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Research report

Clinical features associated to refractory obsessive–compulsive disorder

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Abstract

Some patients with obsessive–compulsive disorder (OCD) exhibit an unsatisfactory reduction in symptom severity despite being treated with all the available therapeutic alternatives. The clinical variables associated with treatment-refractoriness in OCD are inconsistently described in the literature.

Methods: To investigate factors associated with treatment-refractoriness of patients with OCD, we conducted a case-control study, comparing 23 patients with treatment-refractory OCD to 26 patients with treatment-responding OCD.

Results: The factors associated with refractoriness of OCD were higher severity of symptoms since the onset of OCD ($p<0.001$), chronic course ($p=0.003$), lack of a partner ($p=0.037$), unemployment ($p=0.025$), low economic status ($p=0.015$), presence of obsessive–compulsive symptoms of sexual/religious content ($p=0.043$), and higher scores on family accommodation ($p<0.001$). Only the three latter variables remained significantly associated with treatment-refractoriness after regression analyses. Limitations: small sample size, the biases and drawbacks inherent to a case-control study, and the inclusion criteria used to define the study groups may have limited the generalisation of the results.

Conclusion: A major strength of this study is the systematic and structured evaluation of a vast array of variables related to the clinical expression of OCD, including epigenetic factors and ratings derived from instruments evaluating family accommodation. The presence of sexual/religious symptoms, low economic status and high modification on family function due to OCD were independently associated with treatment-refractoriness. Future longitudinal studies are warranted to verify if these variables represent predictive factors of treatment non-response.

Keywords: Obsessive–compulsive disorder; Treatment response; Predictive factors

1. Introduction

Despite the proven effectiveness of cognitive-behavioural therapy (CBT) and selective serotonin reuptake

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inhibitors (SSRIs) in the treatment of obsessive–compulsive disorder (OCD), trials employing these two treatment strategies have demonstrated, respectively, inadequate responses in approximately 20% (Piacentini et al., 2002; The Pediatric OCD Treatment Study (POTS) Team, 2004) and 40% (DeVaugh-Geiss et al., 1990; Jenike and Rauch, 1994; Pallanti et al., 2002) of OCD patients. Factors that have been associated with poor response to treatment in OCD include sexual/religious obsessions (Alonso et al., 2001; Mataix-Cols et al., 2002a,b), hoarding (Black et al., 1998; Saxena et al., 2002), psychiatric comorbidity (Minichello et al., 1987; McDougle et al., 1990; Baer, 1994; Mundo et al., 1995; Shavitt et al., in press), poor insight (Neziroglu et al., 1999; Erzegovesi et al., 2001), early onset and chronic course of obsessive–compulsive (OC) symptoms (Ackerman et al., 1994; Ravizza et al., 1995; Skoog and Skoog, 1999; Rosario-Campos et al., 2001; Erzegovesi et al., 2001; Fontenelle et al., 2003), absence of sensory phenomena and greater symptom severity (Hollander et al., 2002; Shavitt et al., in press), lack of family history (Erzegovesi et al., 2001), and family involvement in the OC symptoms (Guedes, 1997; Steketee et al., 1999; Steketee and VanNoppen, 2003). This study aimed to identify intrinsic clinical characteristics to the phenotypic expression of OCD (such as content and formal aspects of OC symptoms, as well as OCD course and patterns of co-morbidity) and other factors regarding demography, epigenetic factors and family history, as well as aspects of family functioning, that could be associated with OCD patient refractoriness to treatment.

2. Methods

Patients with OCD according to DSM-IV criteria (American Psychiatric Association, 1994) were consecutively recruited from three Brazilian treatment reference centres (1) the Obsessive–Compulsive Spectrum Disorders Clinic of the Hospital Presidente Vargas ($n=36$), (2) the Anxiety Disorders Clinic of the Universidade Federal do Rio Grande do Sul Hospital das Clínicas ($n=6$); and (3) the OCD clinic of the Universidade de São Paulo Hospital das Clinicas Institute of Psychiatry ($n=7$). The first two centres are located in the city of Porto Alegre, and the third is in the city of São Paulo. The distribution of the patients in each group did not differ in terms of the recruitment site ($\chi^2=4.23$; $df=1$, $p=0.12$). Inclusion criteria were (1) age between 18 and 65 years, (2) OCD as the most significant current psychiatric diagnosis, (3) absence of general medical or neurological diseases. Prior to being enrolled in the study, which was carried out in accordance with the latest version of the Declaration of Helsinki, all patients gave written informed consent, which was approved by the local ethics committees.

Jenike and Rauch (1994) used the terms "treatment-resistant" to describe individuals with OCD who do not respond satisfactorily to any first-line therapy and "treatment-refractory" to refer to those patients with OCD who, despite being treated with all available therapeutic alternatives, do not present a satisfactory reduction in symptom severity. To study possible factors associated with treatment-refractory OCD, two well-defined and operational sub-groups were compared: one composed of OCD patients who were refractory to conventional treatments and the other of patients with OCD who had been shown to be treatment responders.

In this case-control study, patients with treatment-refractory OCD (refractory group) were defined by the following criteria: (1) a decrease of less than 25% in the initial Yale-Brown Obsessive Compulsive Scale (YBOCS) score or a less than minimal improvement on the Clinical Global Impressions (CGI) scale after treatment with first-line drugs for at least 16 weeks each. First-line drugs, according to March et al. (1997), are clomipramine (maximum recommended dose [MRD] of 300 mg/day), fluoxetine (MRD of 80 mg/day), fluvoxamine (MRD of 300 mg/day), sertraline (MRD of 250 mg/day), paroxetine (MRD of 60 mg/day), citalopram (MRD of 60 mg/day); (2) at least three therapeutic trials with first-line drugs (necessarily including clomipramine), at maximum recommended or tolerated doses, for 16 weeks each; (3) at least two pharmacological augmentation strategies (including other SSRIs or neuroleptics); and (4) at least 20 h of Cognitive and Behaviour Therapy (CBT) (exposure and response prevention). Subjects were considered treatment-responsive OCD patients (responder group) if, after treatment with any conventional therapy (not necessarily the first trial with a SRI or CBT), they presented at least a 35% decrease in the initial YBOCS score, were rated "better" or "much better" on the CGI scale, and had maintained improvement for at least 1 year. The refractory group consisted of 23 patients, and the responder group consisted of 26.

