosinor) of Y-BOCS and YGTSS scores ($N = 37$).

	p-value	PR (%)	MESOR [mean and 95 % CI]	Amplitude [mean and 95 % CI]	Acrophase *Degrees* [mean and 95 % CI]	*Season*
Y-BOCS	= 0.007	50.1	11.1 [8.7–13.5]	3.8 [4.1–6.2]	45 [4.7–85.3]	Autumn-Winter
YGTSS*	ns	-	-	-	-	

PR: percentage of rhythm. MESOR: Midline Estimating Statistic of Rhythm. Amplitude: half the difference between the highest and the lowest points of the cosine function best fitting the data. Acrophase (degrees and season) indicates the time in which the highest values occur. Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; YGTSS: Yale Global Tic Severity Scale.

* YGTSS scores did not show a significant circannual rhythm therefore no rhythmometric parameters are report (see Table 2 for details of season differences).

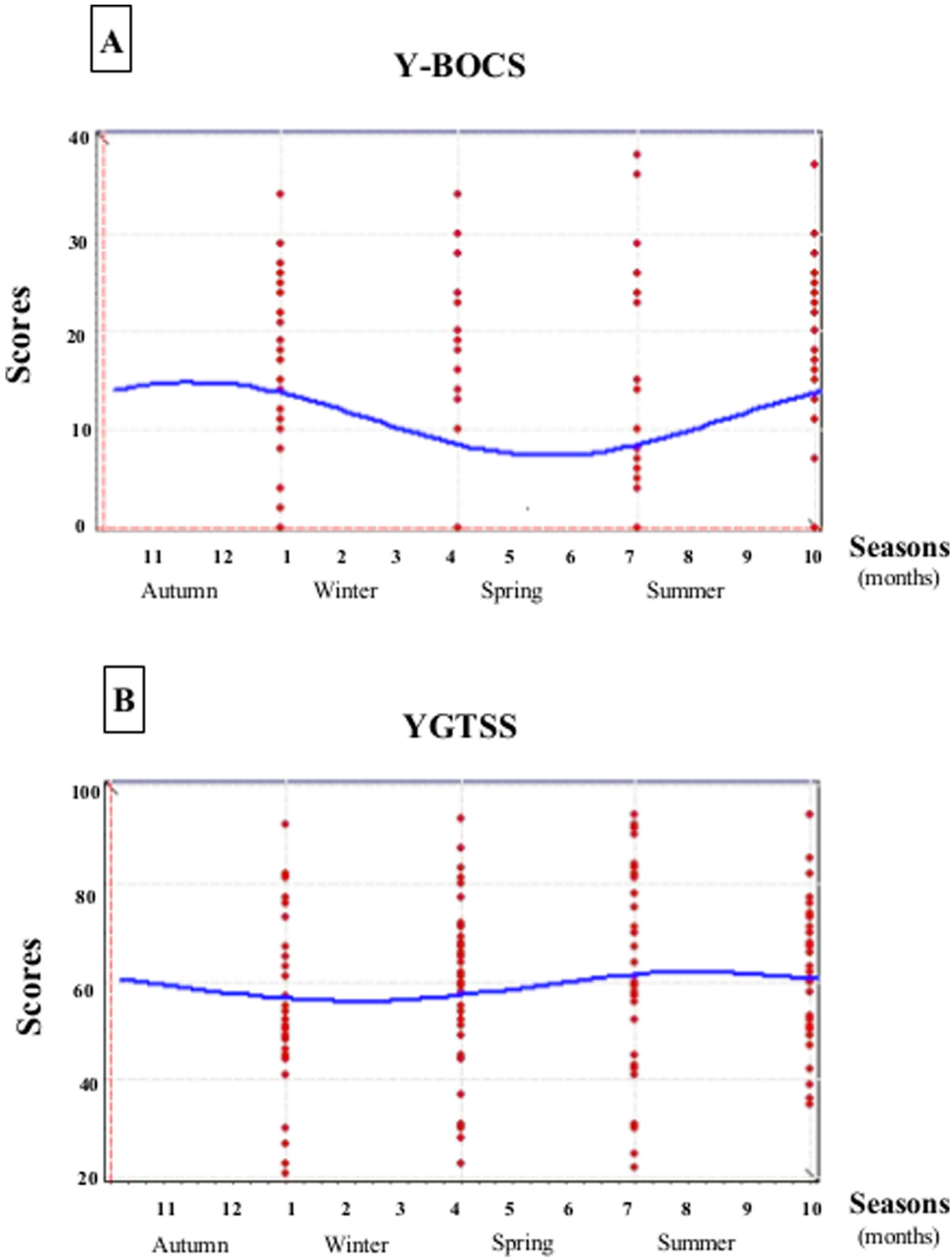

Fig. 1. Circannual rhythms of Y-BOCS (panel A) and YGTSS (panel B) showing both the mean cosine curve and individual data of all subjects (N = 37). On the x-axis are reported the months (0–12) and the corresponding seasons (Winter, Spring, Summer and Autumn) and on the y-axis the scores of the questionnaires.

frequent in winter and OCD more frequent in Autumn (de Graaf et al., 2005). Similarly, a retrospective study found that 53 % of 34 patients with OCD reported seasonal symptom variations (Yoney et al., 1991), with another case study of an OCD patient showing OC symptom onsets during winter and remission in Summer (Sinha et al., 2014). Conversely, another study tested the degree of