2.1. Assessment

The instruments were administered by two experienced psychiatrics, one of whom was always present at either sites (YAF and NRB in Porto Alegre and YAF and MEM or ACL in São Paulo). Whenever possible the raters were blinded as to the treatment response status (with the exception of three patients who had to be

interviewed at home because of the severity of their symptoms).

To investigate the intrinsic clinical characteristics to the phenotypic expression of OCD, the following structured instruments were employed: (1) the YBOCS and its Symptom Checklist for the assessment of severity and content of obsessions and compulsions (Goodman et al., 1989a,b). (2) The Dimensional YBOCS (DYBOCS). This instrument measures the severity for each of six symptom dimensions (contamination/cleaning, hoarding, symmetry, aggressive, sexual/religious, and miscellaneous). Innovative features include the joint consideration of obsessions and compulsions in assessing the severity of each domain, separation of specific forms of checking, division of repetition and mental rituals into discrete dimensions, and inclusion of avoidance in measurements of severity. This instrument has recently been validated (Rosario-Campos et al., 2006). (3) The 14-item Hamilton Anxiety scale (HAM-A) and the 21-item Hamilton Depression scale (HAM-D) (Hamilton, 1959; Hamilton, 1967). (4) The Medical Outcomes Study 36-Item Short-Form Health Survey (MOS SF-36), a self-report instrument with 36 questions, divided into eight dimensions reflecting quality of life (Ware and Gandek, 1998). (5) The Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1997), including a section on Impulse Control Disorders not classified elsewhere. (6) The Structured Interview for DSM-IV Personality Disorders (Pfohl et al., 1997), applied by at least two interviewers, who later reach a consensus. (7) The Yale Global Tic Severity Scale (YGTSS), for the assessment of vocal and motor tics (Leckman et al., 1989). (8) The Brown Assessment of Beliefs Scale (BABS), which measures patient conviction and insight about the obsessions (Eisen et al., 1998). (9) A self-report instrument that consists of five visual analogical scales with possible OCD course types (under request). Two of them express intermittent (symptoms waxing-and-waning) course and other 3, chronic course of obsessive–compulsive symptoms. It is part of The Structured Interview for Socio-demographic data, developed at the (PROTOC-USP) OCD Clinic (available upon request). (10) The Psychiatric State Rating (PSR), which measures the severity of OC symptoms during four disease states (sub-clinical OC symptoms, clinical OC symptoms, the worse episode of OC symptoms and the current episode of OC symptoms). It also collects information about onset of OC symptoms (abrupt or insidious) (Keller et al., 1987). (11) The USP-Harvard Repetitive Behavior Interview (Miguel et al., 1997). To study other features related to demographic and epigenetic factors, as well as to family history and functioning (extrinsic variables), the following instruments were also used. (12) The Structured Interview for Socio-demographic data, developed at the (PROTOC-USP) OCD Clinic. This instrument was designed to gather information about marital, educational, occupational and socio-economic status (the socio-economic classification in Brazil is based upon the consideration of economic characteristics of products and services as well as social standing (such as profession and education) ranging from class A, which includes the higher managerial and professional occupations, to class E, which includes nonworkers and routine occupations); family history; epigenetic factors; medical history and previous psychiatric treatments (details available upon request). (13) The Family Accommodation Scale (FAS) (Calvocoresi et al., 1995), which assesses family accommodation of the OCD patient symptoms, family distress and patient reactions to family member resistance to accommodation. A family member was interviewed for this and also for family history and epigenetic factors checking.

2.2. Statistical analysis

The Student's *t*-test or the Mann–Whitney test was used to compare continuous variables, which were tested for homogeneity of variance. The chi-square test with Yates' correction or Fisher's exact test was used to compare categorical variables. Two stepwise logistic regressions were employed to identify factors independently associated with refractoriness, controlling for possible confounding factors. Variables with a p value of 0.10 or less in the univariate analysis were incorporated into the models. The first model included aspects directly related to the phenotypic expression of OCD (intrinsic variables), and the second included aspects not directly related to such expression (extrinsic variables) but deemed relevant for clinical practice. The level of statistical significance adopted was 5%. The Statistical Package for Social Sciences for Windows, version 10.0 (SPSS 10.0) was employed.

3. Results

3.1. General clinical variables

General demographic data of the patients with OCD are shown in Table 1. Patients from the refractory group were more frequently single, more often unemployed, and tended to be of lower educational and socio-economic status.

Table 1
Comparison of demographic variables between refractory and respondent Obsessive–Compulsive Disorder (OCD) groups

	Refractory (n=23) n (%)	Responder (n=26) n (%)	Analysis	
			χ^2 Yates	P
Male	12 (52.2)	10 (38.5)	0.46	0.499
Caucasian	21 (91.3)	24 (92.3)	*	1.00
Marital status (no spouse)	18 (78.3)	5 (19.2)	6.62	0.037
Occupation (unemployed)	14 (60.9)	6 (23.1)	5.04	0.025
Socio-economic classification				
Class A	1 (4.3)	2 (7.7)	**	0.015
Class B	5 (21.7)	13 (50.0)		
Class C	14 (60.9)	11 (42.3)		
Class D	3 (13.0)	0 (0.0)		
	Mean (S.D.)	Mean (S.D.)	t	P
Current age	35.22 (10.74)	41.35 (11.45)	1.918	0.061
	Median (25% and 75% quartile)	Median (25% and 75% quartile)	U	P
Education level	4 (2;6)	6 (4;7)	204.5	0.054

*Fisher's exact test; **Mann–Whitney U=189,50; S.D., standard deviation.

3.2. Previous psychiatric treatments

As expected from the selection criteria, more patients in the refractory group had received CBT (100% versus 73% in the responder group; Fisher's exact test, p=0.011), had been hospitalised (65% versus 23% in the responder group; χ^2=7.21, df=1, p=0.007), and had been submitted to electroconvulsive therapy (17% versus 3.8% in the responder group; Fisher's exact test, p=0.17), although it is not recommended for OCD, unless a refractory and severe major depression appears in comorbidity with it.

All patients had at least one trial with a serotonergic antidepressant. Twenty-two (96%) individuals in the refractory group and 12 (46%) in the responder group had used antipsychotics (Fisher's exact test, p<0.001), 17 (74%) in the refractory group and 8 (31%) in the responder group had used mood stabilizers (χ^2=9.09, df=1, p=0.004), 14 (61%) in the refractory group and 7 (27%) in the responder group had used tricyclics antidepressants (χ^2=5.74, df=1, p=0.022).

3.3. Symptom severity

The mean and standard deviation (S.D.) were calculated for each YBOCS score. The mean total YBOCS score for the refractory group was 27.82 (S.D., 6.09), compared with 17.42 (S.D., 7.74) for the responder group (t=5.03, p<0.001). The mean YBOCS obsession subscale score was 13.64 (S.D., 2.98) for the refractory group and 8.67 (S.D., 4.47) for the responders (t=4.39, p<0.001). The mean YBOCS compulsions subscale score was 14.18 (S.D., 4.00) for the refractory group and 8.75 (S.D., 4.29) for the responder group (t=4.43, p<0.001). The mean DYBOCS total score for the refractory group was 21.65 (S.D., 4.26) and for the responder group it was 14.69 (S.D., 4.42) (t=5.60, p<0.001). Mean anxiety and depression symptom scores were also higher for the refractory group: HAM-A=13.7 (S.D., 5.37) versus 7.54 (S.D., 4.72) for the responder group (t=4.27, p<0.001), and HAM-D=13.3 (S.D., 5.21) versus 6.89 (S.D., 3.77) for the responder group (t=z4.98, p<0.001).

3.4. Quality of life

Mean quality of life scores, as assessed by the MOS SF-36, were lower for the refractory group than for the responder group in three dimensions: vitality=36.91 (S.D., 21.99) versus 54.61 (S.D., 18.27) (t=3.02, p=0.004); social aspects=37.50 (S.D., 24.04) versus 68.85 (S.D., 21.26) (t=4.74, p<0.001); and mental health=33.91 (S.D., 16.13) versus 57.54 (S.D., 16.08) (t=5.00, p<0.001).

The findings described above, in addition to further validating the entry criteria used for the refractory group, reflect the general severity of OCD and accompanying features, as well as their impact on the patients' lives.

3.5. Clinical variables directly related to OCD phenotypic expression (intrinsic variables)

Content and formal aspects of OC symptoms, patterns of co-morbidity, insight, age at onset of OC symptoms, course of OC symptoms, and duration of OCD are shown in Tables 2–4. A comparison of the

Table 2
Obsessive–compulsive symptoms sub-types according to the Yale-Brown Obsessive–Compulsive Scale (YBOCS) and Dimensional Yale-Brown Obsessive–Compulsive Scale (DYBOCS)

	Refractory *n* (%)	Responders *n* (%)	Analysis	
			χ^2 Yates	*P*
YBOCS–Obsessions of [a]				
Aggression	20 (95.2)	19 (76.0)	*	0.11
Contamination	16 (76.2)	17 (68.0)	0.08	0.775
Sexual content	8 (38.1)	9 (36.0)	0.03	0.87
Hoarding	5 (23.8)	9 (36.0)	0.33	0.566
Religiosity	11 (52.4)	15 (60.0)	0.05	0.825
Symmetry	15 (71.9)	14 (56.0)	0.60	0.44
Somatic content	9 (42.9)	11 (44.0)	0.05	0.825
Other contents	21 (100.0)	21 (84.0)	*	0.11
YBOCS–Compulsions of [a]				
Cleaning/washing	17 (80.9)	17 (68.0)	0.43	0.51
Checking	16 (76.2)	23 (92.0)	*	0.22
Repeating	18 (85.7)	18 (72.0)	*	0.31
Counting	9 (42.9)	7 (28.0)	0.55	0.457
Ordering/arranging	9 (42.9)	13 (52.0)	0.10	0.747
Hoarding	5 (23.8)	9 (36.0)	0.33	0.566
Other contents	20 (95.2)	21 (84.0)	*	0.36
DYBOCS [b]				
Aggression dimension	18 (81.8)	15 (57.7)	1.27	0.26
Sexual/religious dimension	16 (72.7)	10 (38.5)	4.11	0.043
Symmetry/order dimension	18 (81.8)	19 (73.1)	0.00	1.00
Contamination/ cleaning dimension	19 (86.4)	16 (61.5)	*	0.202
Hoarding dimension	5 (22.7)	10 (38.5)	0.34	0.559
Other contents dimension	20 (90.9)	20 (76.9)	*	0.472

*Fisher Test.
[a] Refractory group (n=21) and Respondent group (n=25).
[b] Refractory group (n=22) and Respondent group (n=26).

content of OC symptoms is presented in Table 2. We found a statistically significant difference between the two groups only for sexual/religious content of OC symptoms, which, according to the DYBOCS symptom checklist, was exhibited more frequently in the refractory group (p=0.043). As can be seen in Table 3, there were no differences between the two groups regarding psychiatric co-morbidities (Axis I or Axis II) or the mean number of Axis I co-morbidities.

After the period of time between the age of obsessive–compulsive symptoms onset and the first adequate OCD treatment, all the patients were continuously treated. In spite of the adequate treatment they have received, Table 4 shows a higher frequency of chronic course for the refractory group, in opposition of an episodic course for responding group. The patients of responding group, after the adequate OCD treatment, continued to show residual symptoms, but with a much lower severity and level of morbidity. Table 4 also shows an earlier age at first OCD treatment for the refractory group. The time interval between the age at OC symptoms onset and the initial treatment tended to be shorter in the refractory group.