synchronicity of tics and OC symptoms in a similar population and no dependence upon season was found (Lin et al., 2002), but a valid method to evaluate the rhythmometric pattern of these symptoms was not used. To the best of authors' knowledge, no reports of seasonal OCTD symptoms have been published so far.

It is important to highlight that the reasons for the seasonal variation in OCTD symptoms are not known yet. Ambient temperature and light-time change among seasons and tics and OC symptoms may rely on them for clinical severity (Kessler, 2002; Lange et al., 2012), but also changes in social demands may be involved (Moreno et al., 2019). Furthermore, alterations in monoaminergic neurotransmission in the brain are believed to be the reason for seasonal variations in mood

Table 2
YGTSS and Y-BOCS values in WIN, SPR, SUM and AUT (N = 37).

	WIN	SPR	SUM	AUT	RM-ANOVA	Partial eta-squared	Bonferroni post hoc test
YGTSS	55.4 ± 17.2	58.4 ± 18.1	60.3 ± 20.7	61.9 ± 14.2	ns; p = 0.22	-	-
Y-BOCS*	12.3 ± 10.1	9.9 ± 11.9	7.0 ± 11.0	15.2 ± 10.4	p = 0.0003	$F_{3,36} = 8.0.$, $\eta_p^2 = 0.40$.	WIN ≠ SUM ($p < 0.05$); SUM ≠ AUT ($p < 0.01$)

Data are reported as mean ± SD. WIN: winter: SPR: Spring; SUM: Summer; AUT: Autnumn; RM-ANOVA: Repeated Measures Analysis Of Variance; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; YGTSS: Yale Global Tic Severity Scale.

* Y-BOCS data deviated from a normal distribution therefore the non-parametric Friedman test followed by the Dunn's procedure was used for the comparison.