According to the PSR assessment, when the OC symptoms were sub-clinical (no interference or distress), there was only a trend for a higher symptom severity among refractory patients (t=1.75, p=0.086). When OC symptoms were discomfiting and interfered

Table 3
DSM-IV Axis I and II diagnoses in the refractory and responder OCD groups

	Refractory (n=23)	Responder (n=26)	Analysis	
	n (%)	*n* (%)	χ^2 Yates	*P*
Substance abuse	5 (21.7)	4 (15.4)	*	0.716
Schizophrenia	2 (8.7)	0 (0.0)	*	0.215
Bipolar disorder	0 (0.0)	1 (3.8)	*	1.00
Major depression	17 (73.9)	17 (65.4)	0.11	0.737
Anxiety disorders	9 (39.1)	12 (46.2)	0.04	0.836
Social phobia	3 (13.0)	4 (15.4)	*	1.00
Simple phobia	1 (4.3)	5 (19.2)	*	0.194
Panic/agoraphobia	2 (8.7)	4 (15.4)	*	0.67
Generalised anxiety	3 (13.0)	2 (7.7)	*	0.655
Post-traumatic stress disorder	2 (8.7)	1 (3.8)	*	0.594
Eating disorders	3 (13.0)	0 (0.0)	*	0.096
Tricothilomania/skin picking	4 (17.4)	4 (15.4)	*	1.00
Attention deficit/ hyperactivity disorder	0 (0.0)	1 (3.8)	*	1.00
Tourette syndrome	4 (17.4)	1 (3.8)	*	0.173
Other tics disorder	1 (4.3)	3 (11.5)	*	0.608
Personality disorders	7 (31.8)	8 (30.8)	0.08	0.775
Cluster A	3 (13.05)	4 (15.3)	*	1.00
Paranoid	1 (4.35)	3 (11.5)	*	0.612
Schizoid	2 (8.70)	1 (3.8)	*	0.594
Cluster B	1 (4.35)	1 (3.8)	*	1.00
Histrionic	1 (4.35)	0 (0.0)	*	0.469
Narcissistic	0 (0.0)	1 (3.8)	*	1.00
Cluster C	10 (43.5)	8 (30.8)	0.39	0.533
Avoidant	4 (17.4)	3 (11.5)	*	0.692
Dependent	3 (13.04)	1 (3.8)	*	0.33
Obsessive–compulsive	3 (13.04)	4 (15.4)	*	1.00
Any psychiatric comorbidity	17 (77.3)	14 (53.8)	1.93	0.165
	Mean (S.D.)	Mean (S.D.)	*t*	*P*
Number of axis I comorbidities	2.41 (1.26)	1.92 (1.20)	1.372	0.177

*Fisher Test; S.D., standard deviation.

Table 4
Comparison of insight, course, age at onset and duration of illness between refractory and respondent obsessive–compulsive patients

	Refractory (n=22)	Responder (n=26)	Analysis	
	n (%)	n (%)	χ^2 Yates	P
Chronic course [a]	10 (47.6)	1 (4.2)	*	0.0027
	Mean (S.D.)	Mean (S.D.)	t	P
BABS [b]	7.45 (4.44)	6.67 (5.24)	0.55	0.587
Age at onset (years)	13.5 (6.46)	17.0 (8.82)	1.52	0.135
OCD duration (years)	22.27 (10.55)	25.46 (12.63)	0.92	0.361
Age starting treatment (years)	23.95 (7.04)	32.17 (9.42)	3.32	0.002
Period of time to start treatment (years)	10.32 (7.88)	15.17 (10.45)	1.76	0.085

*Fisher's exact test; S.D., standard deviation; OCD, obsessive–compulsive disorder; BABS, Brown Assessment of Beliefs Scale.
[a] Refractory group (n=21) and Respondent group (n=24).
[b] Refractory group (n=21) and Respondent group (n=26).

with functioning, refractory patients presented greater disease severity (t=3.88, p<0.001). During the worse OC symptoms state, there were no differences between the groups (t=1.53, p=0.133). As expected, current severity of OC symptoms was higher for refractory patients (t=8.67, p<0.001).

Using the USP-Harvard Repetitive Behaviour Interview to analyse the presence of at least one sensory phenomenon preceding the compulsions, we found that 20 (86.9%) of the patients in the refractory group and 22 (88.0%) of those in the responsive group presented this condition, a less than significant difference (Fisher's exact test, p=0.57). We also found no differences in the following specific sensory phenomena: mental sensations, body sensations, "just right" sensations (the need for repeating an act until reaching a sensation that it was done in the "right manner," "perfectly"), energy, premonitory "urges," and feelings of incompleteness.

3.6. Variables indirectly related to OCD phenotypic expression (demographic, epigenetic, family history and family functioning factors—extrinsic variables)

No statistically significant differences were found between the two groups regarding family history of psychiatric disorders (Fisher's exact test, p=0.58), OCD (χ^2 Yates=0.05, p=0.82, df=1) or tics (χ^2 Yates=0.01, p=0.93, df=1), or any of the epigenetic factors studied, which included pregnancy-related events, emotional problems, excessive caffeine consumption, smoking, use of alcohol or illicit drugs during pregnancy, childbirth site (in a hospital or not), childbirth type (caesarean operation or not), forceps use, premature birth, birth weight, and medical occurrences during or after childbirth.

3.7. Family functioning

In the FAS evaluation, the refractory group presented the following: a higher family accommodation index (FAI) rate, with a median of 20 versus 6.5 for the responder group (U=64.5, p<0.001); a higher family distress index (FDI) rate, with a mean of 3.29 (S.D., 2.83) versus 1.27 (S.D., 0.92) for the responder group (t=3.42, p<0.001); and higher scores for patient consequences (anxiety, aggressiveness, and slowness) if family members did not participate in the OC symptoms, with a mean of 5.24 (S.D., 3.00) versus 3.31 (S.D., 2.62) for the responder group (t=2.36, p=0.023). There was a positive correlation between FAI and YBOCS severity scores (r=0.71, p<0.001) and between FDI and YBOCS scores (r=0.50, p<0.001). The correlation between the FAI (r=−0.0013, p=0.931) and the FDI (r=−0.223, p=0.14) with the duration of OCD was less than significant.

In our sample, although the relatives of patients in the responder group were more likely to present limited family accommodation, those of refractory patients displayed significantly higher levels of serious accommodation (U=64.5, p<0.001). Most (76.9%) of the families of patients with treatment-responsive OCD were at the no/limited accommodation level versus only 14.3% of those of patients with treatment-refractory OCD. Whereas 52.4% of the families of refractory patients were at the serious/extreme level, only 3.8% of those of responders were at that level.

3.8. Logistic regression analysis

To verify the independent associations of the variables most significantly (p=0.10) identified with refractoriness in the univariate analysis (dependent variables), we performed two stepwise logistic regression analyses (enter probability of 0.05 and exit probability of 0.10). For the first model, we entered the following intrinsic factors: severity of OC symptoms according to the YBOCS, interval between the onset of OCD and the beginning of treatment, course of the illness, and presence of sexual/religious dimension according to the DYBOCS checklist. For the second

Table 5
Variables independently associated with obsessive–compulsive disorder (OCD) refractoriness to treatment after the logistic regression analyses

Variable	Coefficient (S.E.)	*P*	Odds ratio	95% confidence interval
OCD intrinsic factors				
Sexual/religious dimension	1.50 (0.66)	0.024	0.22	(0.06–0.82)
OCD extrinsic factors [a]				
Lower socio-economic status	3.03 (1.37)	0.027	20.72	(1.42–303.32)
Higher family accommodation index	0.42 (0.16)	0.009	1.53	(1.11–2.10)

S.E.–standard error.
[a] Variable entered in step 1: family accommodation index; variable entered in step 2: socio-economic status.

model, we entered the following extrinsic factors: marital status, educational level, occupation, socio-economic status and FAI. Other variables were not included because of their co-linearity with OC symptom severity or with FAI. Table 5 presents the results of the final logistic regression analysis. As shown, the presence of sexual/religious symptoms, lower socio-economic level and higher FAI scores were the only factors independently associated with OCD refractoriness.

4. Discussion

The criteria we used for refractoriness (less than 25% decrease of the initial YBOCS scores; less than a minimal improvement on CGI; at least three adequate therapeutic trials with first-line drugs; at least two pharmacological augmentation strategies; and at least 20 h of exposure and response prevention) were stricter than those previously adopted by other authors. This strategy allowed a clear-cut comparison between the two groups and was partially justified by the findings of greater OC symptom severity, more symptoms of depression and anxiety, and lower quality of life in the refractory group. Likewise, our responder group included only patients with at least 1 year of proven consistent treatment-related improvement. However, these defining criteria are arbitrary, may limit the generalisation of our findings, and cannot preclude the possibility that current responders may become refractory in the future. A major strength of this study is the systematic and structured evaluation of a vast array of variables related to the clinical expression of OCD, including scores derived from a new instrument (the DYBOCS, especially designed to describe the OCD phenotype), epigenetic factors and ratings derived from instruments evaluating family accommodation, the latter not having been previously employed.

4.1. Content and formal aspects of OC symptoms

The DYBOCS sexual/religious dimension, more frequently found in the refractory group, has also been associated with poor treatment response in previous studies (Alonso et al., 2001; Mataix-Cols et al., 2002a,b). Using a different instrument than the present study, Mataix-Cols et al., (2002a,b), found that higher scores on the "sexual/religious obsessions" factor were also related to less favourable outcomes of behavioural therapy.

Although Tek and Ulug (2001) found that the expression of the religious obsessive–compulsive symptoms seems not to be related exclusively to cultural influences, this topic needs more descriptive and analytical studies, since it could be a key aspect when establishing differences between sexual and religious obsessive–compulsive symptoms and normal sexuality and religiosity. It could also explain how social and cultural aspects influence obsessive–compulsive symptoms. One aspect that makes this task quite difficult is that the social concepts and ensuing traditions regarding mental illness vary considerably in different cultures. These concepts are determined by religious and superstitious beliefs, moral codes, cultural values, and economic factors. Some cultures still accept attitudes and behaviors that are rejected elsewhere. We could speculate, for example, that, since some sexual and religious contents are particularly unacceptable and, at the beginning of the disease the patient has no idea that he/she has OCD, patients may believe that the obsessional thoughts are really expressions of their own moral values. This could bring serious guilt and sinful feelings, enhancing depressive symptoms and worsening OCD.

Yaryura-Tobias and Neziroglu (1997) suggest that scrupulosity's obsessional content closely relates to morality, sexuality and religiosity. Some scrupulous patients might be religious individuals and when this occurs, OCD, morality and religiosity may blend, worsening the disorder (Yaryura-Tobias and Neziroglu, 1997). Moll et al. (2005), reviewing functional neuroimaging studies of moral cognition, describe consistent involvement mainly of the anterior prefrontal cortex, but also of the temporal sulcus, anterior temporal lobes and limbic structures in moral judgment in normal individuals, postulating a theory that posits mutually competitive roles of cognition and emotion in moral judgement.

They also affirm that prefrontal cortex has a central role in the internalization of moral values and norms through the integration of cultural and contextual information during development (Moll et al., 2005). Neuroimaging studies of OCD patients also reveal some dysfunction of prefrontal cortex, showing hyperfunction of the orbitofrontal areas (Alexander and Crutcher, 1990; Saxena et al., 1998; Saxena and Rauch, 2000), what could lead to a moral "hypertrophy" that could be expressed by religious and sexual dimension on OCD patients.

Recent neuro-imaging studies have provided additional evidence, suggesting different patterns of activation according to different OC symptom dimensions (Rauch et al., 1998; Mataix-Cols et al., 2003). One could speculate that the expression of sexual/religious OC symptoms involves neuro-anatomical regions previously associated with poor treatment response (Rauch et al., 1998; Saxena et al., 1998; Saxena and Rauch, 2000), and that its circuit may overlap with social, cultural and moral neurocircuits.

4.2. Psychiatric co-morbidity

In our sample, 42 patients (85.4%), 21 refractory (90.9%) and 21 responsive (80.8%), presented at least one lifetime psychiatric co-morbidity. These findings are comparable to those found in the literature, where the most prevalent lifetime psychiatric co-morbidities are major depression, simple phobia, social phobia and tics (Rasmussen and Eisen, 1997; Vallejo, 1998).

Although bipolar disorder was mostly absent in our sample, the frequency of bipolar disorders among patients with OCD are said to range from 2% to 3% for Bipolar I and from 8% to 13.6% for Bipolar II Disorders (American Psychiatric Association, 1994; Perugi et al., 1997). It must be noted, however, that "soft bipolarity" (when hypomania and cyclothymia are included) may occur more frequently than previously known in OCD patients according to Cyclothymic Temperament Questionnaire (Hantouche et al., 2003; Akiskal et al., 2003). In fact, it has been shown that "cyclothymic OCD" patients exhibit several features that could lead to treatment resistance or refractoriness, such as more severe obsessive–compulsive symptoms, elevated risk of suicide, greater comorbidity with mania or hypomania and major depression, earlier emotional problems, greater social and conjugal problems, and greater frequency of learning difficulties. Issler et al. (2005), studying the expression of OCD in women with bipolar disorder, found that there was a positive correlation between the score in the YBOCS and the intensity of hipomanic/manic symptoms measured through the Young Mania Rating Scale. In our study, the refractory patients have been more often treated with mood stabilizers and antipsychotics, although it must be stressed that this may only be due to their refractoriness. It could also be argued, for example, that if these patients with OCD were more often cyclothymic in temperament, the intense use of antidepressant, perhaps especially clomipramine at high doses, could worsen their clinical picture towards a more mixed (and refractory) state. As the Structured Clinical Interview for DSM-IV Axis I Disorders is conservative in detecting bipolar disorder type II (Akiskal and Benazzi, 2005), this may have been a limitation of our study.