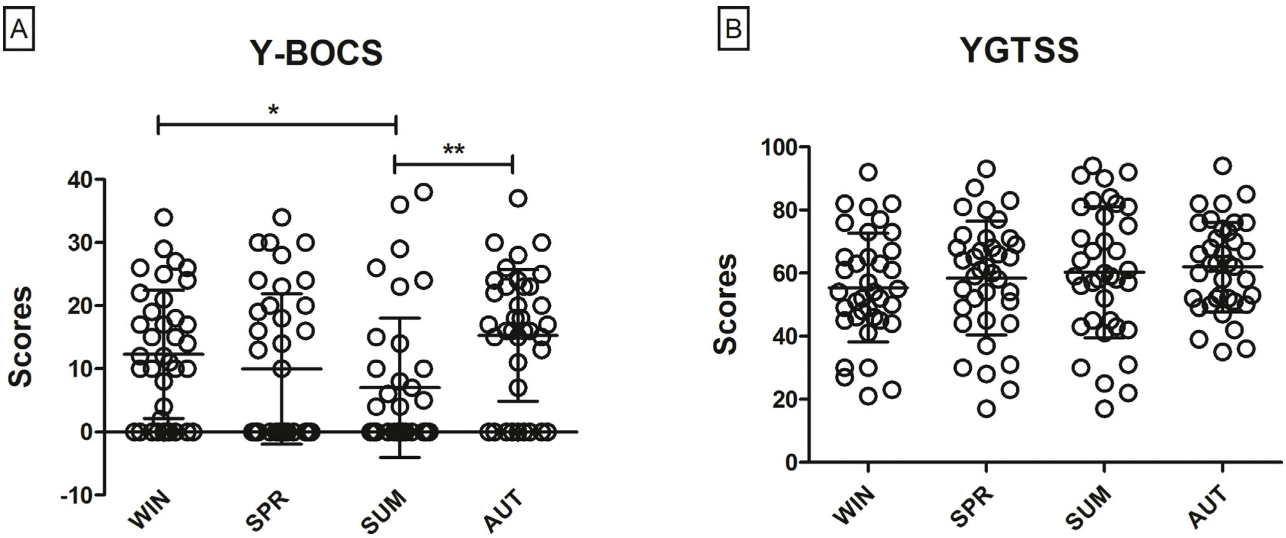

Fig. 2. Individual data plots of all subjects (N = 37; white circles), together with mean values ± SDs (black lines), of Y-BOCS (panel A) and YGTSS (panel B) in the four seasons of the year. Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; YGTSS: Yale Global Tic Severity Scale; WIN: winter: SPR: Spring; SUM: Summer; AUT: Autumn. Legend. *: $p < 0.05$; **: $p < 0.01$ (see Table 2 for details).

disorders. It was indeed found that the rate of production of serotonin by the brain was directly related to the duration of bright sunlight and increase rapidly with greater duration of sunlight (Lambert et al., 2002). These findings are supportive of the notion that changes in release of serotonin by the brain may underlie seasonal variations in OCD. It should be also noted that dietary pattern are more likely to change between seasons, especially for what concerns fruit and vegetable intakes. We found that different foods may influence both tics and OC symptoms (Briguglio et al., 2017, Briguglio et al., 2019) and that specific nutraceuticals affect drug efficacy (Briguglio et al., 2018; Briguglio et al., 2018). Therefore, it would be reasonable to assume that clinical fluctuations of symptoms in OCTD patients could be influenced by a specific seasonal dietary pattern.

A second aim of this pilot study was to evaluate the effect of chronotype on tics and OC symptoms in the four seasons of the year. First, we observed a higher prevalence of M-types (40.5 %) and N-types (40.5 %) than E-types (19.0 %) among OCTD patients, and this result is in contrast with previous data regarding the chronotype distribution of healthy age-matched populations (Vitale et al., 2015). In particular, it was showed that morningness types could be found in females in higher