Shavitt et al. (in press) found that a higher number of co-morbid psychiatric disorders, although unrelated to OCD severity, were related to a poor response to clomipramine. In our study, the presence and number of co-morbid conditions were not related to refractoriness. However, it is likely that the sample size was too small to evince the expected differences between groups (type II error).

4.3. Sensory phenomena

Leckman et al. (1994) suggest that basal ganglia are composed of pathways that contribute to the multiple parallel cortical–striatal–thalamo–cortical circuits that concurrently subserve a wide variety of sensoriomotor, motor, oculomotor, cognitive, and limbic "processes." They also suggest that Tourette Syndrome and etiologically related forms of OCD are associated with a failure to inhibit subsets of the cortical–striatal–thalamo–cortical minicircuits. Therefore, as we speculated that sensory phenomena could be related to a dopaminergic subtype of OCD (similar to Tourette Syndrome), we expected that it could be more frequent in refractory patients, but there were no differences between groups. Kane (1994) proposed that pre-tic sensory experiences result from a specific attentional deficit. Based on his own introspective case study, the author argues that the premonitory urges that precede tics are not unique sensory events, but rather manifestations of somatosensory hyperawareness, which serves as an aversive stimulus toward which tics are purposively directed.

4.4. Course of OC symptoms

In the refractory patients we studied, the illness was more likely to have a chronic course, whereas an intermittent course was more common among the responders. Similar results were reported by Hollander et al. (2002), who found that the disease presented a

chronic course in approximately 90% of refractory OCD patients (versus 70% of responders). Our PSR results showed that refractory patients, in addition to displaying a more chronic course, had more severe symptoms from the onset, even before meeting OCD criteria. This probably leads to more interference in emotional, social and professional functioning, which may in turn contribute to a less favourable treatment response.

4.5. Age at onset and duration of OCD

In our sample, the mean age at which treatment began was lower among refractory patients than among responders ($p=0.002$); the latter tended to go untreated for an average of 5 years longer ($p=0.08$). As opposed to what we expected, no differences were found between groups regarding age at OCD onset and first treatment. Therefore, refractory patients may seek treatment earlier, either because their OCD is more severe from the onset or because of secondary depressive and anxiety symptoms.

4.6. Socio-demographic aspects

There was a trend toward a statistically significant difference between groups regarding educational level ($p=0.054$). Refractory patients were more likely than responders to be of lower social-economic status ($p=0.015$) and to be single ($p=0.037$). Steketee et al. (1999) found that the chance of presenting partial symptom remission within a 5-year period was two times greater for OCD patients who were married than for those who were single. These findings are in accordance with another study conducted by our group, in which we showed that having a spouse was associated with a greater degree of improvement (Shavitt et al., in press). Thus, it seems that refractory patients with OCD present reduced productivity, resulting in lower wages and probably imposing a considerable economic burden on their families, on their employers, and on society. Our results are in line with those of Stein et al. (1996), suggesting that OCD (especially refractory cases) leads to considerable distress and interferes with social, academic and occupational functioning. Therefore, lower socio-economic status and higher numbers of unmarried patients (as well as lower educational level and higher unemployment) are possibly consequences of the severity of the disorder, although the design of this study does not allow us to draw conclusions about the direction of causality. The burden associated with refractory OCD should be investigated further.

4.7. Family functioning

Our sample evinced significant differences for all scores on the FAS. The participation of relatives in patient rituals and the modification of family functioning due to OC symptoms compose what Calvocoresi et al. (1995) called the family accommodation index (FAI). When the relative performs a ritual together with the patient, the symptom is reinforced. The family distress index (FDI) refers to the direct distress that OCD causes to the family member. The way in which patients react when relatives do not participate in their compulsions contributes to family accommodation. This study found significantly higher FAI, FDI and patient reactions in the refractory group. Guedes (1997), evaluating 26 OCD patients, found that all of the families presented some degree of family accommodation and found a positive correlation between FAI and higher YBOCS scores ($r=0.41$, $p=0.003$). This correlation was also found in the present study ($r=0.71$, $p<0.001$).

The higher FAIs may lead to a less favourable patient response to CBT techniques (Steketee and VanNoppen, 2003) as some family members, rather than responding adaptively by engaging in problem solving with the patient, become over-involved, frustrated, angry, or rejecting. Maladaptive reactions increase patient stress, possibly leading to symptom aggravation and relapse. There is some evidence that hostility and emotional over-involvement, as well as any statements perceived by the patient as criticism, have a negative effect on CBT outcome. As previously mentioned, family accommodation is predictive of poorer family functioning and more severe OC symptoms after behavioural treatment (Steketee and VanNoppen, 2003). Conversely, the phenomenon of accommodation could be also secondary to case severity or complexity. Prospective studies are needed to better understand the causal direction of this and other associations—to investigate, for example, whether family accommodation and low socio-economic status are risk factors or consequences of refractoriness.

The clinical implications of this study include that sexual/religious obsessions in OCD patients and greater symptom severity from the onset may constitute warning signs for clinicians to establish a more comprehensive protocol for initial treatment in order to prevent future refractoriness. Also, we found that high impact on family function is associated with a less favourable response to treatment. In dealing with patient symptoms, it is also important to target the maladaptive behaviours of family members. Our findings corroborate the importance of early treatment interventions, together

with social and family approaches, in order to minimise the negative impact of OCD on the social, educational and occupational functioning of the individual.