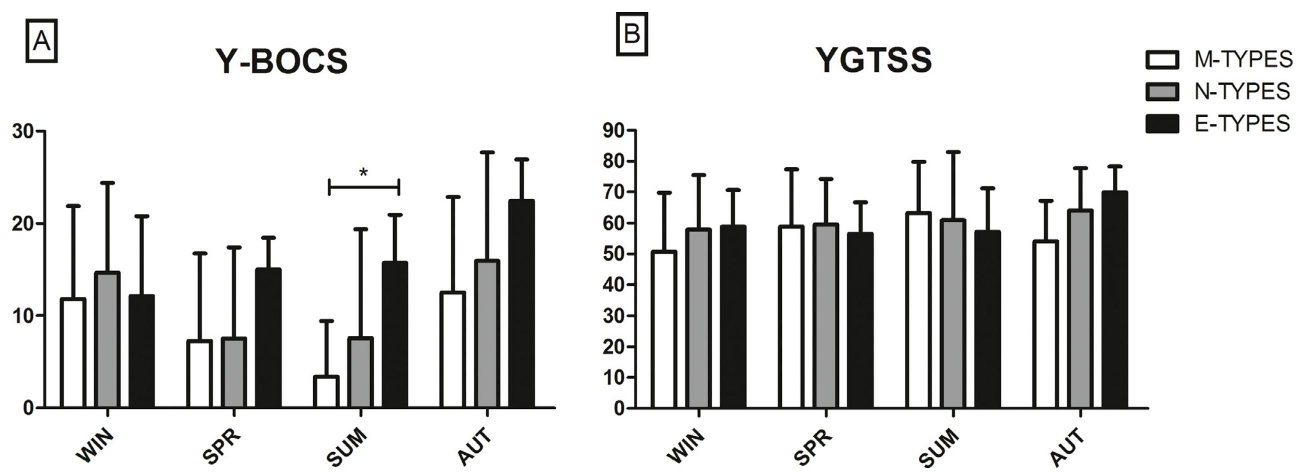

Fig. 3. Histograms with mean values ± SDs of Y-BOCS (panel A) and YGTSS (panel B) in the four seasons of the year for M-type (N = 15; white histograms), N-type (N = 15, grey histograms), and E-type (N = 7, black histograms) OCTD patients. Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; YGTSS: Yale Global Tic Severity Scale; WIN: winter: SPR: Spring; SUM: Summer; AUT: Autumn. Legend. *: $p < 0.05$.

numbers and that they tend to increase with age (Adan et al., 2012). Since we recruited more males than females, we initially expected to find a higher frequency of E-types. However, we found more M- and N-types. Second, we showed that tics did not vary among seasons in different chronotypes while OC symptoms have been influenced by the chronotype: E-types had, in general, significantly higher scores in Y-BOCS than M-type subjects and, to confirm this, we also testified that E-type subjects had significantly greater OC symptoms than M- and N-types specifically in Summer, when there is a large number of hours of light exposure (see Figure 3 for details). This novel result is in line with previous studies that suggested that eveningness may contribute to the development of greater OC symptoms (Cox et al., 2018). Indeed, it has been showed that E-type adolescents had higher mood seasonality than M- and N-types (Tonetti et al., 2012) and, furthermore, a seasonal worsening of mood during winter months is accompanied with a shift towards eveningness (Murray et al., 2002). This circannual rhythm disorder may be caused by desynchronization between the light/dark cycle and the human biological clock during seasons with shorter photoperiods (Lewy et al., 2006) and this seems to affect in a greater extend the evening-oriented OCTD patients.

These results entail important practical implications for OCTD management. Since OC symptoms may show a circannual rhythm, treatment options should be found for the prevention of the next full-blown episode, possibly occurring in Autumn and Winter. Moreover, patients with different MEQ scores might respond in a different way to same drug therapy. In fact, a dysregulated internal clock has already been shown to mirror distinct clinical phenotypes (Estrada-Prat et al., 2019). This is not a new concept as, for instance, a pharmacological dose of vitamin D is known to be useful during cold seasons, but probably unnecessary during warmer seasons when sun exposure is at its highest (Briguglio et al., 2018).

5. Limitations

Our findings must be considered in the context of the study limitations. First, our recruited sample showed a large range of age (i.e. 7–39 years old), thus possibly mingling subjects who have already experienced the worst-ever symptom period and those who haven't yet. However, our otherwise interesting results may have proved the existence of self-similar seasonal patterning even among population groups. Second, possible study confounders should be pointed out. The natural history of tics is known to be "burstlike" in nature, and this non-rhythmic feature of tics could have possibly affected the results of YGTSS over seasons. For this reason, it would be interesting to investigate the existence of circannual rhythms over the course of more than one year. Moreover, recruited patients adhered to different pharmacological treatments, primarily involving antipsychotics, anti-hypertensives, anticonvulsants, anxiolytics, and antidepressants and it is essential to plan clinical studies to evaluate the seasonal differences in OC symptoms and tics during a washout period too. Nonetheless, this is the first study offering an evidence of the existence of a circannual rhythm of OC symptoms, and the efficacy of future pharmacological treatments might rely not only on individual variances and pharmacogenomics, but also on environmental factors, such as the season of treatment.

CRediT authorship contribution statement

Jacopo A. Vitale: Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Matteo Briguglio:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Roberta Galentino:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Bernardo Dell'Osso:** Data curation, Formal analysis, Writing - review & editing. **Antonio Malgaroli:** Data curation, Formal analysis, Writing - review & editing. **Giuseppe Banfi:** Conceptualization, Data curation, Formal analysis, Writing - review & editing. **Mauro Porta:** Data curation, Formal analysis, Writing - review & editing.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.11.040.

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