Other clinical and neurobiological studies, with larger samples, adequate instruments of assessment and prospective research designs, should investigate further how symptoms of sexual and religious content may contribute to refractoriness of OCD patients. Therapeutic interventions on family functioning are warranted when OCD patients are not responding to conventional treatment approaches. As our findings are clinically relevant, they should be replicated by other research centres, in order to determine predictive factors of treatment non-response in OCD.

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References

Ackerman, D.L., Greenland, S., Bystritsky, A., 1994. Predictors of treatment response in obsessive–compulsive disorder: multivariate analyses from a multicenter trial of clomipramine. J. Clin. Psychopharmacol. 14, 247–254.

Akiskal, H.H., Hantouche, E.G., Lancrenon, S., 2003. BP-II with and without cyclothymic temperament: "dark" and "sunny" expressions. J. Affect. Disord. 73, 49–57.

Akiskal, H.S., Benazzi, F., 2005. Optimizing the detection of bipolar II disorder in outpatient private practice: toward a systematization of clinical diagnostic wisdom. J. Clin. Psychopharmacol. 66, 914–921.

Alexander, G.E., Crutcher, M.D., 1990. Substrates of parallel processing. TINS 13, 266–271.

Alonso, P., Menchon, J.M., Pifarre, J., 2001. Long-term follow-up and predictors of clinical outcome in obsessive–compulsive patients treated with serotonin reuptake inhibitors and behavioral therapy. J. Clin. Psychopharmacol. 62, 535–540.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, DSM-IV, 4th edition. APA, Washington, DC.

Baer, L., 1994. Factor analysis of symptom subtypes of obsessive–compulsive disorder and their relation to personality and tic disorders. J. Clin. Psychopharmacol. 55, 18–23. Suppl.

Black, D.W., Monahan, P., Gable, J., et al., 1998. Hoarding and treatment response in 38 nondepressed subjects with obsessive–compulsive disorder. J. Clin. Psychopharmacol. 59, 420–425.

Calvocoresi, L., Lewis, B., Harris, M., et al., 1995. Family accommodation in obsessive–compulsive disorder. Am. J. Psychol. 152, 441–443.

DeVaugh-Geiss, J., Katz, R., Landau, P., et al., 1990. Clinical predictors of treatment response in obsessive compulsive disorder: exploratory analyses from multicenter trials of clomipramine. Psychopharmacol. Bull. 26, 54–59.

Eisen, J.L., Phillips, K.A., Baer, L., et al., 1998. The Brown Assessment of Beliefs Scale: reliability and validity. Am. J. Psychol. 155, 102–108.

Erzegovesi, S., Cavallini, M.C., Cavedini, P., et al., 2001. Clinical predictors of drug response in obsessive–compulsive disorder. J. Clin. Psychopharmacol. 21, 488–492.

First, M.B., Spitzer, R.L., Gibbon, et al., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders: Clinical Version (SCID-CV). American Psychiatric Press, Washington, DC.

Fontenelle, L.F., Mendlowic, M.V., Marques, C., Versiani, M., 2003. Early- and late-onset obsessive–compulsive disorder in adult patients: exploratory clinical and therapeutic study. J. Psychol. Res. 37, 127–133.

Goodman, W.K., Price, L.H., Rasmussen, S.A., et al., 1989a. The Yale-Brown Obsessive Compulsive Scale: development, use and reliability. Arch. Gen. Psychiatry 46, 1006–1011.

Goodman, W.K., Price, L.H., Rasmussen, S.A., et al., 1989b. The Yale-Brown Obsessive Compulsive Scale: validity. Arch. Gen. Psychiatry 46, 1012–1016.

Guedes, M.L., 1997. Transtorno Obsessivo–Compulsivo: um estudo do processo de acomodação familiar. São Paulo. 80p. Dissertação (Mestrado)–Escola Paulista de Medicina. Universidade Federal de São Paulo.

Hamilton, M., 1959. The assessment of anxiety states by rating. Br. J. Med. Psychol. 32, 50–55.

Hamilton, M., 1967. Development of a rating scale for primary depressive illness. Br. J. Soc. Clin. Psychol. 6, 278–296.

Hantouche, E.G., Angst, J., Demonfaucon, C., Perugi, G., Lancrenon, S., Akiskal, H.S., 2003. Cyclothymic OCD: a distinct form? J. Affect. Disord. 75, 1–10.

Hollander, E., Bienstock, C.A., Koran, L.M., et al., 2002. Refractory obsessive–compulsive disorder: state-of-the-art treatment. J. Clin. Psychopharmacol. 63 (Suppl 6), 20–29.

Issler, C.K., Amaral, J.A., Tamada, R.S., et al., 2005. Clinical expression of obsessive–compulsive disorder in women with bipolar disorder. Rev. Bras. Psiquiatr. 27, 139–142.

Jenike, M.A., Rauch, S.L., 1994. Managing the patient with treatment-resistant obsessive–compulsive disorder: current strategies. J. Clin. Psychopharmacol. 55, 11–17. Suppl.

Kane, M.J., 1994. Premonitory urges as "attentional tics" in Tourette's syndrome. J. Am. Acad. Child Adolesc. Psych. 33 (6), 805–808.

Keller, M.B., Lavori, P.W., Friedman, B., et al., 1987. The longitudinal interval follow-up evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. Arch. Gen. Psychiatry 44, 540–548.

Leckman, J.F., Riddle, M.A., Hardin, M.T., et al., 1989. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J. Am. Acad. Child Adolesc. Psych. 28, 566–573.

Leckman, J.F., Walker, D.E., Goodman, W.K., Pauls, D.L., Cohen, D.J., 1994. "just right" perceptions associated with compulsive behavior in Tourette's Syndrome. Am. J. Psychiatr. 151, 675–680.

March, J.S., Frances, A., Carpenter, D., Kanh, D.A., 1997. The expert consensus guidelines series: treatment of obsessive–compulsive disorder. J. Clin. Psychopharmacol. 58 (suppl 4), 4–64.

Mataix-Cols, D., Rauch, S.L., Manzo, P.A., Jenike, M.A., Baer, L., 2002a. Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the

treatment of obsessive–compulsive disorder. Am. J. Psychol. 156, 1409–1416.

Mataix-Cols, D., Marks, I.M., Greist, J.H., et al., 2002b. Obsessive–compulsive symptom dimensions as predictors of compliance with and response to behavior therapy: results from a controlled trial. Psychother. Psychosom. 71, 255–262.

Mataix-Cols, D., Cullen, S., Lange, K., et al., 2003. Neural correlates of anxiety associated with obsessive–compulsive symptom dimensions in normal volunteers. Biol. Psychol. 53, 482–493.

McDougle, C.J., Goodman, W.K., Price, L.H., et al., 1990. Neuroleptic addition in fluvoxamine-refractory obsessive–compulsive disorder. Am. J. Psychol. 147, 652–654.

Miguel, E.C., Baer, L., Coffey, B.J., et al., 1997. Phenomenological differences appearing with repetitive behaviours in obsessive–compulsive disorder and Gilles de la Tourette's syndrome. Br. J. Psychol. 170, 140–145.

Minichello, W.E., Baer, L., Jenike, M.A., et al., 1987. Schizotypical personality disorder: a poor prognostic indicator for behavioral therapy in the treatment of obsessive–compulsive disorder. J. Anxiety Disord. 1, 273–276.

Moll, J., Zahn, R., Oliveira-Souza, R., Krueger, F., Grafman, J., 2005. The neural basis of human moral cognition. Nat. Rev. 6, 799–809.

Mundo, E., Erzegovesi, S., Bellodi, L., 1995. Follow-up of obsessive–compulsive patients treated with proserotonergic agents. J. Clin. Psychopharmacol. 15, 288–289.

Neziroglu, F.A., Stevens, P.K., Yaryura-Tobias, J.A., 1999. Overvalued ideas and their impact on treatment outcome. Rev. Bras. Psiquiatr. 21, 209–216.

Pallanti, S., Hollander, E., Bienstock, C., et al., 2002. Treatment non-response in OCD: methodological issues and operational definitions. Int. J. Neuropsychopharmacol. 5, 181–191.

Perugi, G., Akiskal, H.S., Pfanner, C., Presta, S., Gemignani, A., Milanfranchi, A., Lensi, P., Ravagli, S., Cassano, G.B., 1997. The clinical impact of bipolar and unipolar affective comorbidity on obsessive–compulsive disorder. J. Affect. Disord. 46, 15–23.

Pfohl, B., Blum, N., Zimmerman, M., 1997. Structured Interview for DSM-IV Personality (SIDP-IV). American Psychiatric Press, Washington, DC.

Piacentini, J., Bergman, R.L., Jacobs, C., et al., 2002. Open trial of cognitive behavior therapy for childhood obsessive–compulsive disorder. J. Anxiety Disord. 16, 207–219.

Rasmussen, S.A., Eisen, J.L., 1997. Treatment strategies for chronic and refractory obsessive–compulsive disorder. J. Clin. Psychopharmacol. 58, 9–13.

Rauch, S.L., Dougherty, D.D., Shin, L.M., et al., 1998. Neural correlates of factor-analyzed OCD symptom dimensions: a PET study. CNS Spectr. 3, 37–43.

Ravizza, L., Barzega, G., Bellino, S., et al., 1995. Predictors of drug treatment response in obsessive–compulsive disorder. J. Clin. Psychopharmacol. 56, 368–373.

Rosario-Campos, M.C., Leckman, J., Mercadante, M., et al., 2001. Adults with early-onset obsessive–compulsive disorder. Am. J. Psychol. 158, 1899–1903.

Rosario-Campos, M.C., Miguel, E.C., Quatrano, S., Chacon, P., Ferrao, Y., Findley, D., Katsovich, L., Scahill, L., King, R.A., Woody, S.R., Tolin, D., Hollander, E., Kano, Y., Leckman, J.F., 2006. The Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS): an instrument for assessing obsessive-compulsive symptom dimensions. Mol. Psych. 11, 495–504.

Saxena, S., Rauch, S.L., 2000. Functional neuroimaging and the neuroanatomy of obsessive–compulsive disorder. Psychol. Clin. North Am. 23, 563–586.

Saxena, S., Brody, A.L., Schwartz, J.M., et al., 1998. Neuroimaging and frontal–subcortical circuitry in obsessive–compulsive disorder. Br. J. Psychol. 35, 26–37.

Saxena, S., Brody, A.L., Schwartz, J.M., et al., 1998. Neuroimaging and frontal–subcortical circuitry in obsessive–compulsive disorder. Br. J. Psychol. 35, 26–37.

Shavitt, R.G., Belotto, C., Curi, M., et al., in press. Clinical features associated to treatment response in obsessive–compulsive disorder. Comprehensive Psychiatry.

Skoog, G., Skoog, I., 1999. A 40-year follow-up of patients with obsessive–compulsive disorder. Arch. Gen. Psychiatry 56, 121–127.

Stein, D.J., Roberts, M., Hollander, E., et al., 1996. Quality of life and pharmaco-economic aspects of obsessive–compulsive disorder. A South African survey. Afr. Med. J. 86, 1582–1585. Suppl.

Steketee, G., Eisen, J., Dyck, I., 1999. Predictors of course in obsessive–compulsive disorder. Psychol. Res. 89, 229–238.

Steketee, G., VanNoppen, B., 2003. Family approaches to treatment for obsessive–compulsive disorder. Rev. Bras. Psiquiatr. 25, 43–50.

Tek, C., Ulug, B., 2001. Religiosity and religious obsessions in obsessive–compulsive disorder. Psychol. Res. 104, 99–108.

The Pediatric OCD Treatment Study (POTS) Team, 2004. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive–compulsive disorder. J. Am. Med. Assoc. 292, 1969–1976.

Vallejo, J., 1998. Relación de los transtornos obsesivos con otras patologías psíquicas, In: Vallejo, J., Berrios, G.E. (Eds.), Estados Obsesivos, 2a. Ed. Masson, Madrid, pp. 71–90.

Ware, J.E., Gandek, B., 1998. Overview of the SF-36 Health Survey and the International Quality of Life Assessment Project. J. Clin. Epidemiol. 5, 1903–1912.

Yaryura-Tobias, J.A., Neziroglu, F.A., 1997. History, culture and clinical aspects of OCD. In: Yaryura-Tobias, J.A., Neziroglu, F.A. (Eds.), Obsessive-Compulsive Disorder Spectrum. American Psychiatric Press, Inc., Washington, D.C., pp. 3–32.